ASTHMA-RELATED MORBIDITY AND MORTALITY IN PATIENTS EXPOSED TO INHALED LONG-ACTING BETA-2-ADRENOCEPTOR AGONIST BRONCHODILATORS

By

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To the 300 million individuals in the world who are afflicted with asthma

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Bronchial asthma is a chronic inflammatory disease of the respiratory system, with increasing prevalence and severity in society. Inhaled long-acting beta-agonist (LABA) bronchodilators are considered part of the regular maintenance therapy in asthmatic patients. Although the purpose of asthma treatment is to control the disease with medications that have satisfactory safety profile, there has been mounting concern about the safety of inhaled LABA bronchodilators as monotherapy, including increased asthma deaths and poor asthma outcomes. The role of inhaled corticosteroids (ICS) in asthma management is crucial, and regular inflammation preventer therapy with ICS is associated with lower asthma mortality and morbidity rates. However, ICS have safety concerns as well. While it is recommended to use inhaled LABA bronchodilators in combination with ICS to attain and maintain acceptable outcomes, increased risks of asthma deaths and exacerbations are reported with the combination therapy. The aim of this study is to use advanced and novel approaches in causal inference to evaluate asthma-related outcomes in patients exposed to inhaled LABA bronchodilators as monotherapy, and ICS combination therapy. Among the 51,103 adults with asthma who

met the inclusion criteria and followed for 12 months after receiving first prescription of study drugs from January 4, 1993 to August 20, 2010, about 92% initiated ICS monotherapy, 1% initiated LABA monotherapy, and 7% initiated ICS/LABA combination therapy. Among the ICS/LABA combination therapy initiators, 78% were in single-device formulations and 22% were in separate-devices. Among the 3,226 asthmatics who initiated ICS/LABA combination therapy, 14.2% continued on original strength ICS/LABA combination regimen, 26.5% reduced the dose of ICS to 50% while continuing LABA as combination regimen, and 59.3% discontinued LABA and continued ICS in original strength as monotherapy. The findings suggest presence of time-dependent confounding of asthma exacerbations requiring prescriptions of oral corticosteroids by inhaled LABA products, but absence of time-dependent confounding of accident and emergency department visits for asthma attacks or asthma-related deaths or all-cause deaths. Compared with ICS monotherapy, LABA monotherapy is associated with 10% increased risks of asthma exacerbations requiring short courses of oral corticosteroids (HR, 1.10; 95%CI, 1.07-1.18). Initiators of ICS/LABA combination therapy are respectively 62% and 50% less likely to receive prescriptions of oral corticosteroids for asthma exacerbations than initiators of ICS (HR, 0.38; 95%CI, 0.12-0.66) or LABA monotherapies (HR, 0.50; 95%CI, 0.14-0.78). Compared to continuing original combination therapy regimens, step-down therapy approaches by LABA discontinuation or ICS dose reduction are associated with significant reduction in asthma morbidity. Nevertheless, within step-down therapy approaches, LABA stoppers are associated with worsened asthma (short courses of oral corticosteroids) than ICS/LABA dose reducers when ICS monotherapy is in medium strength (HR, 1.24;

95%CI, 1.07-5.01). When ICS monotherapy is in high strength, withdrawing LABA is associated with better asthma control than continuing LABA as reduced ICS/LABA regimen (HR, 0.35; 95%CI, 0.06-0.51). Patients who survived for a minimum of 12 months after initiating LABA monotherapy are 25% more likely to die from asthma than patients who initiated ICS monotherapy (HR, 1.25; 95%CI, 1.11-3.01). There were no differences in asthma-related deaths, all-cause deaths, and asthma-related visits to accident and emergency departments between exposure groups. In conclusion, inhaled LABA should not be prescribed as monotherapy to adults with asthma, and should be used as an add-on to ICS as maintenance therapy. For patients with less severe asthma, discontinuing LABA appears to worsen disease control, and such step-down therapy approach appears more beneficial in patients with more severe disease state.

CHAPTER 1
BACKGROUND

Definition of Asthma

Asthma is a chronic pulmonary disorder that was recognized since ancient times. The symptoms of asthma and an apparatus used to relieve them were first described in cuneiform clay tablets found in ancient Mesopotamia—modern-day Iraq (Cserháti, 2004). The term *asthma* (αστμα) is Greek in origin denotes to panting or exhaling with an open mouth (Cserháti, 2004). Asthma is a chronic inflammatory disorder of the airways that is characterized by chronic bronchial inflammation, hyperresponsiveness, and reversible bronchoconstriction (GINA, 2009). These pathophysiological features cause the distinctive signs and symptoms of asthma: wheezing, shortness of breath, chest tightness, coughing, and tachypnea (BTS, 2009). These signs and symptoms are crucial in the diagnosis, treatment, and monitoring of the disease.

With the progress in understanding disease pathophysiology, the definition of asthma has changed over time. Reversible airway obstruction and hyperresponsiveness were the predominant characteristics of asthma definition in the 1950s and 1960s (Guilbert & Krawiec, 2003). The concept of preventing bronchoconstriction was first introduced in the 1970s (Guilbert & Krawiec, 2003). In the 1980s, inflammation was recognized as a predominant disease process in asthma (Nadel, 1985; Guilbert & Krawiec, 2003). Acute and chronic inflammation occurs in patients with varying severity of asthma which causes bronchial infiltration with inflammatory mediators, e.g. eosinophils, mast cells, and interleukins; airway remodeling—manifested by hyperplasia and hypertrophy of bronchial smooth muscles; and mucus plugging of the bronchial lumen. The effectiveness of bronchodilators is minimized when extensive mucus

plugging occurs in severe asthma (Hopp & Townley, 2006). Medications with anti-inflammatory effects, such as inhaled corticosteroids, oral corticosteroids, and leukotriene modifiers are increasingly becoming the mainstay of asthma therapy.

Bronchial hyperresponsiveness in asthmatic patients occurs due to increased sensitivity of the airways to irritants, such as pollens and tobacco smoke. Reversible airway obstruction (bronchoconstriction) is a common corollary to airways inflammation and hyperresponsiveness.

Natural History of Asthma

The development and consequences of untreated asthma are described in light of measures of disease assessment and monitoring that are recommended by the National Heart Lung and Blood Institute (NHLBI) guidelines for the diagnosis and management of asthma (NHLBI, 2007). The degree of bronchoconstriction is proportional to the duration and severity of asthma. Adults with asthma have significantly greater loss in pulmonary function than non-asthmatics. The daytime and nighttime symptoms of shortness of breath, wheezing, and coughing induce functional impairment in terms of disturbance of sleep and missing school and work days. The progressive decline in lung functions raises the risks of unpleasant events in terms of exacerbations. Therapeutic interventions improve disease symptoms and minimize functional impairment and the risks of untoward events. However, such interventions have no influence on the underlying pathogenesis of asthma. For instance, countering bronchopulmonary inflammation with inhaled corticosteroids (ICS) improves symptoms and reduces exacerbations, but, symptoms are rebounded after ICS withdrawal (NHLBI, 2007).

Asthma and Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder that includes chronic bronchitis and emphysema. Both asthma and COPD account for the majority of the obstructive respiratory disorders (Ryu & Scanlon, 2001). In the US, about 24 million adults have COPD (12 million physician-confirmed and 12 million under-diagnosed) (CDC, 2011b). Globally, COPD is projected to be the fifth leading burden of illnesses in 2020—as measured by disability-adjusted life years (Lopez & Murray, 1998). Also, mortality rates from COPD are projected to increase over the next eight years (Murray & Lopez, 1997).

In early 1960s, the “Dutch hypothesis” suggested that both asthma and COPD should be considered as two different representations of the same disease (Orie, Sluiter, DeVries, Trammeling, & Wiktop, 1961). This is because both disorders share similar pathophysiological characteristics (e.g. chronic inflammation, airway obstruction, and airway remodeling) and genetic and environmental risk factors (e.g. atopic tendency, airway hyperresponsiveness, and tobacco smoke). However, the current consensus in pulmonary medicine weighs against this hypothesis, and both conditions are considered distinct disorders that have distinct clinical presentation, prognosis, and therapeutic management guidelines (Bleecker, 2004; Barnes, 2006; GINA, 2009; GOLD, 2010).

Although both asthma and COPD have underlying inflammation in the airways, the inflammatory mechanisms are distinct (GOLD, 2010). The inflammatory reaction in asthma involves CD4+ T-lymphocytes and eosinophils; while in COPD, CD8+ T-lymphocytes, macrophages, and neutrophils (Rang, Dale, Ritter, & Flower, 2007;

GOLD, 2010). This distinction is important regarding therapeutic effectiveness of anti-inflammatory medications, e.g. ICS, where ICS is more effective in mitigating asthma-type (eosinophilic) inflammation than COPD-type (neutrophilic) inflammation (Buist, 2003). The consequential airflow limitation is reversible in asthma, while it is not fully reversible in COPD (GOLD, 2010), a feature that shows episodic breathlessness in asthmatic patients and continuous breathlessness in COPD patients. The pulmonary pathological expressions that attribute to the reversibility of airflow limitation are different in both disorders. In asthma, bronchoconstriction is mainly due to inflammatory cytokines that mediate airway smooth muscle contractions; whereas in COPD the bronchoconstriction arises from structural remodeling of the airways and surrounding lung parenchyma (Barnes, 2000; Ichinose, 2009). However, underlying inflammation and airflow limitation in asthma can be similar to that of COPD when asthmatics are chronically exposed to noxious substances, including cigarette smoke (GOLD, 2010). Equally, patients with COPD can present inflammatory profiles similar to that in asthmatic patients (Chanez et al., 1997).

The most important risk factor for COPD is smoking. It is estimated that 15% of smokers have COPD, which corresponds to about 16 million Americans (Ryu & Scanlon, 2001); cigarette smoking accounts for 75% of COPD cases in the US (CDC, 2011b). Occupational exposure accounts for 15% of the cases; and other factors, including uncontrolled asthma contributes to additional 10% COPD cases (CDC, 2011b).

Controlling asthma plays a role in COPD prevention, where uncontrolled asthma advances to progressive airflow limitation and COPD-like clinical presentation (Lange,

Parner, Vestbo, Schnohr, & Jensen, 1998; CDC, 2011b). A longitudinal study showed that asthmatics had about 12 times higher risk to develop COPD than non-asthmatic counterparts after controlling for smoking status (HR 12.5, 95%CI 6.84-22.8) (Silva, Sherrill, Guerra, & Barbee, 2004).

Coexisting asthma and COPD. Due to inherent challenges in the differential diagnosis of asthma and COPD, both disorders can coexist. Since different therapeutic guidelines are available for both conditions, patients with coexisting asthma and COPD present additional challenges to healthcare teams in terms of suiting appropriate disease management strategies. Generally, patients with more than one obstructive respiratory disease e.g. asthma and COPD are older than 50 years of age (Guerra, 2005), and asthma comorbidity with COPD is associated with increased risks for morbidity and mortality (Guerra, 2005). A longitudinal study showed that 4.3% of Americans have physician-confirmed concurrent asthma and COPD (compared to 7.3% physician-confirmed asthma, and 11.1% physician-confirmed COPD) (Sherrill, Guerra, Bobadilla, & Barbee, 2003).

In the United Kingdom (UK), the annual prevalence of asthma defined by general practitioner (GP) consultations is about 9%; for COPD, it is about 11%. However, asthma accounts for 1.17% of respiratory disease-related mortality, compared to 23.4% cases due to COPD. The figures for coexisting asthma and COPD are not conclusive. Asthma accounts for about 10% of hospital admissions for respiratory diseases in the UK. COPD accounts for about 17% of hospital admissions. About 4% and 21% of all respiratory bed-days of inpatient stay are due to asthma and COPD, respectively (BTS, 2006).

In the United States (US), about 24 million adults have COPD and about 24 million adults and children have asthma. Asthma and COPD respectively account for 1.6% and 53.7% of respiratory-related mortality. Thirteen percent of respiratory hospital attendances are attributed to asthma, while 20% of respiratory hospitalizations are due to COPD. On average, length of hospital stays for asthma is 3.2 days, and for COPD is 4.4 days (respectively corresponding to 60% and 83% of total length of stay for all respiratory admissions). In the US, 30% and 46% of all GP respiratory visits were for asthma and COPD, respectively (NHLBI, 2009).

Morbidity, mortality, and healthcare utilization figures for coexisting asthma and COPD are not well established. Since such patients are usually excluded from clinical trials, pharmaceutical outcomes research in terms of medication effectiveness and safety in this population is desired.

Asthma as a risk factor for COPD. Asthma is an underestimated risk factor for COPD. In absence of comorbid conditions, asthma does not affect patient's life expectancy; however, untreated and undertreated asthma can progress to COPD and thereby diminishes patient survival (Lange, Parner, Vestbo, Schnohr, & Jensen, 1998; Silva, Sherrill, Guerra, & Barbee, 2004; CDC, 2011a). It is recommended to consider COPD as a possible prognosis in asthmatic patients with refractory response to treatment and deteriorated clinical presentation (Decramer & Selroos, 2005).

Epidemiology of Asthma

Despite the tangible progress in scientific and clinical research, the availability of novel pharmaceutical and biological interventions, and the development in medication delivery device technology, asthma became a common medical problem in the world

with growing prevalence, severity, and consequent individual, societal, and economic burdens (Long, 2011; CDC, 2011a).

Burden of Asthma

According to 2011 estimates of the World Health Organization (WHO), 235 million individuals in the world endured asthma (WHO, 2011). In the US, about 1 in 12 Americans (about 25 million; 8% of the US population) suffered from asthma in 2009, which corresponded to 3,447 deaths in 2007; about 12 million asthma attacks in 2008; and approximately $56 billion in medical expenses and lost work-days (CDC, 2011a). In the UK, about 1 in 12 Brits (about 5.4 million; 9% of the UK population) had asthma in 2010, with 1,204 deaths in 2008; over 79,794 hospital admissions in 2008-09; about 1.1 million lost work-days; and about $1.64 billion a year in medical costs. Approximately 864 thousand asthmatics received asthma medications in 2010 in Northern Ireland, Scotland, and Wales (Asthma UK, 2010). Asthma accounted for about 38% of allergic disorder general practice visits in the UK; and about 57% (37.8 million) of the prescriptions for allergic disorders dispensed in England's community pharmacies during 2001 were for asthma medications. During the same year, asthma accounted for 87% of all allergic condition hospitalizations in the UK (Gupta, Sheikh, Strachan, & Anderson, 2004). The prevalence of asthma in both countries is steadily increasing by about 1% annually (CDC, 2011a; Asthma UK, 2010).

In the UK, medications used for indications in the respiratory system accounted for 7.4% of all prescriptions in 2004, corresponding to £971 million. Inhaled bronchodilators accounted for the majority of respiratory drugs (49%), corresponding to £254 million; inhaled corticosteroids accounted for (26%), which tallied to £411 million. In 2004, 23.8

million GP consultations were for respiratory diseases, corresponding to about £501 million. About 13% of hospital admissions were for respiratory diseases (including lung cancer), which accounted for about £1496 million (BTS, 2006).

Although asthma is an incurable disease, appropriate disease management attributes to symptom control and acceptable quality of life. About 75% of asthma hospitalizations and 90% of asthma deaths in the UK are deemed preventable (Asthma UK, 2010).

Risk Factors

There are many characteristics associated with an increased likelihood of asthma occurrence, which include environmental factors as well as intrinsic factors that are inherent to the individual. Atopy is a form of allergy in which hypersensitivity reactions could be distant from the region of contact with the allergenic substance. Atopic conditions may include eczema, allergic dermatitis, hay fever, allergic rhinitis, allergic conjunctivitis, and asthma. Patient's atopic status is highly correlated with the development of persistent asthma; some studies showed that childhood atopy is associated with the development of adulthood asthma (Guilbert & Krawiec, 2003). Similarly, encountering asthma symptoms early in life is associated with higher risk of severe asthma development later in life (Guilbert & Krawiec, 2003). However, recent genetic studies showed limited correspondence between the genes that control immunoglobulin E (IgE) production and the genes that control asthma predisposition; such findings suggest that atopy could be a corollary of asthma rather than a triggering factor (Zhang, Moffatt, & Cookson, 2012). Family history of asthma is a well-recognized risk factor for having asthma. Individuals with moderate to high family history of asthma

are 2-4 times more likely to develop asthma than individuals with average familial risks (Liu, Valdez, Yoon, Crocker, Moonsinghe, & Khoury, 2009). Current research in disease genetics revealed the association of multiple genes with the development and progression of asthma (Zhang, Moffatt, & Cookson, 2012). These findings will bring future challenges in understanding the functions of these genes in relation to the pathogenesis and pharmacogenetics of asthma.

Regardless of individual's atopic status, obesity is associated with an increased risk of asthma development and worsening exacerbations in both children and adults (Visness et al., 2010; Fitzpatrick, Joks, & Silverberg, 2012). However, the exact biochemical and pathological mechanisms correlating both conditions remain not well understood, and research in this area is in demand (van Huisstede & Braunstahl, 2010; DHHS, 2011). Furthermore, studies investigating asthma treatment outcomes in obese asthmatics are encouraged in the field of outcomes research.

The incidence and severity of childhood asthma is more common in boys than in girls; however, the status reverses after puberty, where the condition becomes more common and severer in women than in men, particularly after the age of 20-40 years (Guilbert & Krawiec, 2003). These chronological differences in disease occurrence and severity between genders are attributed to pulmonary physiological changes and hormonal homeostasis (Guilbert & Krawiec, 2003).

Exposure to cigarette smoking—active or passive exposure—is a well-recognized risk factor for many respiratory disorders, e.g. lung cancer, COPD, and asthma. Cigarette smoke plays a role in both the development of asthma and the deterioration of existing asthma, which increases airway sensitization and hyperactivity (Guilbert &

Krawiec, 2003). Likewise, maternal exposure to cigarette smoke is associated with increased risk of asthma-like symptoms in newborns, and the development of childhood asthma (Guilbert & Krawiec, 2003). In addition to exposure to cigarette smoke, indoor and outdoor air pollution with aeroallergens, e.g. house dust mites, molds, cockroaches, noxious fumes, cold and humid temperatures, and some household pets are associated with increased likelihood of atopy and subsequent asthma (Guilbert & Krawiec, 2003). A study showed that asthmatic patients have high IgE levels in response to sensitization to specific allergens derived from species of house dust mites (*Dermatophagoides farina, Dermatophagoides pteronyssinus, and Blomia tropicalis*); however, the sensitization had no effect on asthma symptoms or disease control by asthma medications (Albano & Ramos, 2011).

Recurrent childhood viral infections that affect the lower respiratory tract, e.g. respiratory syncytial viral infections are more probable risks for the development of childhood asthma than infections that affect the upper respiratory tract (Guilbert & Krawiec, 2003). However, upper respiratory tract infections by human rhinoviruses are risk factors for worsening asthma symptoms in children (Miller et al., 2012).

The role of cholecalciferol (vitamin D) and its deficiency in the occurrence and progression of asthma was investigated in observational studies and clinical trials. A recent cross-sectional study showed that asthmatics with lower serum vitamin D levels are associated with increased airway smooth muscle mass (hypertrophy), which affects bronchodilator responsiveness (Gupta et al., 2011). The findings suggest a beneficial role for vitamin D in the progression of asthma; however, current consensus regarding the recommendation of vitamin D supplementation as a prophylaxis against or an

adjuvant therapy for asthma is postponed until the findings from ongoing clinical trials are published (Paul, Brehm, Alcorn, Holguin, Aujla, & Celedón, 2012).

Asthma Pharmacotherapy

The goal of asthma therapy is to maximize asthma control by effective, safe and cost-effective therapeutic interventions. Asthma control is achieved by eradication of daytime, nocturnal, and exercise-induced symptoms; prevention of exacerbations; and attaining and maintaining normal lung function (Shaw, Haldar, & Pavord, 2007). Pharmacologic approaches for the management of asthma involve two categories: reliever medications (bronchodilators) and controller medications (anti-inflammatory). Bronchodilators include beta-2-adrenoceptor agonists, muscarinic receptor antagonists, and methylxanthines. Anti-inflammatory agents include corticosteroids, leukotriene modifiers, mast cell stabilizers (cromolyn sodium and nedocromil), and monoclonal immunoglobulin E antibody (omalizumab). Some anti-inflammatory agents exert bronchodilator effects and vice versa, rendering this classification rather not mutually exclusive (Rang, Dale, Ritter, & Flower, 2007). Inhaled beta-2-adrenoceptor agonists and inhaled corticosteroids are considered the main bronchodilator and anti-inflammatory agents, respectively (GINA, 2009). Based on the pharmacokinetic properties of individual agents, inhaled beta-2-adrenocpetor agonist bronchodilators are subdivided into two categories: short-acting beta-agonists (SABA), e.g. salbutamol (albuterol) (effect lasts 3-5 hours); and long-acting beta-agonists (LABA), which include formoterol and salmeterol (effect lasts 8-12 hours). Inhaled corticosteroids (ICS) are further subdivided by their relative potency into standard (low) strength, and medium-high strength.

From therapeutic perspective, asthma medications can be classified as quick reliever medications (rescue therapy), and long-term controller medications (preventer therapy). Quick relievers are used to relieve the symptoms of acute asthma and involve short-acting beta-agonists and muscarinic receptor antagonists. Long-term controllers are used to control chronic asthma and involve inhaled corticosteroids, long-acting beta-agonists, leukotriene modifiers, methylxanthines, and mast cell stabilizers.

Targeting inflammation is the mainstay of asthma pharmacological treatment, and findings from effectiveness and safety research showed no significant differences between individual agents within controller classes (Jonas et al., 2011). Yet, compared to current asthma medications, ICS are considered the most effective therapeutic modality (Suissa, Ernst, & Kezouh, 2002; Jonas et al., 2011; Nair, 2011). However, some patients have refractory responses to standard and increased doses of ICS, and novel pharmacological interventions are under development which can be used in such patients (Colice, 2011).

Asthma Management Guidelines

Current therapeutic guidelines proposed by the Global Initiative for Asthma (GINA) (GINA, 2009), the British Thoracic Society (BTS) (BTS, 2009), and the US National Heart, Lung, and Blood Institute (NHLBI) (NHLBI, 2007) for the management of asthma in adults and children comprise of defined therapeutic steps. The GINA and BTS guidelines consist of five steps, while the US guideline encompasses six steps, where steps 3 and 4 are merged into the third step in the earlier guidelines (Table 1-1). These guidelines recommend individualization of asthma therapy based on patient profile, and are not intended as a substitute for clinical judgment at the practice level, where clinical

information in a particular case might require deviation from these guidelines. According to the BTS guidelines (BTS, 2009), mild intermittent asthma is treated with an inhaled SABA as a reliever therapy alone (step I). If no symptom control is achieved, the addition of an ICS as a preventer therapy is required (step II). If symptoms are still not controlled, the addition of an inhaled LABA to the earlier step is suggested (step III). If the disease still uncontrolled, either the potency of the ICS is increased with continuous LABA, or the potency of the ICS is increased with LABA discontinuation (step IV). The addition of another asthma medication (e.g. a leukotriene modifier or a methylxanthine) is considered in step IV as well. Likewise, other anti-inflammatory alternatives might be considered in steps II-IV. In severer cases, a supplement of the lowest effective dose of an oral corticosteroid is added to the previous step for continuous control (step V). Other agents should be considered at the last step to minimize patient's exposure to systemic corticosteroids.

Although most patients achieve asthma control in this stepwise approach, many are still uncontrolled (Holgate, Price, & Valovirta, 2006; Long, 2011). The anti-IgE omalizumab is considered as an add-on therapy in patients with severe persistent allergic asthma who are exposed to high-strength ICS and inhaled LABA (Step IV) (BTS, 2009; EMC, 2011).

Patients move up and down between the steps depending upon the severity of their disease state (GINA, 2009). Variable patient response could occur between steps, and alternative treatments might be selected within each step before stepping up therapy. Prescribers should consider the following factors prior to stepping-up treatment: patient education—including a personal asthma action plan; medication

adherence; inhaler technique; environmental control and triggers; comorbidities; asthma symptoms; functional limitations, including lost work/school days, limitations of daily activities, sleep disturbances, and poor quality of life; spirometry and peak expiratory flow rates; and utilization rates of inhaled rescue medications. Patients are stepped-down in their treatment protocol when asthma is well controlled for at least three months (NHLBI, 2007; GINA, 2009). The risks for exacerbations, and asthma-related hospitalizations and accident and emergency (A&E) department visits in the coming year can be assessed by evaluating these risks in the past year (NHLBI, 2007).

Inhaled Long-Acting Beta-2-Adrenoceptor Agonists

Beta-2-adrenoceptor agonist bronchodilators play a fundamental role in the acute and maintenance management of asthma. SABA inhalers are used as rescue bronchodilators to relieve intermittent episodes of bronchospasm and breathlessness. LABA inhalers on the other hand, are used as maintenance therapy in addition to ICS (Cazzola, Calzetta, & Matera, 2011). The introduction of LABA inhalers considered a major advance in bronchodilator therapy. Currently, there are two LABA agents approved for use in the US and the UK, formoterol and salmeterol. Both agents are available as single-ingredient inhalers and as single-device ICS combined inhalers. Table 1-2 lists LABA products that are approved for marketing by the US Food and Drug Administration (FDA), and the UK Medicines Healthcare Products Regulatory Agency (MHRA) (EMC, 2011; FDA, 2011a). Figures 1-1 and 1-2 respectively show the chemical structure of the approved LABA and ICS products.

In addition, new LABA products are development and others are under development which as ultra-LABA agents with longer half-lives, including carmoterol,

indacaterol, LAS100977, olodaterol, PF-610355, and vilanterol (Cazzola, Calzetta, & Matera, 2011). Among these agents, indacaterol (Onbrez Breezhaler, Novartis) was approved for marketing in the UK on November 30, 2009 as a treatment for COPD, but not for asthma (EMC, 2011). The product's new drug application is currently under review by the FDA (Novartis Briefing Document, 2011). On the other hand, vilanterol in combination with fluticasone (Relovair, GlaxoSmithKline) as a treatment for COPD and asthma is in the submission process in both the European Union (EU) and the US (Hill, 2012). Similarly, Boehringer Ingelheim, the developer of olodaterol is currently intending to seek FDA-approval as a bronchodilator treatment for COPD (Garde, 2012).

As the guidelines show, LABA inhalers are not indicated for the relief of acute exacerbations, rather they should be reserved as an adjunct therapy with ICS for the prevention of nocturnal and exercise-induced symptoms of chronic and persistent asthma. Inhaled LABA as a treatment modality was introduced in asthma management guidelines because studies showed that patients who are not well controlled on ICS monotherapy had a better response when LABA inhalers were added (Bateman et al., 2004; Greenstone et al., 2005; Masoli, Weatherall, Holt, & Beasley, 2005; Barnes, 2007).

Pharmacology of LABA Products

The human beta-adrenergic receptors (adrenoceptors) are comprised of 413 amino acids and physiologically divided into three types: β_1, β_2, and β_3 (Johnson, 1998). β_1 receptors are found in the heart; β_2 receptors are dispersed in the respiratory tract smooth muscles; and β_3 receptors are found in the adipose tissue (Johnson, 1998). Stimulation of β_1 receptors increases cardiac output and oxygen consumption, which is

antagonized by beta-blockers and used as antihypertensive and antiarrhythmic medications; β_2 agonists are used as bronchodilators in obstructive pulmonary conditions, e.g. asthma; and β_3 agonists increase lipolysis and used as anti-obesity agents (de Souza & Burkey, 2001).

Inhaled LABA agents are administered to the bronchial epithelium and smooth muscles through oral inhalation. These agents are found to have higher β_2 receptor affinity than inhaled SABA bronchodilators, which translates into higher binding capacity to the receptor (Johnson, 1998). Inhaled SABA molecules are hydrophilic, which exert bronchodilation at the extracellular level with a rapid onset (5-15 minutes) and short duration of action (3-6 hours) (Op't Holt, 2007). On the other hand, inhaled LABA molecules are lipophilic, which diffuse into the cell with relatively slower onset (15-20 minutes) and longer duration of action (8-12 hours) (Op't Holt, 2007). The duration of airway dilation for β_2 adrenoceptor agonists is in the following order: formoterol > salmeterol > albuterol > terbutaline (Johnson, 1998; Op't Holt, 2007). Undoubtedly, the bioavailability and subsequent effectiveness of inhaled bronchodilators—and anti-inflammatory agents—are contingent upon the type of inhalation device used in drug delivery (Virchow et al., 2008) and proper inhaler technique (Ovchinikova, Smith, & Bosnic-Anticevich, 2011).

When locally administered into the bronchi via oral inhalation, formoterol is deposited on bronchial epithelium and stored in the plasma membrane of bronchial smooth muscle cells, and slowly released to the extracellular compartment to interact with β_2 receptors to exert bronchodilation; the plasma membrane storage size is proportional to the drug dose that is deposited on bronchial epithelium; therefore, the

duration of bronchodilation for formoterol is dose-dependent (Johnson, 1998). Salmeterol on the other hand, has a side chain (Figure 1-1) that interacts with the hydrophobic site of the β_2 receptor within the plasma membrane of bronchial smooth muscle cells. This anchoring mechanism prevents salmeterol molecule from detachment from the receptor while the active side of the molecule remains freely interacting with the active receptor site located on the outer layer of the cell membrane, which continually attaches and detaches from the active site with a prolonged duration of action (Johnson, 1998; Op't Holt, 2007).

LABA Safety Controversy

In March 2, 2006, the FDA issued a Black Box Warning regarding all LABA products warning patients and healthcare professionals about an increased risk of asthma-related death in patients exposed to LABA products (FDA, 2010a). In February 18, 2010, this action was subsequently followed by the agency's requirement of issuing a Medication Guide to all patients who are using any LABA product (FDA, 2010b). The FDA's decision of requiring a Risk Evaluation and Mitigation Strategy (REMS) and class-labeling changes to all LABA products is largely based on the results of two clinical studies: The Serevent Nationwide Surveillance Study (SNS) (Castle, Fuller, Hall, & Palmer, 1993) and The Salmeterol Multicenter Asthma Research Trial (SMART) (Nelson et al., 2006).

The 2007 NHLBI asthma management guidelines recommend— and in tandem with the FDA's 2006 black box warning—the addition of LABA to a low dose ICS rather than increasing the dose of ICS at step III of the stepwise therapeutic approach (NHLBI, 2007). Although therapeutic guidelines and the FDA recommend ICS/LABA combination

therapy, there is no evidence that ICS protect the patient against LABA-induced worsened asthma outcomes. Consequently, the FDA in the second quarter of 2011 required the manufacturers of LABA products to conduct five long-term, large-scale randomized, double-blind, controlled clinical trials to further investigate the safety of ICS/LABA combination therapy in comparison with ICS monotherapy, with expected findings to be published in 2017 (FDA, 2011b). Additionally, LABA products became the priority of drug safety research by the European Medicines Agency (EMA) (EMA, 2010). The controversy about the safety of regular use of inhaled LABA in asthmatic patients is significant and the answer for it is eagerly needed.

LABA safety in experimental studies context

Drug efficacy is the ability of a drug to produce the expected therapeutic effect under standardized or experimental conditions (ideal effect), e.g. clinical trials. The LABA safety issue is closely related to its efficacy (or effectiveness in observational context), and can be examined as the reciprocal of its efficacy or effectiveness. The SNS is a randomized, controlled clinical trial (RCT) of 25,180 asthmatic patients who received either salmeterol (50 mcg twice daily) or albuterol (200 mcg four times daily) and followed for 16 weeks. The study was conducted in the UK by salmeterol manufacturer in the request of the MHRA to assess the safety of LABA in asthmatic patients. The majority of the patients were adults (about 6% were under 18 years old). The study showed a statistically non-significant increase in the risk of asthma-related mortality in salmeterol group (RR=3.00; p value=0.105) with no association with asthma-related hospitalization (Castle, Fuller, Hall, & Palmer, 1993). The increased mortality was attributed to baseline disease severity, rather than salmeterol (Castle,

Fuller, Hall, & Palmer, 1993; Op't Holt, 2007). When the SNS study was inconclusive, the FDA requested salmeterol manufacturer to conduct another study to further assess the safety matter. The SMART was incepted in 6,163 sites in the US as a RCT which enrolled 26,355 asthmatic patients who were randomly assigned to inhaled salmeterol (42 mcg twice daily) or identical placebo and followed for 28 weeks. About 12% of the patients were children (12-18 years old). The study was early terminated by the FDA for increased life-threatening events, including asthma-related mortality rates in salmeterol group (RR=4.37; 95%CI=1.24-15.3) (Nelson et al., 2006).

Although both studies aimed at assessing the safety of LABA monotherapy, the participants in both studies were on ICS at baseline (69% in SNS; 47% in SMART). We cannot conclude from either study if the addition of ICS to salmeterol has a positive or negative effect on asthma outcomes. Nevertheless, the FDA included in the Black Box Warning a recommendation to use LABA in combination with ICS and to discontinue LABA upon achieving asthma control (Product Label: www.serevent.com); however, discontinuing LABA after accomplishing control with ICS/LABA combination therapy could result in a failure in asthma control and rebound symptom manifestations (Sears, 2011). Despite the inconclusive results of the SNS and the SMART studies, the FDA, at that time might be concerned with the over utilization of LABA products in the population, and interested in reducing exposure to LABA. The utilization of inhaled LABA products is not consistent with the proposed guidelines. Although the guidelines recommend using ICS as the preferred therapy, most of the patients are started on LABA. In the US, about 62% of asthmatic patients who received combined ICS/LABA products didn't meet guidelines criteria to prescribe LABA products (Ye, Gutierrez,

Zarotsky, Nelson, & Blanchette, 2009). Similarly, combination therapy is used more than indicated by the guidelines in other countries (Bisgaard & Szefler, 2006).

After the SMART study, the FDA and individual investigators presented meta-analyses of large RCTs to evaluate the safety of LABA inhalers with and without concomitant ICS in asthmatic patients. The findings revealed an increased risk for asthma-related mortality and morbidity in LABA groups regardless of concomitant use of ICS (Salpeter, S, Buckley, Ormiston, & Salpeter, E., 2006; Levenson, 2008; Salpeter, Wall, & Buckley, 2010). However, two additional meta-analyses contended against FDA's regulatory decision. The analyses showed that LABA inhalers didn't increase the risk of asthma-related mortality and morbidity, whether alone or in combination with ICS (Jaeschke et al., 2008; Nelson et al., 2010). A meta-analysis of Novartis-sponsored clinical trials in 2,452 asthmatic adults (>18 years) compared formoterol with placebo showed no significant increase in the risk of serious asthma exacerbations in formoterol users (OR=1.3; 95%CI=0.4-3.7); however, about 71% of the patients were on concomitant ICS use at baseline (Kemp, Armstrong, Wan, Alagappan, Ohlssen, & Pascoe, 2011). Another meta-analysis of randomized trials showed that ICS/LABA combination therapy is significantly protective against asthma exacerbations when compared with ICS monotherapy that has similar dose of the ICS in the combination group (RR=0.80; 95%CI=0.73-0.89). However, the statistical significance disappeared when ICS dose in the monotherapy group was higher than the counterpart in the combination group (RR=0.88; 95%CI=0.76-1.01) (Gibson, Powell, & Ducharme, 2007), suggesting a plateau phenomenon in dose-response relationship between ICS and asthma outcomes, where benefits from dose increment reaches a plateau on the

expense of an increase in adverse reactions (Figure 1-3). In addition, one meta-analysis showed statistically not significant differences between fluticasone/salmeterol and budesonide/formoterol single-device combination inhalers in terms of serious asthma-related morbidity (Lasserson, Ferrara, & Casali, 2011).

These studies are limited in their generalizability, uncertainty of the pooled estimates when the number of events is small, and the application of weighted fixed-effects models, which overlooked the fact that individual trials are heterogeneous and the assigned weights are random entities (Shuster, Jones, & Salmon, 2007; Shuster, 2010).

LABA safety in observational studies context

Drug effectiveness is the ability of a drug to demonstrate the therapeutic effect under real conditions of prescription and use (pragmatic effect). Randomized clinical trials are considered the gold-standard for the assessment of treatment effects. Randomization ensures equal distribution of measured and unmeasured confounders across exposure groups, and when masking and placebo-control are properly applied, bias from selection and measurement errors can be eliminated. However, these designs aim at testing drug efficacy in experimental conditions that do not reflect the variable conditions of clinical practice, prescribing behavior, and patient adherence. Therefore, findings from such studies are less generalizable, and detection of rare and serious adverse outcomes is limited. On the other hand, findings from observational designs are more generalizable to clinical practice and target patient population, albeit lack of randomization predisposes these studies to different types of biases (Laupacis & Mamdani, 2004). However, properly designed observational studies complement the

findings from randomized trials, and many such studies have been conducted to evaluate the effectiveness and safety of inhaled LABA products in large population of asthmatic patients.

Observational studies in the form of retrospective database analyses are reported with conflicting findings regarding LABA safety. An earlier study did not show an increased risk among asthmatic patients exposed to salmeterol in comparison with theophylline (OR=0.90; 95%CI=0.13-5.0) and ipratropium (OR=0.12; 95%CI=0.02-0.71) (Meier & Jick, 1997); however, another study showed an association between salmeterol and asthma-related morbidity (emergency department and hospital attendance), albeit statistically not significant compared to theophylline (Lanes, Lanza, & Wentworth, 1998). In a case-control study, salmeterol was significantly associated with near-fatal asthma events, the analysis however was not adjusted for asthma severity (OR=2.32; 95%CI=1.05-5.16) (Williams et al., 1998). Nevertheless, the significance was removed after subgroup analyses are conducted within patient groups who were prescribed oral corticosteroids at the near-fatal event date (OR=2.29; 95%CI=0.39-13.53) and those who were hospitalized for asthma during the 12 months prior to the near-fatal event (OR=1.42; 95%CI=0.49-4.10) (Williams et al., 1998). A case-control analysis of the GPRD data showed that chronic LABA users are found to be 3.2 times more likely to die from asthmatic attacks than nonusers (RR=3.2; 95%CI=0.7-14.1); chronic users is defined by receiving more than eight LABA prescriptions during the 12 months prior to the occurrence of asthma-related death (Lanes, Garcia-Rodríguez, & Huerta, 2002). Conversely, patients exposed to salmeterol within 12 months prior to experiencing asthma-related death are found in another case-

control study to be less likely to experience death than unexposed counterparts (OR=0.95; 95%CI=0.70-1.29) (Anderson et al., 2005).

Inhaled LABA monotherapy and ICS/LABA combination therapy were compared with inhaled SABA therapy in asthmatic patients. The study found a reduced risk of emergency department visits, and an increased risk of asthma-related hospitalizations and intubations for LABA and ICS/LABA (Guo, Tsai, Kelton, Bian, & Wigle, 2011). Similar to a meta-analysis (Lasserson, Ferrara, & Casali, 2011), a cohort study showed that budesonide/formoterol is less likely to be associated with asthma-related morbidity than fluticasone/salmeterol, yet statistically not significant (Blais, Beauchesne, & Forget, 2009).

In another study, asthmatic patients in the GPRD who were initiators of ICS are followed until the addition of LABA or continuation of ICS (Thomas, von Ziegenweidt, Lee, & Price, 2009). The findings were conflicting in terms of asthma-morbidity outcomes. Compared to ICS users, patients exposed to ICS/LABA are found to have lower hazards of rescue SABA utilization; yet, have higher hazards of oral corticosteroid use and asthma-related hospitalizations (Thomas, von Ziegenweidt, Lee, & Price, 2009). Another GPRD study compared LABA monotherapy users with inhaled SABA users, and found the earlier group is more likely to die of asthmatic attack than the latter (RR=2.5; 95%CI=1.6-3.8); likewise, for hospitalization rates (RR=4.9; 95%CI=3.1-7.8), and GP visits for exacerbations (RR=3.2; 95%CI=3.1-3.4) (de Vries, Setakis, Zhang, & van Staa, 2010). Similar analyses conducted to compare ICS/LABA combination therapy with inhaled SABA, which showed an increased risk of asthma-related death (RR=2.7; 95%CI=1.9-3.9) and asthma-related hospitalization rates (RR=3.4;

95%CI=2.3-5.0) with high-dose ICS/LABA combination, and reduced risk of asthma-death (RR=0.9; 95%CI=0.4-2.1) with standard-dose ICS/LABA combination (de Vries, Setakis, Zhang, & van Staa, 2010). Another study adjusted for ICS dose showed ICS/LABA combination therapy more beneficial in terms of reduced asthma exacerbations than ICS monotherapy (HR=0.65; 95%CI=0.47-0.90) (Wells, Peterson, Ahmedani, Severson, Gleason-Comstock, & Williams, 2012).

These findings reflect the presence of residual confounding by time-dependent confounders, especially confounding by disease severity. Despite identifying relevant surrogate variables for asthma severity, these studies failed to account for the time-dependent nature of these variables, which predict study outcome (asthma mortality and morbidity), determine future exposure (bronchodilator and anti-inflammatory type), and affected by previous exposure.

Heterogeneity of Response to LABA

The findings from experimental and observational research suggest a bimodal response to LABA inhalers in asthmatic patients, a beneficial response by patients who are not well controlled on ICS alone; and a deleterious response by some patients regardless of concomitant use of ICS. Although the association of LABA with serious asthma outcomes seems paradoxical to pharmacodynamic characteristics of such agents that are full agonist at the beta 2 receptors, the following hypothetical mechanisms are proposed: LABA bronchodilators have a steroid-sparing effect, which masks the underlying inflammatory process of asthma (McIvor, Pizzichini, Turner, Hussack, Hargreave, & Sears, 1998); LABA bronchodilators improve asthma symptoms, which give mistaken sense of disease control and potential cease of anti-

inflammatory medications that treat the disease itself (Op't Holt, 2007); chronic LABA exposure reduces the number of cell surface receptors due to receptor cell internalization (receptor desensitization) and shrinks the net number of cellular receptors (receptor down-regulation) to prevent receptor overstimulation with beta-agonists (Simons, Gerstner, & Cheang, 1997; Tan, Grove, McLean, Gnosspelius, Hall, & Lipworth, 1997; Johnson, 1998; Op't Holt, 2007); increased bronchial hyperactivity in response to regular beta-agonists exposure (Op't Holt, 2007); and genotypic variation in beta 2 receptors (Palmer, Lipworth, Lee, Ismail, Macgregor, & Mukhopadhyay, 2006). The response of LABA monotherapy is found to be variable across different beta 2 receptor polymorphisms (Bleecker et al., 2010); however, pharmacogenetic studies showed that the addition of an ICS to a LABA is associated with improved asthma outcomes regardless of genotypic differences in the beta 2 receptors (Wechsler et al., 2009; Bleecker et al., 2006). On the other hand, individuals identified as non-White are more at risk of exacerbations than Whites (NHLBI, 2007), and worsened asthma outcomes are observed in African Americans exposed to inhaled LABA (Nelson et al., 2006) who often have Arginine/Arginine genotype polymorphism for the beta-2 receptor gene and suboptimal asthma control on ICS monotherapy, even though maximal doses are used (Glassroth, 2006).

Table 1-1. Comparison of the stepwise approach for the treatment of asthma in adults (>12 years old) across different asthma management guidelines

Asthma type	Step	Asthma management guidelines*		
		GINA, 2009	BTS, 2009	NHLBI, 2007
Intermittent	I	SABA	SABA	SABA
Persistent asthma	II	SABA + L ICS SABA + LTM	SABA + L ICS	SABA + L ICS SABA + LTM SABA + MCS SABA + Xanthine
	III	SABA + L ICS + LABA SABA + M ICS SABA + H ICS SABA + L ICS + LTM SABA + L ICS + Xanthine	SABA + L ICS + LABA SABA + M ICS + LABA SABA + M ICS SABA + M ICS + LTM SABA + M ICS + Xanthines	SABA + L ICS + LABA SABA + M ICS SABA + L ICS + LTM SABA + L ICS + Xanthine
	IV	SABA + M ICS + LABA SABA + H ICS + LABA SABA + M ICS + LTM SABA + H ICS + LTM SABA + M ICS + Xanthine SABA + H ICS + Xanthine	SABA + H ICS + LABA SABA + H ICS + LABA + LTM SABA + H ICS SABA + H ICS + LABA + Xanthine SABA + H ICS + LABA SABA + H ICS + LABA + Anti-IgE	SABA + M ICS + LABA SABA + M ICS + LTM SABA + M ICS + Xanthine
	V	SABA + M ICS + LABA + Oral CS§ SABA + H ICS + LABA + Oral CS§ SABA + M ICS + LABA + Anti-IgE SABA + H ICS + LABA + Anti-IgE	SABA + H ICS + LABA + Oral CS§	SABA + H ICS + LABA + Anti-IgE
	VI	n/a	n/a	SABA + H ICS + LABA + Anti-IgE + Oral CS§

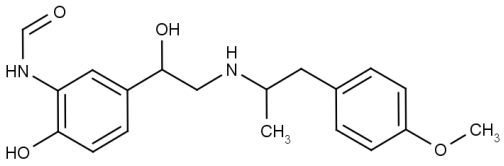
GINA, Global initiative for asthma
BTS, British thoracic society
NHLBI, National heart, lung, and blood institute

SABA; Short-acting beta-agonist
ICS, Inhaled corticosteroids
LABA, Long-acting beta-agonist
LTM, Leukotriene modifiers
MCS, Mast cell stabilizers
Anti-IgE, Anti-immunoglobulin E (e.g. omalizumab)
CS, Corticosteroids
L, Low-strength
M, Medium-strength
H, High-strength
n/a, Not applicable
* Step up treatment after considering patient education, including personal action plan; adherence; inhaler technique; environmental control and triggers; comorbidities; symptoms; spirometry and peak expiratory flow rates; and utilization rate of SABA rescue drugs. Step down treatment after checking if asthma is well controlled during the past 3 months. Consider patient referral to asthma specialist when reaching step 3
§ Lowest effective dose of oral corticosteroids that produce control. Other treatments should be considered at the last steps to minimize the exposure to systemic corticosteroids.

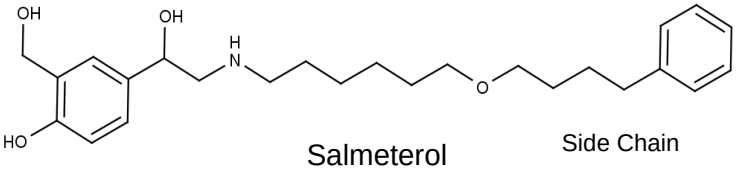
Table 1-2. Availability of long-acting beta-agonist products in the US and the UK as of June 2011

Product*	Ingredient	Marketing authorization date	
		FDA	MHRA
Foradil	Formoterol	February 16, 2001	September 12, 1997
Serevent	Salmeterol	February 4, 1994	October 14, 1996
Symbicort	Budesonide/Formoterol	July 21, 2006	May 15, 2001
Dulera	Mometasone/Formoterol	June 22, 2010	NA
Advair HFA	Fluticasone/Salmeterol	June 8, 2006	NA
Advair Diskus	Fluticasone/Salmeterol	August 24, 2000	NA
Seretide	Fluticasone/Salmeterol	NA	February 1, 1999

* Product brand names are the property of their respective manufacturers
Other generic products are not listed
NA, Not available in the respective country

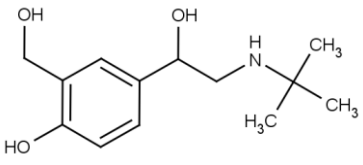


Formoterol

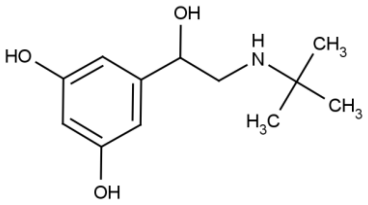


Salmeterol Side Chain

A)



Albuterol (Salbutamol)



Terbutaline

B)

Figure 1-1. Chemical structure of inhaled beta agonist bronchodilators commonly prescribed for asthma in the UK. A) Long-acting. B) Short-acting. (Source: http://www.drugbank.ca/drugs. Last accessed July 23, 2012).

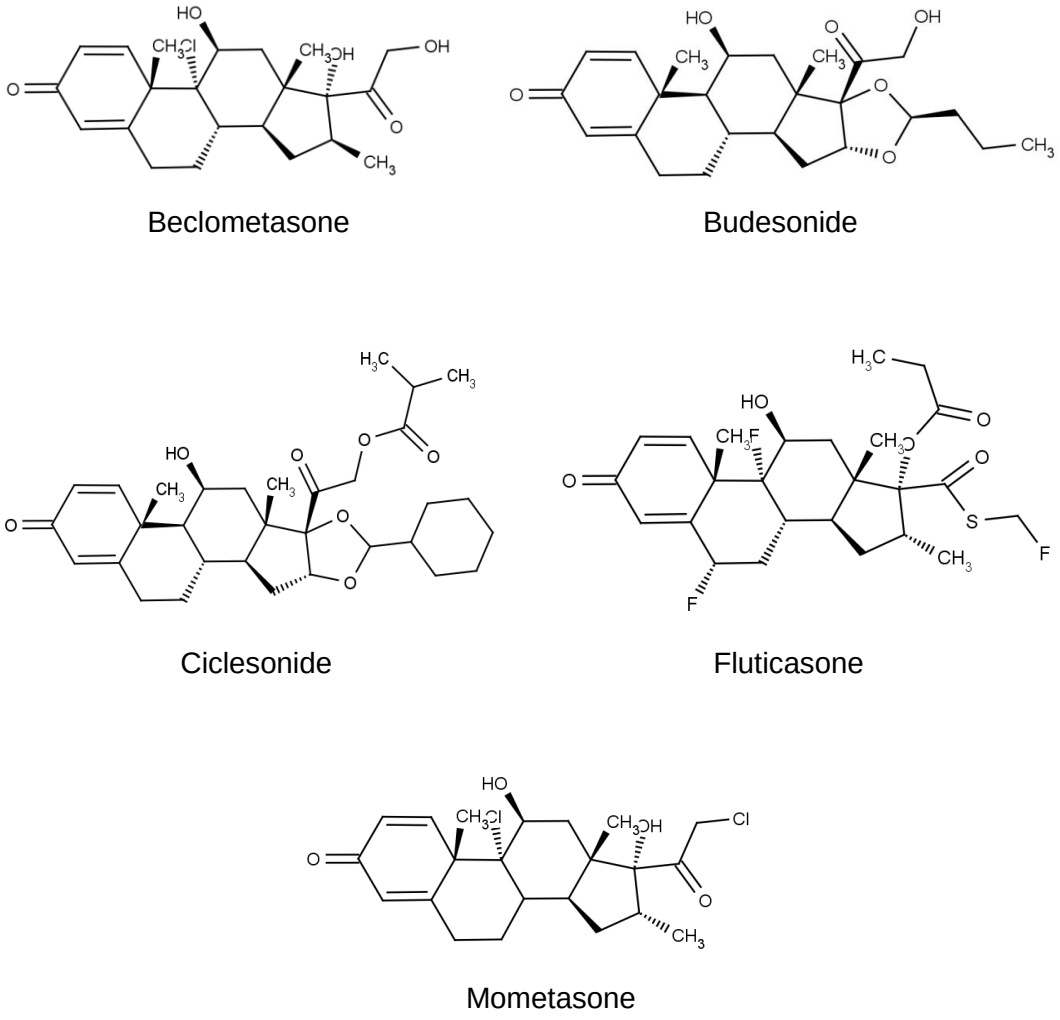


Figure 1-2. Chemical structure of inhaled corticosteroids commonly prescribed for asthma in the UK. (Source: http://www.drugbank.ca/drugs. Last accessed July 23, 2012).

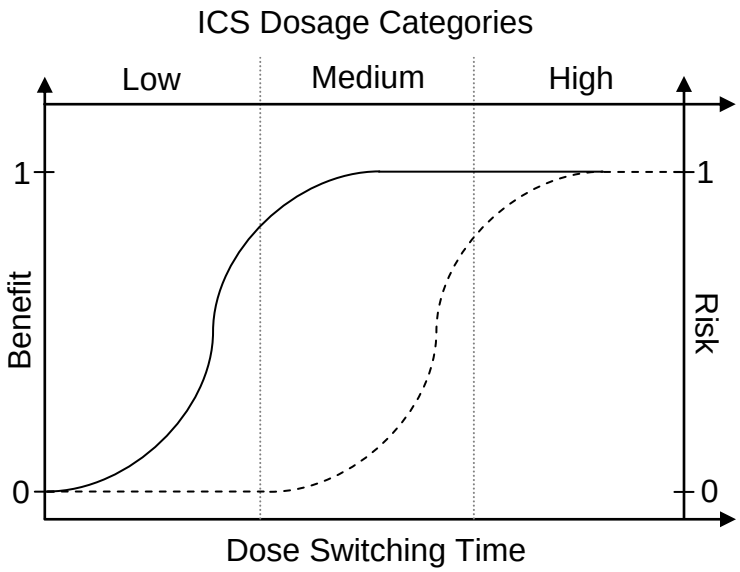


Figure 1-3. Illustration of the relationship between inhaled corticosteroid dosage and benefit/risk balance

CHAPTER 2
PHARMACOEPIDEMIOLOGICAL PERSPECTIVE

Methodological Challenges in Observational Research

In observational pharmacoepidemiology, exposure to drugs is not at random and probabilities of exposures are not the same across different populations; certain people with covariate structures have higher tendencies to be exposed to a specific treatment than others. The non-experimental nature of observational designs presents challenges in accurately and reliably estimating the association between exposures and outcomes. Three sources of bias can distort this association in observational designs: confounding, selection bias, and measurement bias (Rothman, Greenland, & Lash, 2008).

Confounding

In clinical practice, medications are not prescribed (and therefore, not utilized) at random; prescribing by physicians take into considerations multiple factors, such as patient, disease diagnostic, and disease prognostic characteristics. Such factors play the role of exposure determinants, which lead to the two most common types of confounding in pharmacoepidemiology: confounding by indication, and time-dependent confounding (Schneeweiss, 2008). Furthermore, failure to account for all confounding characteristics in an observational study leads to residual confounding, which is the third common type of confounding in observational pharmacoepidemiology (Glymour & Greenland, 2008).

Confounding is Latin in origin (*confudere*), which means "*to mix together*". Epidemiological confounding is defined as the distortion of exposure-outcome relationship by some other variable, i.e. confounder (Schneeweiss, 2008). The distortion can lead to overestimation, underestimation, or reversal of exposure effect

(Schneeweiss, 2008). A confounder Z_t is associated with the exposure E_t and the outcome O , accounts for some or all of the observed exposure effect, and not in the exposure-outcome causal pathway (Figure 2-1, A). Here, association means that the risk of the outcome is different among people with the confounder compared to those without $HR_{(Zt-O)} \neq 1$, and the distribution of the confounder is different among people with exposure compared to those without (or those with other comparator exposure category), i.e. the distribution of the confounder is unbalanced between exposure groups $HR_{(Zt-Et)} \neq 1$.

Confounding by indication

Confounding by indication is defined as a distortion in the association between the drug and the outcome, which occurs when a drug (or a class of drugs) is preferentially prescribed to patients with specific baseline characteristics, such as those with worse disease state at baseline (confounding by disease severity), or those with preexisting comorbidity at baseline (channeling bias) (Bégaud, 2000). In case of confounding by disease severity, the observed exposure effect could be mixed with an effect of severer disease state (Hudson & Suissa, 2010). Both types of confounding by indication are common in chronic disease pharmacoepidemiology (Psaty & Siscovick, 2010); however, confounding by disease severity may be the most important type in respiratory disease studies, including asthma; where inhaled medications are preferentially prescribed to patients with variable baseline disease severity states.

Time-dependent confounding

Time-dependent confounding is defined as an alteration in the association between the exposure $E_{t-1} \sim E_{t+1}$ and the outcome O as a result of a variable $Z_{t-1} \sim Z_{t+1}$ that may vary over time and concurrently acts as a confounder and an intermediary (Figure 2-1, B) (Kattan & Cowen, 2009). In pharmacoepidemiology, drug effects are time-dependent, and are affected by time-dependent confounders that themselves are affected by previous drug exposure, and affect subsequent drug exposure and outcome. This phenomenon is common in usual-care “real-world” settings, including pulmonary medicine, and conclusions drawn from studies that fail to account for time-dependent confounding could be misleading.

Residual confounding

Databases may contain an array of variables; however, even the most complete and detailed database fails to include all potentially important confounding variables. The presence of confounding despite adjustment is referred to as residual confounding. Failure to account for all confounding variables can rise from unmeasured variables (Glymour & Greenland, 2008), or measurement errors in the variables (Stram, Huberman, & Wu, 2002). Further, grouping a confounder that is on the continuous scale of measurement, e.g. age into few categories may result in inadequate confounding control in the observed exposure-outcome relationship (Brenner & Blettner, 1997). Unmeasured confounders are either measurable but unmeasured in the main study or immeasurable (unknown or difficult to measure) (Schneeweiss, 2008).

Examples of variables that are frequently unavailable (unmeasured) in databases that are used for pharmacoepidemiologic research include: behavioral information

(smoking, alcohol drinking, nutrition and eating habits, exercise, substance abuse, and therapy adherence measures); laboratory information (blood tests, lung function tests, and other functionality tests); and exposure information (over-the-counter products, nutraceuticals and herbal remedies, and immunization history).

In randomized, controlled clinical trials, randomization equally (or near equally) balances confounders across exposure groups. Pharmacoepidemiologists aim at evaluating the causality of associations between drugs and outcomes; lack of randomization in observational studies casts additional challenges in evaluating causal associations. Moreover, depending on the therapeutic effectiveness of a medication in an individual patient, subsequent medication use may change; patients who tolerate the unintended side-effects or experience the intended therapeutic effects of a medication are more likely to continue using it in the future compared to those who experience side-effects or those who do not perceive the beneficial effects of a medication.

Confounding is one of the most important sources of bias in observational studies, and any observed association in such studies is confounded to some degree (Jepsen, Johnson, Gillman, & Sørensen, 2004). However, well designed and well conducted rigorous observational studies have increasingly important clinical, regulatory, and public health impacts.

Effect Modification

Observing exposure effect in a subset of patients defined by particular characteristics is effect modification. In another word, the average causal effect of the exposure on the outcome is different across levels of the effect modifying factor. Unlike confounding, effect modification is not a source of bias; rather it may be of public health

importance, e.g. identifying exposure groups at risk. Both confounding and effect modification can exist together ($HR_{overall}$ incorrectly estimates average causal effect—confounded, $HR_{Z0} \neq HR_{Z1}$), or separately ($HR_{overall}$ correctly estimate average causal effect—not confounded, $HR_{Z0} \neq HR_{Z1}$; $HR_{overall}$ confounded, $HR_{Z0} = HR_{Z1}$). Stratified analysis is used to elucidate the association between exposure and outcome across levels of the factor. E.g. the association between obesity and asthma prevalence is different between men and women (Loerbroks, Apfelbacher, Amelang, & Strümer, 2008). In some epidemiology references, the term "*effect-measure modification*" is used to signify the point that identifying the presence of effect modification is contingent upon the type of effect measure used—additive vs. multiplicative (Greenland, Rothman, & Lash, 2008). An effect modifier may change the direction or the magnitude of exposure effect. When the direction of exposure effect is the same in all subsets of the modifier but the magnitude is strengthened or weakened between subsets, quantitative effect modification occurs. When the average causal effects are in opposite directions in subsets of the effect modifier (i.e. the exposure and the outcome are associated in the presence of the effect modifier but not associated in the absence of the effect modifier, and vice versa), qualitative effect modification occurs. In case of qualitative effect modification, both additive and multiplicative effect modifications are present (Thompson, 1991). In the absence of qualitative effect modification, effect modification may be present in one scale of measurement than the other (Greenland, Rothman, & Lash, 2008). Therefore, the concept of effect modification in pharmacoepidemiology should always be examined in light of the chosen scale of effect measure, e.g. risk ratio (multiplicative), risk difference (additive).

Additive effect-measure modification:

$$\Pr[(O=1 \mid E=1) \mid Z=1] - \Pr[(O=1 \mid E=0) \mid Z=1] \neq \Pr[(O=1 \mid E=1) \mid Z=0] - \Pr[(O=1 \mid E=0) \mid Z=0]$$

Multiplicative effect-measure modification:

$$\frac{\Pr[(O=1 \mid E=1) \mid Z=1]}{\Pr[(O=1 \mid E=0) \mid Z=1]} \neq \frac{\Pr[(O=1 \mid E=1) \mid Z=0]}{\Pr[(O=1 \mid E=0) \mid Z=0]}$$

Selection Bias

Selection bias is a distortion in the association between exposure and outcome that arises from systematic errors in the way study sample was selected. This type of bias can arise in both randomized and observational studies. In randomized studies, randomization prevents confounding and selection bias when patient selection takes place after randomization to exposure arms; intention to treat (ITT) and last observation carried forward (LOCF) analyses are valid in this situation. However, selection bias may be imposed when patient selection occurs after assigning exposures (post randomization process). In cohort studies, the outcome of interest can be over- or under-represented in the preferentially selected sample of patients who have higher or lower likelihood of presenting the outcome (Bégaud, 2000); therefore, the sample will be unrepresentative of the target population to which study results are extrapolated (Figure 2-2).

There are many forms of selection bias, including: informative censoring; missing data bias; survivor bias (depletion of susceptibles); admission (referral) bias; diagnostic bias; incidence-prevalence bias; volunteer (self-selection) bias; and healthy-user

effect—the latter is considered a type of confounding more than of selection bias– (Hernán, Hernández-Díaz, & Robins, 2004). In retrospective database analyses, informative censoring and depletion of susceptibles are probably the most important types of selection bias.

Informative censoring

In the context of survival analysis, censoring refers to the termination of observations when they are not followed long enough to observe the outcome of interest (Bégaud, 2000); the conditions for such termination are usually defined by study investigator. When censoring occurs due to reasons that are not under the control of the investigator, random censoring is said to happen (Allison, 2010). Within this framework, informative censoring is likely to occur (Allison, 2010) (Figure 2-3). If the censored individuals are biased subsample of the uncensored individuals who have similar covariate distribution (i.e. censored individuals have systematically higher or lower risks of observing the outcome than the uncensored counterparts), the censoring mechanism could be due to the exposure or the outcome, i.e. informative. Informative censoring can lead to biased estimates of the association between the exposure and the outcome, which is likely in longitudinal studies with time-dependent confounding (van der Laan & Robins, 2003).

Selection bias due to random censoring can be prevented by including the variables that affect censoring and event times in the multivariate regression model, e.g. study starting time (index date) in case of random study entry and termination times (Allison, 2010). Calculating the inverse probability of censoring weighted (IPCW) estimator as part of the marginal structural models technique can account for

informative censoring; however, the procedure is inefficient when censoring is due to competing outcomes (van Wonderen et al., 2009) that compete with the study's outcome of interest to remove susceptible patients from the risk-set pool (Rothman & Greenland, 2008). If the rate of competing outcome is higher in the exposed, the HR will be overestimated. Sensitivity analyses on the other hand can be employed to see how sensitive the estimates are to informative censoring (Allison, 2010). For example, the investigator may assume that censored individuals are at high risk of observing the outcome (outcome occurs immediately after censoring), or the reverse (censored individuals have longer time-to-event than any other individual in the sample). When association estimates from sensitivity analyses bracket the estimates from original analysis (i.e. act as a confidence limits), conclusions are not affected by treating censoring reason (e.g. other death, COPD) as non-informative.

In the GPRD, patient transfer out of the general practice or disenrollment from the healthcare insurance plan are unlikely related to the exposure or the outcome; this is because healthcare is universal in the UK and such transfer or disenrollment could be due to patient migration outside the country as an example. However, drugs administered in hospitals are not recorded in the unlinked-GPRD, and if admission to hospital and death are among the censoring conditions set by the investigator, selection bias can occur if the outcome of interest is time to hospitalization. This is because censored patients are usually sicker than uncensored patients. The risk of asthma hospitalization is associated with the risk of asthma death (Omachi, 2009), and in a study assessing the effect of ICS on asthma hospitalization in comparison to LABA, if ICS is effective in delaying or preventing asthma mortality, ICS will be associated with

increased risk for asthma hospitalization compared to LABA when asthma death is used as a censorship criterion. This is because ICS patients will survive longer than the LABA patients and be hospitalized.

Depletion of susceptibles

There are many terms for this type of selection bias, including “survivor bias” (Glymour & Greenland, 2008), “crossing of hazards” (Hernán, 2010), and “survivor cohort effect” (Arrighi & Hertz-Picciotto, 1994). Depletion of susceptibles is the most commonly used term in pharmacoepidemiology. Depletion of susceptibles is defined as the gradual exclusion of a subgroup of patients who are susceptible to the outcome of interest from one exposure group, which leads to subsequent selection of another subgroup of patients who are less susceptible to the outcome from another exposure group (provided that exposure groups are comparable with regard to other factors other than exposure categories). This phenomenon is common in studies using prevalent users instead of incident users (Ray, 2003; Szklo & Nieto, 2004; Danaei, Tavakkoli, & Hernán, 2012). Figure 2-4 illustrates the depletion of susceptibles concept in a retrospective cohort design assessing the association of a drug with an adverse drug reaction. At earlier time of the study (Period 1), patients at risk of experiencing the outcome are expected to develop the outcome and thereby excluded from the follow up. This will eventually leave a subgroup of patients who have low risk of experiencing the outcome at later time (Periods 2-3). If the drug of interest causes the outcome of interest (i.e. effective in comparative effectiveness research (CER), or less safe in a drug safety study), susceptible patients will differentially be excluded from the drug exposure group (Drug A, gray shaded blocks) than the other comparator group (Drug

B). The overtime depletion of susceptibles from Drug A group leads to the selection of susceptibles (who were less susceptible in prior periods) from Drug B group. Overtime (Periods 3-6), Drug A will appear inferior to Drug B (less effective in CER, or protective/safe in a drug safety study) when it is not in earlier periods. This phenomenon leads to the crossing of survival curves at a point of time due to the depletion of susceptibles and differential selection of less susceptibles overtime (HR>1 Periods 1-3; HR<1 Periods 4-6). Therefore, caution should be exercised in interpreting "time-varying period-specific HR" (Hernán, 2010), where they are prone to selection bias due to this phenomenon; as a solution, adjusted survival curves utilizing inverse probability of treatment weighted (IPTW) estimator can be compared in terms of survival history of the entire sample when everybody exposed to Drug A, and the survival history of the entire sample when everybody exposed to Drug B (Cole & Hernán, 2004; Hernán, 2010). Prevalent users invoke selection bias in two mechanisms: depletion of susceptibles, and adjusting for confounders that are affected by past exposures (Danaei, Tavakkoli, & Hernán, 2012).

Furthermore, prevention of selection bias induced by prevalent users is possible at the design stage of the study, where follow up is restricted to those patients who were not exposed to the drug of interest for a period of time, then became exposed after the end of the specific period, when they will be considered exposure initiators after being unexposed (Danaei, Tavakkoli, & Hernán, 2012).

Measurement Bias

Measurement (information) bias is a distortion in the association between the exposure and the outcome that arises from systematic errors in the way variables of

interest are measured for the comparison groups (Bégaud, 2000). In retrospective database analysis, information ("unobserved construct"; E, O, Z) regarding true exposures, outcomes, and other variables are recorded in form of indicators ("observed measures"; Ĕ, Ŏ, Ž) to mimic these true experiences (Hernán & Cole, 2009); thus for example, drug exposure ascertainment in a database is not the reflection of true drug utilization, rather a reflection of a measured drug utilization. When these observed measures do not accurately reflect unobserved constructs, measurement error—or misclassification (!e, !o, !z) is said to happen (Grimes & Schulz, 2002).

Measurement bias in pharmacoepidemiology is classified into four types (Figure 2-5): independent nondifferential misclassification; independent differential misclassification; dependent nondifferential misclassification; and dependent differential misclassification (Hernán & Cole, 2009). Independent nondifferential misclassification denotes to the independence between the measurement errors in the exposure and that in the outcome; however, exposure misclassification is not affected by true outcome value (i.e. exposure misclassification is nondifferential across levels of the outcome), and likewise in outcome misclassification (Figure 2-5, A). Independent differential misclassification refers to the independence between the measurement errors in the exposure and that in the outcome; however, the true value of the outcome affects exposure classification (i.e. exposure misclassification is differential across levels of the outcome) (Figure 2-5, B), and similarly in outcome misclassification (Figure 2-5, C). Dependent misclassification happens when measurement errors in the exposure and that in the outcome are dependent on each other, e.g. because they share same mechanism of abstracting information such as recall bias in pregnancy outcome. Like

independent misclassification, dependent misclassification can be nondifferential (Figure 2-5, D) and differential (exposure misclassification, Figure 2-5, E and outcome misclassification, Figure 2-5, F). Confounder misclassification is depicted in Figure 2-6, which is similar to the framework of residual confounding. This type of misclassification may incline investigators to erroneously conclude the presence of effect modification by the confounder, when none exists (Hernán & Cole, 2009).

Nondifferential misclassification drives estimates of association between exposure and outcome towards the null hypothesis; differential misclassification on the other hand drives estimates either towards or away from the null values (Rothman, Greenland, & Lash, 2008). In addition to measurement errors in abstracting the information, grouping categorical or continuous variables into fewer categories can revert nondifferential misclassification to differential misclassification (Rothman, Greenland, & Lash, 2008); and association estimates can be driven away from the null estimates even when the misclassification is nondifferential. This may occur in multi-category exposures, and when exposure or outcome misclassification depends on misclassification in other variables in the dataset, e.g. confounders (Rothman, Greenland, & Lash, 2008).

Exposure misclassification

Characterization of exposure in observational designs is a challenging task. There is a myriad of reasons for imposing measurement bias in exposure characterization when utilizing retrospective database analyses. In pharmacoepidemiology, measures of drug exposure are not necessarily accurate reflections of true drug exposure. In databases, prescribing a drug to a patient doesn't necessarily mean that the patient has actually received the medication from the pharmacy and has actually taken it with

adherence to prescriber's instructions. Patients may take or receive too little (e.g. incorrect inhaler technique) or too much of the correct drug (e.g. too high dose for the indication, and interactions), or they may not take or receive the drug prescribed (e.g. product not affordable to the patient or the healthcare insurance system; product is inconvenient to use, e.g. inhaler coordination; instructions not understood or remembered or even agreed upon by the patient; experiencing undesirable effects; failure to experience perceived benefits; product unavailability; or health beliefs and cultural factors). Thus, such patients may be classified as exposed to the drug of interest, when they may be not exposed or exposed to a variable amount of the drug.

Similarly, exposure misclassification can occur in randomized, controlled trials (Figure 2-7). In open-label and non-placebo-controlled trials in which patients are noncompliant, the randomized exposure R will be a misclassified measure of the true exposure E , i.e. the randomized drug is different from the actually received drug (Figure 2-7, A); however, the association between the randomized exposure and the outcome of interest can be interpreted as an average causal effect when blinding and placebo-controlled randomized trials are employed (Figure 2-7, B) (Hernán & Cole, 2009). When patients do not adhere to the randomized exposure, they may not be similar to those who adhered in terms of some characteristics, e.g. disease severity. This unmeasured confounding U can lead to biased estimates when the aim of the study is to quantify the effect of the actually received exposure, unless accounted for utilizing IPTW for example (Toh & Hernán, 2008). Likewise, biased estimates can be attributed to selection bias that can be invoked when patient censoring or loss to follow up occurs after randomization (Toh & Hernán, 2008). On the other hand, if the study

aims at estimating the effect of the randomized exposure (i.e. the outcome when having the intention of treating with the drug), ITT analysis gives valid causal estimates of the ITT effect of the randomized drug R ; however, it is a misclassified estimate of the actual exposure E . The magnitude of the ITT effect is proportional to the degree of compliance with randomization (the arrow $R \rightarrow E$), which gives conservative estimates that correspond to the lower limit of the effect measure confidence interval.

Medication adherence measures are developed to measure the extent of drug utilization in pharmacy administrative claims databases that record medication filling and dispensing information. However, these measures have limited applications in prescribing databases, e.g. the GPRD, where dispensing information is not recorded. Unlike the US, patients in the UK are required to return to their general practitioner to get a new prescription to refill their original one (Figure 2-8). Indicators in the GPRD from this routine can be used as a measure of adherence and improve exposure characterization, e.g. prescription issue sequence number, which denotes to the number of the refill if the medication is part of a repeat prescription. In the UK, the general practitioner issues either a repeat or a one-off prescription to the patient. The patient is expected to take the prescription to the community pharmacy, where the medications are dispensed along with a repeat medications slip by the pharmacist. When the patient runs off the medication (or when a refill is needed for any reason), she visits the general practitioner to get a new prescription issued based upon the repeat slip presented by the patient (Tim Williams, GPRD, personal communication, May 22, 2011). Furthermore, the GP is notified about prescription refills when repeat dispensing is practiced by community pharmacists, which usually takes place in a form similar to a

medication therapy management plan as a consented scheme between prescribers, pharmacists, and patients, in which the GP prescribe a prescription for 28-day supply with a repeat order (NPC, 2008). The patient takes the prescription to the pharmacy that is part of the scheme where the prescription is filled. When the patient needs a refill, she doesn't need to return to her GP to reissue a repeat prescription, rather she returns to the pharmacy to get another refill for her medication. Upon dispensing the final batch of the medication, the patient returns to the GP to get another prescription reissued upon clinical assessment. Regardless of the way medication refills are practiced (repeat prescribing at the GP level or repeat dispensing at the pharmacist level), the GP records—hence, the GPRD—are well recorded, where full prescription information for each patient is directly logged from the GP computer (Khan, Harrison, & Rose, 2010).

Immortal time bias. Immortal time bias is a form of exposure misclassification that is increasingly found in pharmacoepidemiologic studies (Suissa, 2008); it arises from cohort definition in which patients meet certain survival criterion of follow up from index date, in which patients should survive for a specific duration of time since exposure (Rothman & Greenland, 2008) (Figure 2-9). Failure to account for immortal person-time results in biased estimates of the association between exposure and outcome, which is an underestimation of the true association in the absence of this bias (If survival rate is higher in the exposed group, the HR will be reduced), and the magnitude of bias is proportional to the duration of immortal person-time (Suissa, 2003, 2008).

Immortal time bias can be prevented at the design and the analysis stages of the study. At the design stage, patient follow up should start after the immortal person-time period; while at the analysis stage, this period can be excluded from the analysis of the

denominator person-time calculations for the risk estimates (Suissa, 2008; Rothman & Greenland, 2008). In addition, Cox proportional hazards regression analyses with time-dependent exposures and IPTW analyses can be used to account for immortal-time bias that might arise from time-dependent exposures (Suissa, 2008). In the present study, patients are characterized to have a maximum of 12 months of follow up after the first prescription of the exposure of interest. This 12 month-period is considered an immortal person-time. The ensuing bias will not be present in estimating the morbidity outcomes of interest; however, the bias will be induced in estimating mortality outcomes if immortal person-time was not excluded from the analyses and patients follow up continued from exposure index date, rather than from the survival criterion index date (i.e. after 12 months post first prescription; Chapter 3).

Diagnostic misclassification

Diagnostic (disease) misclassification refers to the differential classification of the clinical condition among patients. Diagnostic misclassification is a form of measurement bias and should be distinguished from diagnostic bias, which is a type of selection bias in which patients are differentially diagnosed depending on exposure to specific risk factors (Bégaud, 2000). Specifying the population's clinical condition of interest is usually the first step in pharmacoepidemiologic research design. The validity of disease diagnoses in pharmacoepidemiologic databases varies by the type and the source of the database. Some databases record diagnoses utilizing disease classification codes, e.g. international classification of diseases (ICD) and Read clinical terms; others use clinical terminologies, e.g. medical dictionary for regulatory activities (MedDRA) and systematic nomenclature of medicine (SNOMED). Incorrect coding may arise at the

general practice, hospital, health insurance system, or the database administrator. Patients may be misclassified as having the disease of interest, when in reality they are not and vice versa. In databases, the accuracy of the diagnosed condition is contingent upon the validity of the diagnosis process (at the practitioner level), and the extent of association of the classification code with the documented diagnosis (at the database level), where the code serves as a surrogate measure for the true diagnosis (van Walraven & Austin, 2012).

The GPRD provides the practitioners with specific guidelines on how to record diagnoses and other clinical and therapeutic events using a specific software system called the Vision General Practice Management Software (GPRD, 2004). Furthermore, the validity of diagnostic codes in the GPRD was established in multiple conditions, including asthma and COPD (Hollwell, 1997; Hansell, Hollowell, Nichols, McNiece, & Strachan, 1999; Herrett, Thomas, Schoonen, Smeeth, & Hall, 2010; Khan, Harrison, & Rose, 2010). Moreover, the GPRD programmers were provided Read clinical terms that reflect asthma diagnoses for the present study.

Outcome misclassification

In retrospective database research, patient outcomes of interests are measured by a set of definitions that serve as a proxy to the true outcomes, e.g. asthma morbidity is sometimes measured by patient's referral to emergency departments or hospitals due to asthma exacerbations, and prescribing and utilization rates of rescue inhaler medications and oral corticosteroids (NHLBI, 2007). Like exposures, outcomes are prone to misclassification in pharmacoepidemiologic research. When outcome misclassification is nondifferential (Figures 2-8, A & 2-8, D), the association will be

driven towards the null; and it will be driven away from the null if the misclassification is differential (Figures 2-8, C & 2-8, F). For example, if exposure to a specific asthma drug increases (or decreases) the probability of misclassifying the patient as having hospitalized for asthma exacerbations, the association between the exposure and the outcome will be biased away from the null estimate.

Developing algorithms to identify outcomes that include a mixture of clinical, referral, and prescription information can improve the validity of outcome measurement (Khan, Harrison, & Rose, 2010; van Walraven & Austin, 2012). For example, if the outcome of interest is asthma exacerbations, the investigator can search for Read clinical terms for asthma exacerbations in addition to referral information to an emergency department and relevant medication history. Likewise, utilizing linked databases can help in the identification of relevant outcomes. For example, the mortality database that is linked to the GPRD is sensitive to the causes of death, and each record has more than one cause-of-death field (ONS, 2009), which improve outcome ascertainment compared to similar datasets with one cause-of-death field.

Modeling Techniques to Control Bias and Confounding

In observational designs, the application of correct methodologies at study design and analysis stages minimizes—or prevents bias and confounding (Rubin, 2007) (Figure 2-10). Randomized, controlled trials are not always feasible to conduct, have limited external validity, and sometimes, limited internal validity as stated earlier. Therefore, it is important to design and conduct observational studies that mimic randomized trials in order to achieve causal interpretation of the observed association (Cain, Robins, Lanoy, Logan, Costagliola, & Hernán, 2010; Hernán, 2011). Approaches

at the design stage include: restriction (excluding patients with the confounder); matching (compare patients with identical confounder distribution); new-user design (incident users); crossover design (exposed patients become their own control as they move in and out the exposure time period); active comparator design (compare exposure groups that have identical safety and effectiveness); and validation studies (two-stage sampling and external adjustment) (Schneeweiss, 2008). The last three methods are used to account for unmeasured confounding. Moreover, the following approaches are applied at the analysis stage: regression modeling; stratification (conduct separate analyses for subgroups of confounder); standardization (stratify by the confounder and apply stratum-specific event rates for each exposure group to the number of patients in the corresponding stratum in the standard population); instrumental variables (identify a variable that is associated with the exposure but not the outcome); and sensitivity analyses (examine the effect of changing variable values on the modeling results) (Schneeweiss, 2008). Regression modeling is the most common approach to surmount confounding during the analysis stage of a study. The following is a review of regression modeling approaches to control bias and confounding in observational designs with longitudinal time-dependent data.

Multiple Regression Analysis

Multiple regression analysis is a statistical technique that is used to estimate the association between the exposure and the outcome by virtue of a mathematical model that better predicts the value of the outcome as a function of the exposure after holding all other covariates constant. The association estimates are adjusted when confounding variables are included in the covariate pool, which will minimize or eliminate the effect of

the differential distribution of the confounders between exposure comparison groups. If confounders have large influence on the association, the adjusted estimates may differ significantly from the unadjusted (crude) estimates. Examples of multiple regression analyses include linear, logistic, Poisson, and Cox proportional hazards. The validity and causal interpretation of the calculated estimates are contingent upon model fitting specifications and other assumptions, e.g. absence of unmeasured confounding (Christenfeld, Sloan, Carroll, & Greenland, 2004; Robins, Hernán, & Brumback, 2000).

Conventional Cox proportional hazards regression

In 1972, the British statistician David R. Cox developed the Cox proportional hazards regression (PHREG) (Cox, 1972), which today is the most commonly used regression analysis in longitudinal studies that involve survival and time-to-event analyses. Cox PHREG is used to estimate the hazard of an outcome occurrence conditional on confounders and other covariates, including exposure. Hazard is the instantaneous risk that an outcome occurs at time t given the patient survives to time t or later. The hazard is estimated by the hazard function in Equation 2-1:

$$\lambda_i(t) = \lim_{\Delta t \to 0} \frac{\Pr(t \le T < t + \Delta t \mid T \ge t)}{\Delta t} \qquad (2\text{-}1)$$

Where $\lambda_i(t)$ is the hazard function (sometimes denoted as $h(t)$), which refers to the limit of the risk that an outcome will occur at the interval $[t, t+\Delta t)$ given patient survival to the beginning of the interval (the numerator), as Δt approaches zero. Since the likelihood of an outcome to occur is proportional with the length of the interval $[t, t+\Delta t)$, the denominator adjusts for the interval width by shrinking Δt close to zero; therefore, the risk estimates are instantaneously calculated at time t.The outcome time for a particular

patient is expressed as T in the numerator. Figure 2-11, A shows the required data structure for the analysis using Cox PHREG models, where the variable “Time” is the duration of time from the start of follow up until either outcome occurrence or last observation of the patient, i.e. censoring. The variable “Status” refers to the status of the patient at the recorded time, whether the patient experienced the outcome (Status=1) or the patient was censored (Status=0). Even though hazards are defined in terms of probabilities, they are not probabilities, rather are rates expressed in terms of number of events per time interval, and they have values greater than 1 and less than 0, but never negative values. The reciprocal of the hazard yields the expected length of time until outcome occurrence. Of course, the interpretation of the hazard and its reciprocal is contingent upon the assumption that everything about the patient and the ambient environment, including the hazard itself remains constant over time. However, this is not the case in reality, especially in the presence of time-dependent covariates (Allison, 2010). Compared to parametric survival analysis methods (e.g. the Kaplan-Meier, actuarial, and accelerated failure time methods), Cox PHREG is a semiparametric method of creating models that handle data with parametric and nonparametric distributions, tied outcome times, and time-dependent covariates; in addition to having efficient stratification analyses (Allison, 2010). Cox PHREG model is expressed in Equations 2-2 and 2-3:

$$\lambda_i(t) = \lambda_0(t) e^{[\beta_i E_i + \beta_i Z_i]} \tag{2-2}$$

$$\log \lambda_i(t) = \alpha(t) + \beta_i E_i + \beta_i Z_i \tag{2-3}$$

Where the hazard function for an individual i at time t is a product of the baseline hazard $\lambda_0(t)$, which is the hazard function for the individual when the exposure E and

covariate Z values are zero. The exponentiated coefficients β yield the Hazard Ratios (HRs), which for the exposure variable, is interpreted as the ratio of the estimated hazard for one exposure group to the estimated hazard for other exposure group, after controlling for other covariates.

This model assumes the ratio of hazards for all patients is proportional across exposure groups, and stays constant during the study follow up period (Therneau & Grambsch, 2000). Fortunately, this assumption is unnecessary when the model is extended to include time-dependent covariates.

Cox PHREG with time-dependent covariates

Time-dependent covariates are explanatory variables that may change in value over the course of follow up. Repeated measurements on the same variable for the same patient or treatment switching are examples of time-dependent variables. Incorporating time t to the exposure and confounding variables in Equation 2-2 produces the Cox PHREG model with time-dependent covariates in Equation 2-4. Equation 2-5 shows a model with time-dependent exposure; Equation 2-6 shows a model with time-dependent confounder; and Equation 2-7 depicts a model with one fixed, time-invariant confounder, one time-dependent confounder, and one time-varying exposure.

$$\lambda_i(t) = \lambda_0(t) e^{[\beta_i E_i(t) + \beta_i Z_i(t)]} \quad (2\text{-}4)$$

$$\log \lambda_i(t) = \alpha(t) + \beta_i E_i(t) + \beta_i Z_i \quad (2\text{-}5)$$

$$\log \lambda_i(t) = \alpha(t) + \beta_i E_i + \beta_i Z_i(t) \quad (2\text{-}6)$$

$$\log \lambda_i(t) = \alpha(t) + \beta_i E_i(t) + \beta_i Z_i + \beta_i Z_i(t) \quad (2\text{-}7)$$

The Cox PHREG model with time-dependent covariates requires specific data structure to handle time-dependent covariates. The "*counting process*" method generates data structure similar to Figure 2-11, B where there are multiple records per patient and the "Time" variable in conventional Cox PHREG model is replaced with the "Start" and "Stop" variables, which denote to the interval (start, stop] of time in which patient status and time-dependent and time-independent variables are measured. During the interval, the value of the time-dependent variable will be treated as a fixed variable just like in conventional Cox PHREG models (Therneau & Grambsch, 2000). On the other hand, the "*programming statements*" method generates data structure similar to Figure 2-11, C where there is one record per patient, and the time-dependent variables are continued as multiple variables per patient (Allison, 2010). Both methods give similar results when carefully and accurately programmed.

Although the extended Cox PHREG models with time-dependent covariates can efficiently handle time-varying exposures (Figure 2-1, C), it fails to adequately control for time-dependent confounding that is affected by previous exposure (Figure 2-1, B) (Robins, Hernán, & Brumback, 2000; Greenland, 2008); and a systematic review showed that survival analysis studies did not apply appropriate methodology to account for time-dependent confounders and time-dependent exposures (van Walraven, Davis, Forster, & Wells, 2004). Alternatively, Marginal Structural Models technique overcomes these hurdles, and under specific assumptions, the technique allows causal interpretations for exposure-outcome association (Robins, Hernán, & Brumback, 2000).

Marginal structural models

In pharmacoepidemiology, drug effects are time-dependent, and are affected by time-dependent confounders that themselves are affected by previous drug exposure, and affect subsequent drug exposure and subsequent outcome. In such situations, conventional statistical methods (including Cox PHREG models) produce biased estimates of exposure effect, because they fail to account for the time-dependent nature of the confounders and exposures (Suarez, Borràs, & Basagaña, 2011). Moreover, lack of randomization in observational designs prevents bestowing causal interpretations upon observed associations. To overcome these problems, Marginal Structural Models (MSM) technique was developed in 1997 as a new class of causal models, followed by two companion articles in 2000 that paved the way for practical applications of these models, which allow for an unbiased, causal, population level (marginal) effect estimate of exposure on the outcome in the presence of time-dependent confounding and time-dependent exposure in observational data (Robins, 1998; Hernán, Brumback, & Robins, 2000; Robins, Hernán, & Brumback, 2000). The term “Marginal Structural Cox Models” is sometimes used to reflect the extension to account for censoring. MSM is a weighted repeated measures technique that is based on the inverse probability of treatment weighting as an extension of the exposure propensity scores approach. Although MSM is effective in handling time-dependent confounding, the technique is less efficient in estimating effect modification by time-varying covariate than structural nested models (SNM) (Robins, Hernán, & Rotnitzky, 2007).

MSM technique creates at each point of time (risk set) a pseudo-population of counterfactuals (a hypothetical population in which all patients seem as exposed and

unexposed to the drug), in which, time-invariant and time-dependent confounders are balanced, and therefore, causal association between the exposure and the outcome is the same as in the original study population (Hernán, Brumback, & Robins, 2000, 2002). The pseudo-population is created by weighting every patient in the population by the inverse of the conditional probability of being exposed to the treatment that the patient actually received $W_i(t) = 1/\Pr(E_i \mid Z_i)$. MSM compare two counterfactuals: outcome if the entire study population is exposed to the treatment $\Pr(O = 1_{E=1})$ and outcome if the entire study population is not exposed to the treatment $\Pr(O = 1_{E=0})$ (Figure 2-12). Thus, it gives valid causal interpretations between the exposure and the outcome.

Nonetheless, causal inference from MSM is contingent upon inherent assumptions of exchangeability, positivity, consistency, and correct modeling for weighting (exposure model) and analysis (outcome model) (Brumback, Hernán, Haneuse, & Robins, 2004; Mortimer, Neugebauer, van der Laan, & Tager, 2005; Cole & Hernán, 2008). The following rules are termed the causal effect identifiably assumptions (Cole & Hernán, 2008):

1. Exchangeability: lack of unmeasured confounding is referred to conditional exchangeability, where all the variables explaining the exposure and the outcome are included in the analysis. Formally, conditional exchangeability defined as the independence between the prospective counterfactual outcomes and the observed exposures, given previous exposure and confounder history $O_E(t+1) \coprod E(t) \mid E(t-1), Z, V(t)$. To illustrate, the risk of experiencing the outcome under exposure in the exposed patients equals the risk of experiencing the outcome under exposure in the unexposed patients $\Pr(O = 1_{E=1} \mid E = 1) = \Pr(O = 1_{E=1} \mid E = 0)$. Similarly, the risk of experiencing the outcome under no exposure in the exposed patients equals the risk of experiencing the outcome under no exposure in the unexposed patients $\Pr(O = 1_{E=0} \mid E = 1) = \Pr(O = 1_{E=0} \mid E = 0)$. Exchangeability assumption can be assessed by conducting sensitivity analysis proposed by Brumback & colleagues (2004).

2. Positivity: experimental treatment assumption is referred to positivity, which implies the presence of positive probability for patients to receive each exposure category for a set of covariates, including prior exposure and confounding history $\Pr[E(t) \mid E(t-1), Z, V(t)] > 0 \; for \; \Pr[E(t-1), Z, V(t)] > 0$ (i.e. no perfect confounding). Positivity assumption can be assessed by Mortimer and associates approach (2005).

3. Consistency: consistency refers to the outcome for every exposed patient equals the outcome if the patient had remained exposed $O = O_{E=1}$ when $E = 1$, and the outcome for every unexposed patient equals the outcome if the patient had remained unexposed $O = O_{E=0}$ when $E = 0$.

Marginal structural modeling involves two consecutive steps: estimating stabilized inverse probability weights by propensity scoring (exposure selection model), and conducting weighted repeated measures analysis by generalized estimating equations (outcome analysis model) (Cole & Hernán, 2008). Binary logistic regression is used for binary exposure (Rosenbaum & Rubin, 1983; Hernán, Brumback, & Robins, 2000), and multinomial logistic regression with the generalized logit link (GLOGIT) is used for multicategory exposure (Equations 2-9 and 2-10) (Rubin, 1997; Allison, 2012; Chitnis, Aparasu, Chen, & Johnson, 2012; Desai et al., 2012). Similarly, binary logistic regression or generalized linear model is used to estimate censoring probabilities (Equations 12 and 13). Weighted generalized estimating equation is used to estimate the hazard ratio $\beta_1 E(t-1)$ for the causal association between the exposure and the outcome for each patient i at every visit t weighted by the stabilized weights (Equations 2-15 and 2-16). The final model includes time-dependent exposure, but not time-dependent confounders. Time-dependent confounders are accounted for in the weighting process.

Exposure selection model: $$SW_{it}^{E} = \prod_{t=0}^{T} \frac{\Pr[E_i(t) \mid E_i(t-1), Z_i]}{\Pr[E_i(t) \mid E_i(t-1), Z_i, V_i(t), V_i(t-1)]} \qquad (2\text{-}8)$$

Numerator: $\log it \Pr[E(t) \mid E(t-1), Z] = \beta_0(t) + \beta_1 E(t-1) + \beta_2 Z$ (2-9)

Denominator: $\log it \Pr[E(t) \mid E(t-1), Z, V(t), V(t-1)] = \beta_0(t) + \beta_1 E(t-1) + \beta_2 Z + \beta_3 V(t) + \beta_4 V(t-1)$ (2-10)

Censoring model: $SW_{it}^{C} = \prod_{t=0}^{T} \frac{\Pr[C_i(t) \mid C_i(t-1), E_i(t), Z_i]}{\Pr[C_i(t) \mid C_i(t-1), E_i(t), Z_i, V_i(t)]}$ (2-11)

Numerator: $\log it \Pr[C(t) \mid C(t-1), E(t), Z] = \beta_0(t) + \beta_1 C(t-1) \beta_2 E(t) + \beta_3 Z$ (2-12)

Denominator: $\log it \Pr[C(t) \mid C(t-1), E(t), Z, V(t)] = \beta_0(t) + \beta_1 C(t-1) + \beta_2 E(t) + \beta_3 Z + \beta_4 V(t)$ (2-13)

Stabilized exposure selection & censoring weight: $SW_{it}^{E,C} = \prod \left(SW_{it}^{E} \right) \left(SW_{it}^{C} \right)$ (2-14)

Outcome analysis model: $\log it \, \lambda_i(t) = \Pr[O(t) = 1 \mid O(t-1) = 0, E(t-1), Z]$ (2-15)

$\log it \, \lambda_i(t) = \beta_0(t) + \beta_1 E(t, t-1) + \beta_2 Z \approx SW_{it}^{E,C}$ *weighted by* $\beta_3 V(t, t-1)$ (2-16)

- $SW_{it}^{E,C}$: Probability of patient i to receive the observed exposure at time interval $0-t$ given exposure, covariates, and censoring history.
- $O(t)$: Outcome at time t. $O(t) = 1$ if outcome is observed; 0 otherwise.
- $O(t-1)$: Outcome at time $t-1$.
- $E_i(t)$: Exposure at time t for patient i. $E_i(t) = 0$ for ICS; $E_i(t) = 1$ for LABA; $E_i(t) = 2$ for ICS/LABA.
- $E_i(t-1)$: Exposure history prior to time t. $E_i(t-1) = 0$ for ICS; $E_i(t-1) = 1$ for LABA; $E_i(t-1) = 2$ for ICS/LABA.
- $C_i(t)$: Patient censoring status at time t. $C_i(t) = 1$ if patient lost to follow up; $C_i(t) = 0$ if patient continued to time t.

- $C_i(t-1)$: Patient censoring history prior to time t. $C_i(t-1)=1$ if patient lost to follow up; $C_i(t-1)=0$ if patient continued to time $t-1$.
- Z_i: Measured time-independent confounders at baseline.
- $V_i(t)$: Measured time-dependent confounders at time t.
- $V_i(t-1)$: Measured time-dependent confounders at time $t-1$.

Exposure Propensity Scores Technique.

Rosenbaum and Rubin (1983) developed exposure propensity scores (EPS) technique as a mean to account for confounding by indication (especially confounding by disease severity) in the presence of measured confounding variables. The score is defined as the likelihood of a patient being exposed to treatment given a set of measured confounding variables; on average, exposure groups with similar scores are expected to have similar baseline information with respect to confounding variables. Thus, a quasi-randomization state is achieved (Ali, 2011). The inverse of the EPS for exposure groups yields the inverse probability of treatment weighted (IPTW), which creates weights for each patient at each unit of time based on the propensity scores. The weights are interpreted as the number of copies for each observation that are required to form a pseudo-population of counterfactuals in which no time-dependent confounding exists (Hernán, Brumback, & Robins, 2000). The IPTW approach gives unbiased estimates of exposure effects in the presence of time-dependent confounding (Greenland, 2008).

Figure 2-13 illustrates the process of attaining quasi-randomization by virtue of MSM. Suppose in a sample of 100 patients, 80 are exposed to the treatment of interest and 20 are unexposed (Figure 2-13, A). The conjecture of MSM is to recreate this

sample in a way that would equate the selection mechanism between the exposed and the unexposed. Within the exposed group, the probability of exposure given the covariance structure (propensity score—PS) $\Pr(E=1|Z)$ equals 0.8, and the inverse of that probability (inverse probability of treatment weighted—IPTW) $\frac{1}{\Pr(E=1|Z)}$ equals 1.25. By multiplying this inverse probability—as if it was a weight—times the number of people in that group (n=80) a total sample size of 100 is obtained. The same is applied to the unexposed group, where the probability of not exposure $1-\Pr(E=1|Z)$ equals 0.2, and the inverse of the probability equals 5. Similarly, the total sample size of 100 will be obtained after multiplying the inverse probability of exposure by the number of people in the unexposed group (n=20). In effect, the MSM has created two populations with selection mechanism of 50% chance, one treated and the other untreated, i.e. probability of the outcome for the counterfactual groups when treated versus the probability of the outcome for the counterfactual group when not treated $\Pr[O(E=1|Z)]-\Pr[O(E=0|Z)]$; where O is the outcome of interest, E is the exposure of interest ($E=1$, exposed; $E=0$, unexposed), and Z is a vector of confounding variables. This quasi-randomization approach creates selection probabilities that are the same for the exposed and the not exposed. The same principle extends to multiple exposure groups (Figure 2-13, B).

The EPS technique does not account for unmeasured confounding. Therefore, the exposure groups might seem balanced based on the likelihood of receiving treatment when they are not in the presence of unmeasured confounders (Glynn, Schneeweiss, & Strürmer, 2006). Although the utilization of this technique has dramatically grown in the biomedical literature (Glynn, Schneeweiss, & Strürmer, 2006; Kurth & Seeger, 2008),

the majority of studies used this technique yielded results that are essentially similar to ones obtained from traditional regression models (Shah, Laupacis, Hux, & Austin, 2005).

MSM approach controls time-dependent confounding, accounts for informative censoring, and extends to multicategory exposures (van der Laan & Robins, 2003). Conventional regression methods yield non interpretable coefficients after adjusting for time-dependent confounders, which predict future exposures and outcomes, and are affected by past exposures. Causal inference methods, e.g. MSM are required to consistently estimate the causal effect of exposures in such situations.

Instrumental Variable Analysis Technique.

The application of instrumental variable (IV) analysis technique in pharmacoepidemiology is borrowed from econometrics. The IV is an observed variable that is incorporated in regression models in an attempt to prevent residual confounding due to the influence of unmeasured confounders in retrospective database analyses (Johnston, Gustafson, Levy, & Grootendorst, 2008). A perfect IV should meet the following conditions lest give biased estimates (Figure 2-14) (Greenland, 2000):

- The IV is associated with the exposure E, either directly, or both share a common cause W.
- The IV is not associated with the outcome. Not directly, nor through a common cause X. It affects the outcome only through the exposure.
- The IV is not associated with the confounding variables Z.

In retrospective database analysis, it is difficult to find a variable that meets these assumptions. In scenarios where exposure is time-dependent, the identification of a time-varying IV is nearly impossible (Hernán & Robins, 2006). Some researchers used

prescriber's preference to prescribe one medication class over the other as an IV (Brookhart, Wang, Solomon, & Schneeweiss, 2006a); however, the proxy measure used to reflect prescriber's preference violated the assumptions and gave biased estimates (Hernán & Robins, 2006). Such bias can also be raised when the magnitude of confounding due to unmeasured confounder is strong (Martens, Pestman, de Boer, Belitser, & Klungel, 2006). Moreover, additional strong assumptions are required when IV is used to estimate population's average causal effect, e.g. lack of additive effect modification by the IV within exposure groups (Brookhart, Wang, Solomon, & Schneeweiss, 2006b; Hernán & Robins, 2006).

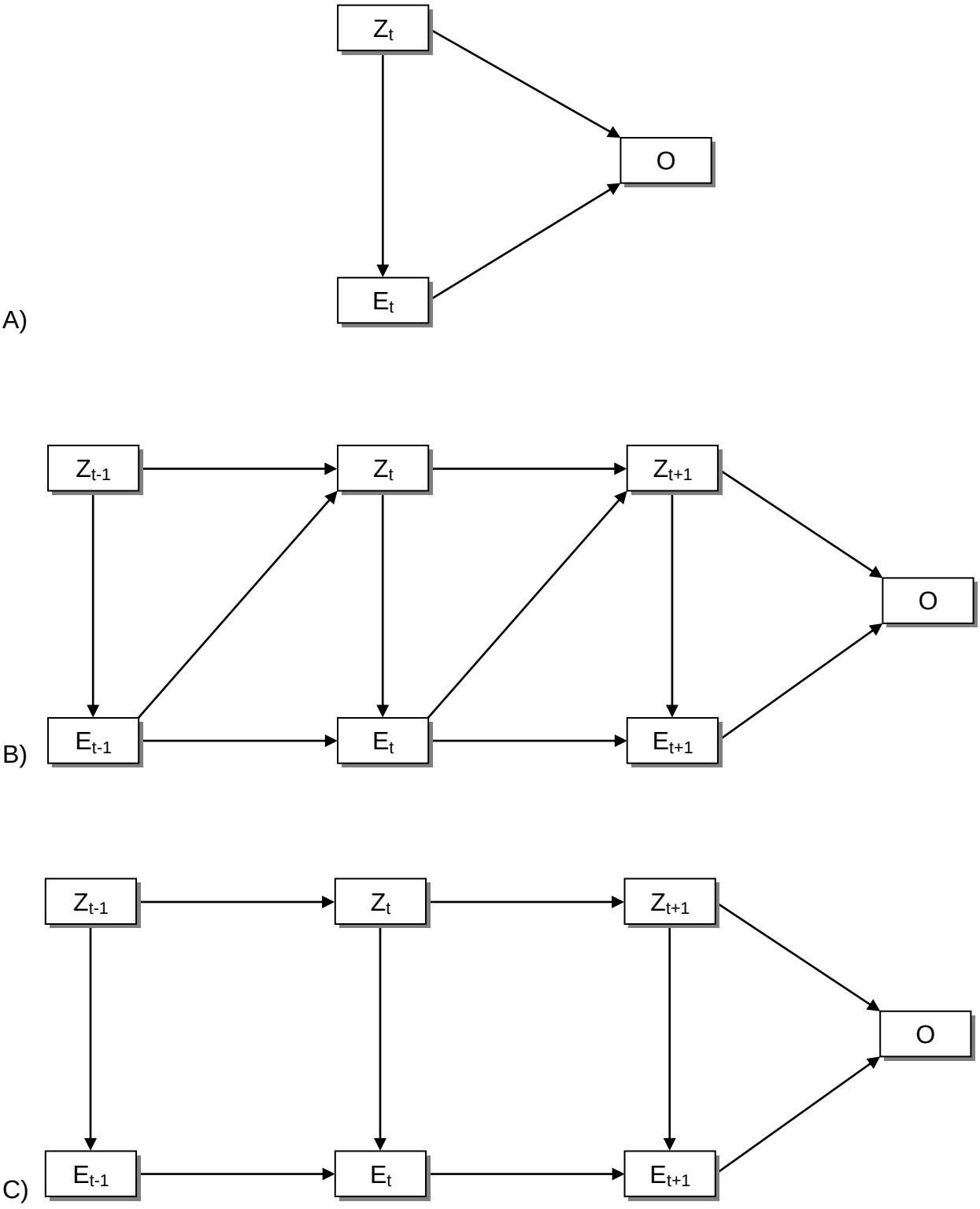


Figure 2-1. Illustration of confounding. A) Classical time-independent confounding, B) time-dependent confounding and time-varying exposure and C) time-varying exposure with no time-dependent confounding.

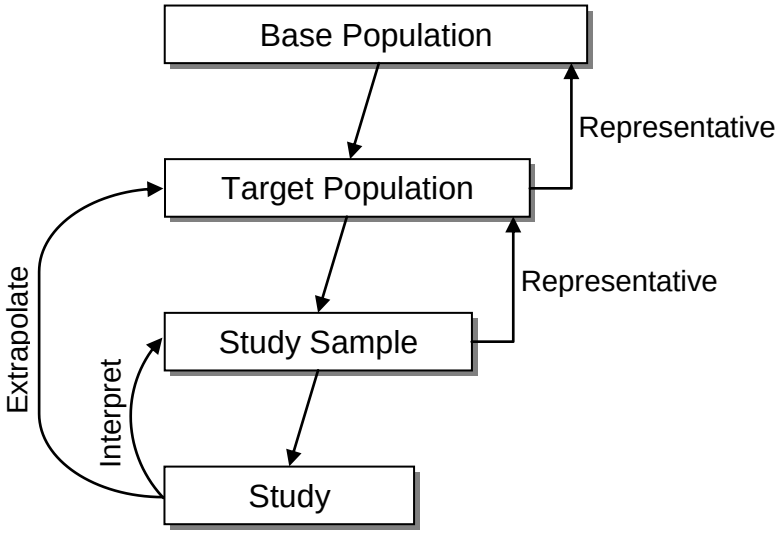


Figure 2-2. Illustration of the relationship between study sample and target population in pharmacoepidemiologic studies

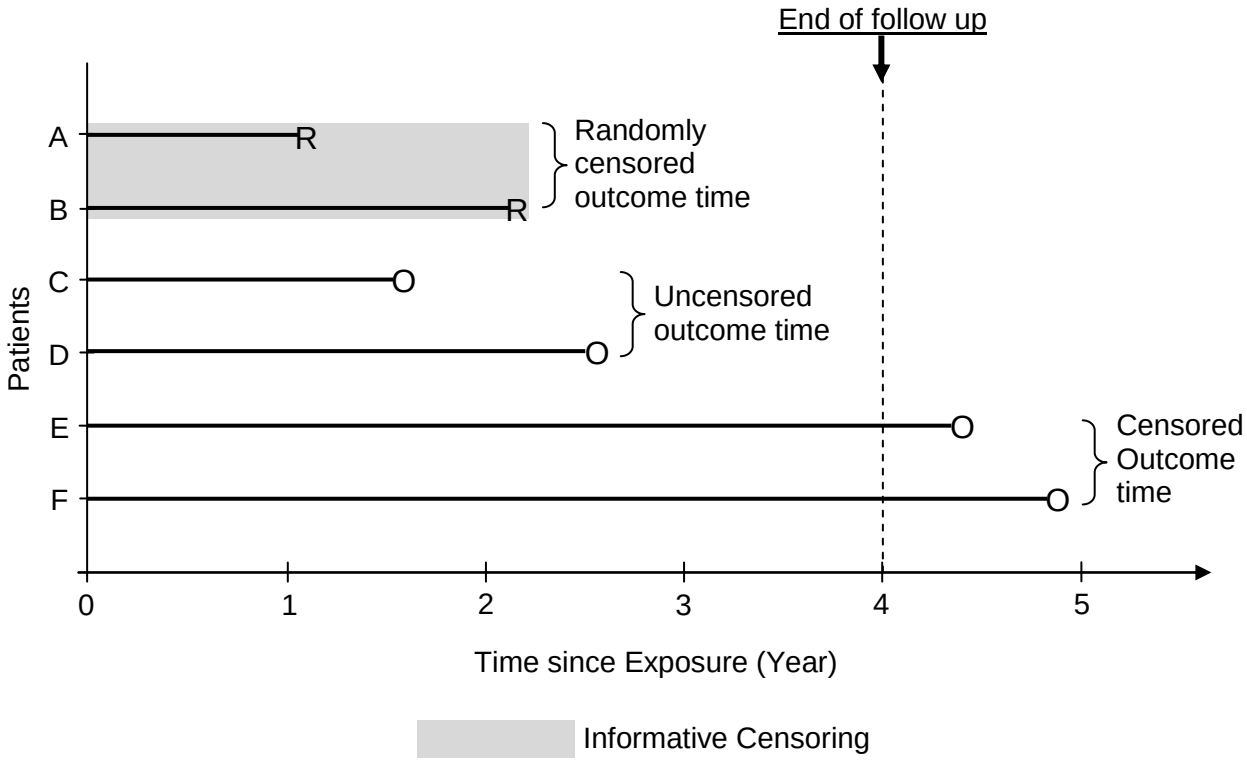


Figure 2-3. Illustration of informative censoring in pharmacoepidemiology

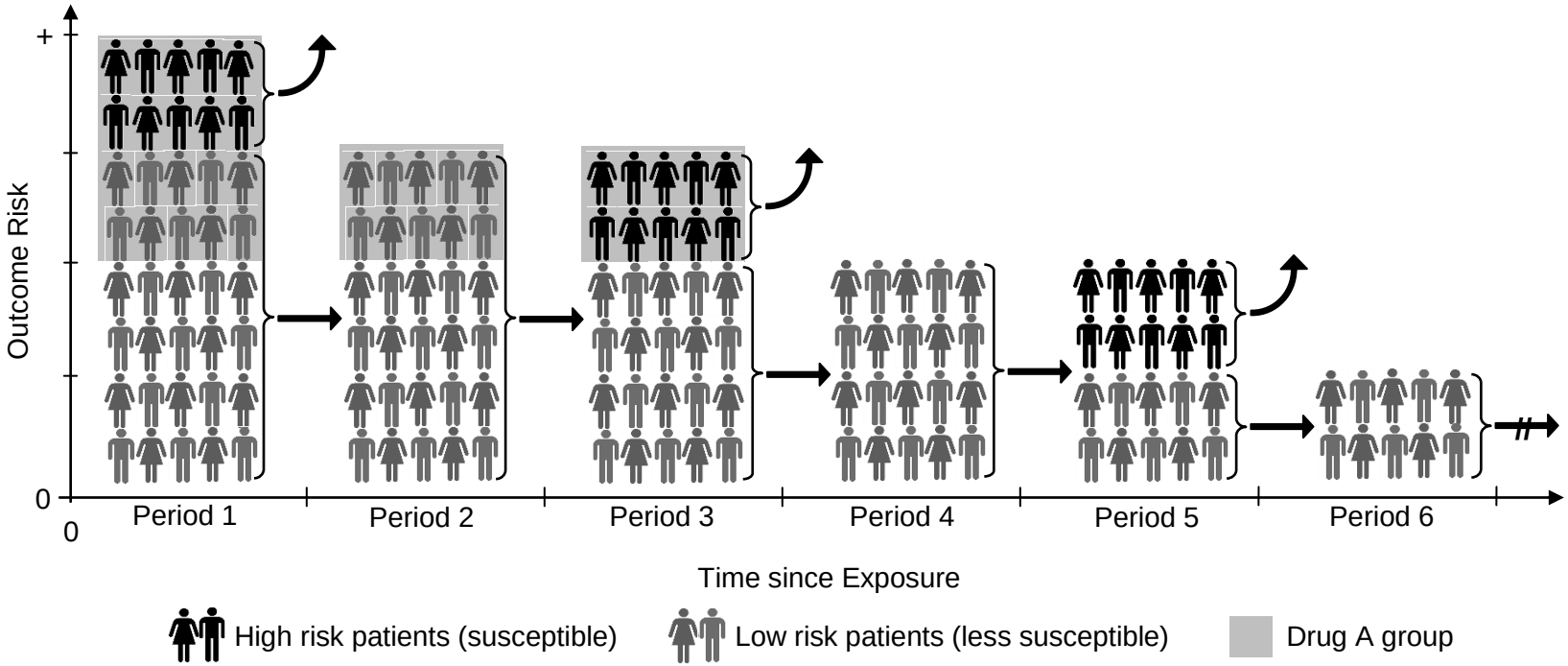


Figure 2-4. Illustration of “depletion of susceptibles” concept in a cohort study examining the association of a drug (exposure) with an adverse drug reaction (outcome). At earlier time of the study (Period 1), patients at risk of experiencing the outcome are expected to develop the outcome and are excluded from follow up, thereby leaving a group of patients who have low risk of experiencing the outcome at later time (Periods 2-3). If the drug causes the outcome (effective/less safe), susceptible patients will differentially be excluded from the drug exposure group (Drug A, gray shaded blocks) than other comparator group (Drug B). The overtime depletion of susceptibles from one exposure group (Drug A) leads to selection of susceptibles (who were less susceptibles in prior periods) from the other group (Drug B). Overtime (Periods 3-6), the exposure group (Drug A) will appear protective against the outcome of interest (i.e. safe), when it was not in earlier periods. This leads to the crossing of survival curves at a time point due to the depletion of susceptibles and differential selection of less susceptibles overtime (HR>1 Periods 1-3; HR<1 Periods 4-6). Therefore, period-specific hazard ratios are prone to selection bias due to the survivor bias phenomenon. Susceptible patients are those who are susceptible to the outcome that is an adverse reaction to the drug of interest.

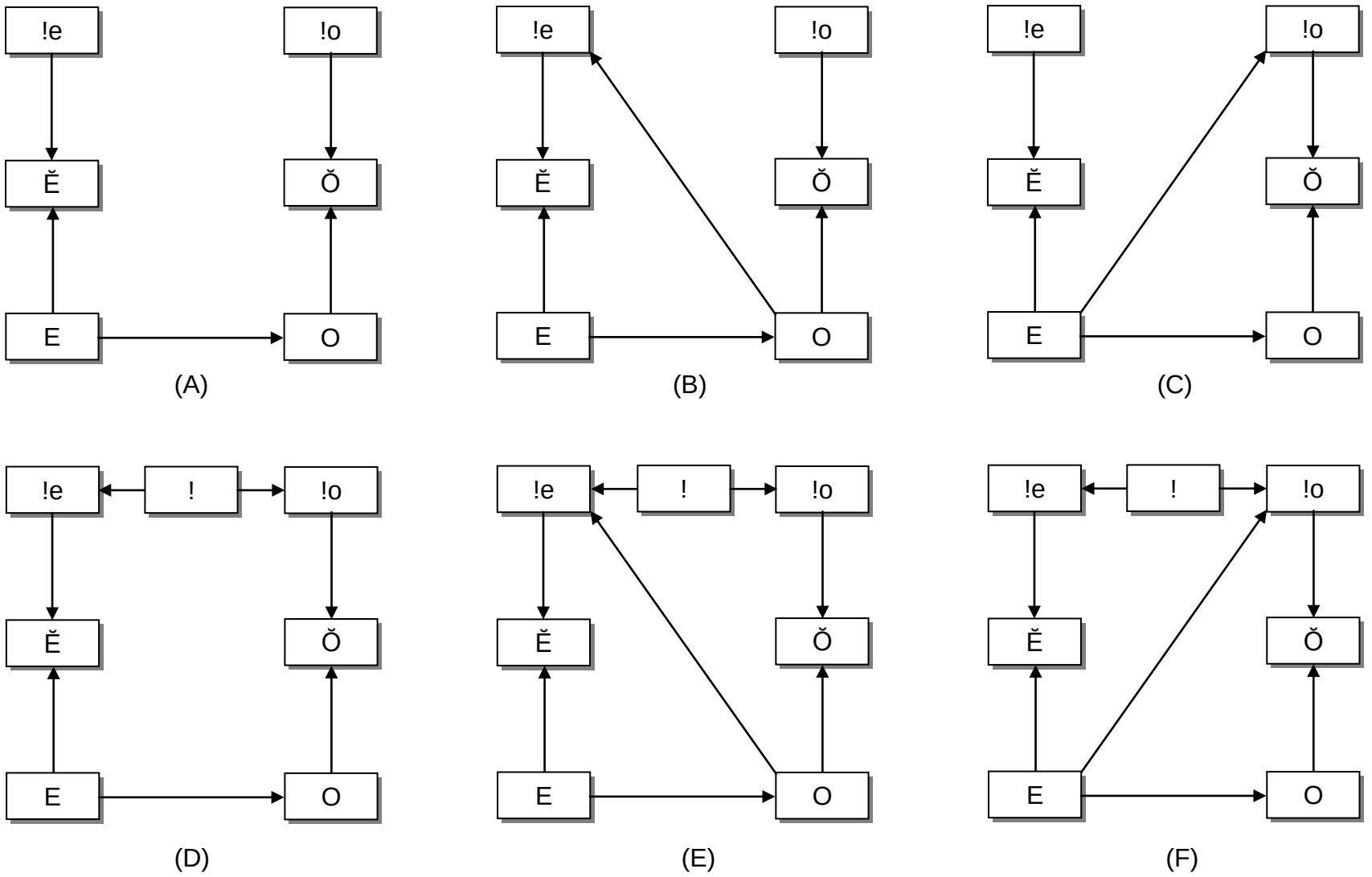


Figure 2-5. Illustration of measurement bias types in pharmacoepidemiology. A) independent nondifferential, B) independent differential exposure, C) independent differential outcome, D) dependent nondifferential, E) dependent differential exposure and F) dependent differential outcome misclassification.

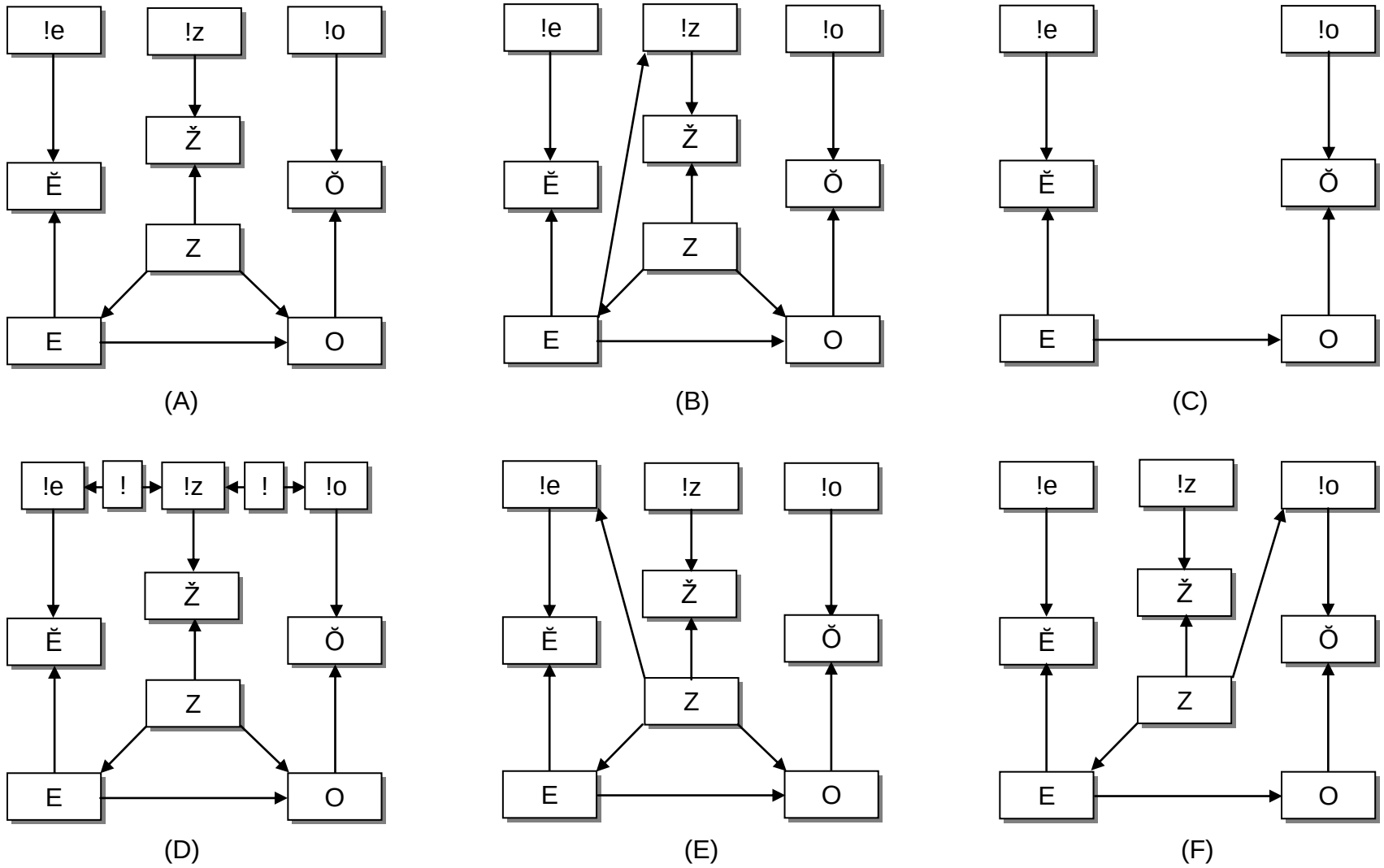
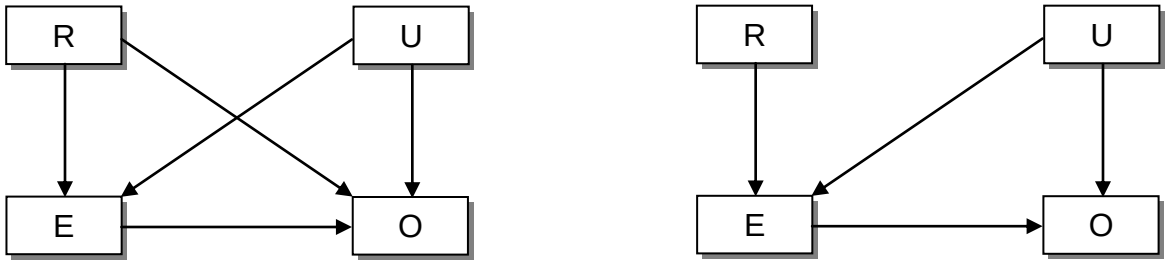


Figure 2-6. Illustration of confounder misclassification in pharmacoepidemiology. A) independent nondifferential, B) independent differential, depends on exposure, C) independent differential, depends on outcome, D) dependent nondifferential, E) exposure misclassification depends on confounder and F) outcome misclassification depends on confounder.



(A) (B)

Figure 2-7. Illustration of exposure misclassification in randomized controlled trials. A) Open-label, non-placebo-controlled and B) double-blind, placebo controlled. In intention to treat (ITT) analyses, the interest is the effect of the intention to randomize exposure. It is valid only in placebo-controlled trials where R is not associated with O (panel B) and in the absence of loss to follow up or censoring. However, ITT has an inherent misclassification bias. When censoring or loss to follow up occurs, pseudo ITT effect is computed within those uncensored until outcome measurement. It gives values closer to the null and are concerning in safety studies. ITT effect is effectiveness; to distinguish it from observational effectiveness the term “experimental effectiveness” is used.

Pharmacy Stamp *Please don't stamp over age box*	Age D.O.B	Title, Forename, Surname & Address Patient No.	"CONFIDENTIAL" Patient name Patient No. D.O.B Address Please give the Practice a minimum of 2 days notice prior to collecting your repeat drugs.
Number of day's treatment N.B. Ensure dose is stated			
Endorsements	Medication 1 Medication 2		There are XX items on this re-order form 01/01/2012 Medication 1 ☑ Medication 2 ☐
Signature of Prescriber	Date		
For dispenser No. of Prescrns. on form NHS *Ayad 2012*	Prescriber Address Prescriber No.		PATIENTS – please read the notes overleaf

The prescriber ticks the box next to the medication to order a repeat prescription, otherwise the prescription is a one-off.

Figure 2-8. Sample of a prescription in the UK general practice

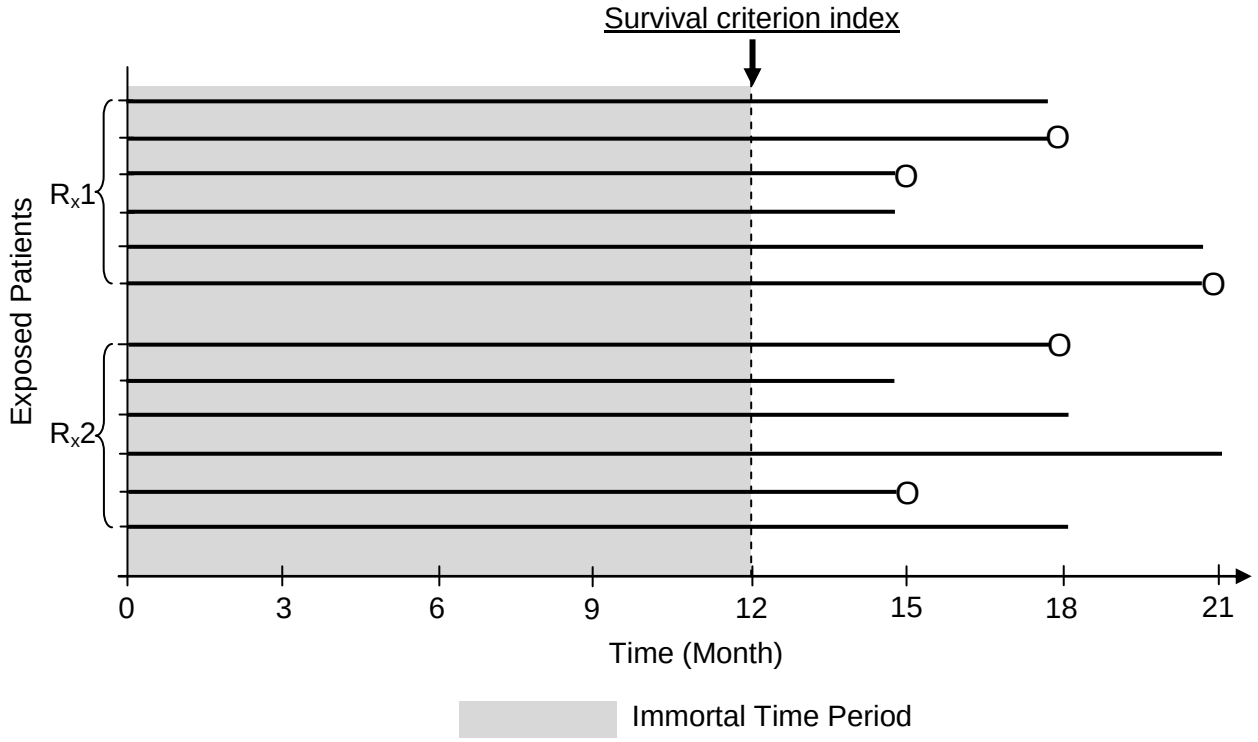


Figure 2-9. Illustration of immortal time bias in pharmacoepidemiology. If a cohort study, patients are required to survive for at least one year after exposure to study drug to be included in the study. This criterion ensures that all patients have survived the first year of exposure and those who did not survive during that period are excluded from the study. If mortality is the outcome of interest, the 1-year immortal person-time should be excluded from the analysis otherwise the estimates will be underestimated. In the illustrated cohort study, 6 patients exposed to Rx1 and 6 patients exposed to Rx2 meet the criterion of being survived for at least 12 months after exposure. If Rx1 patients were followed up to 6 months after this index date, and Rx2 patients to 9 months. Person-month for Rx1=36, and person-month for Rx2=45. Suppose during the follow up period 3 deaths are observed for Rx1 group, and 2 deaths for the Rx2 group. The correct risk ratio is (3/36)/(2/45) = 1.87 and the risk difference is 48/1000 month-1. However, if the 12*6=72 for Rx1 and 72 for Rx2 immortal person-time are included in the denominator of risk estimates, the risk ratio is (3/108)/(2/117) = 1.62 and risk difference is 10/1000 month-1 , i.e. underestimated.

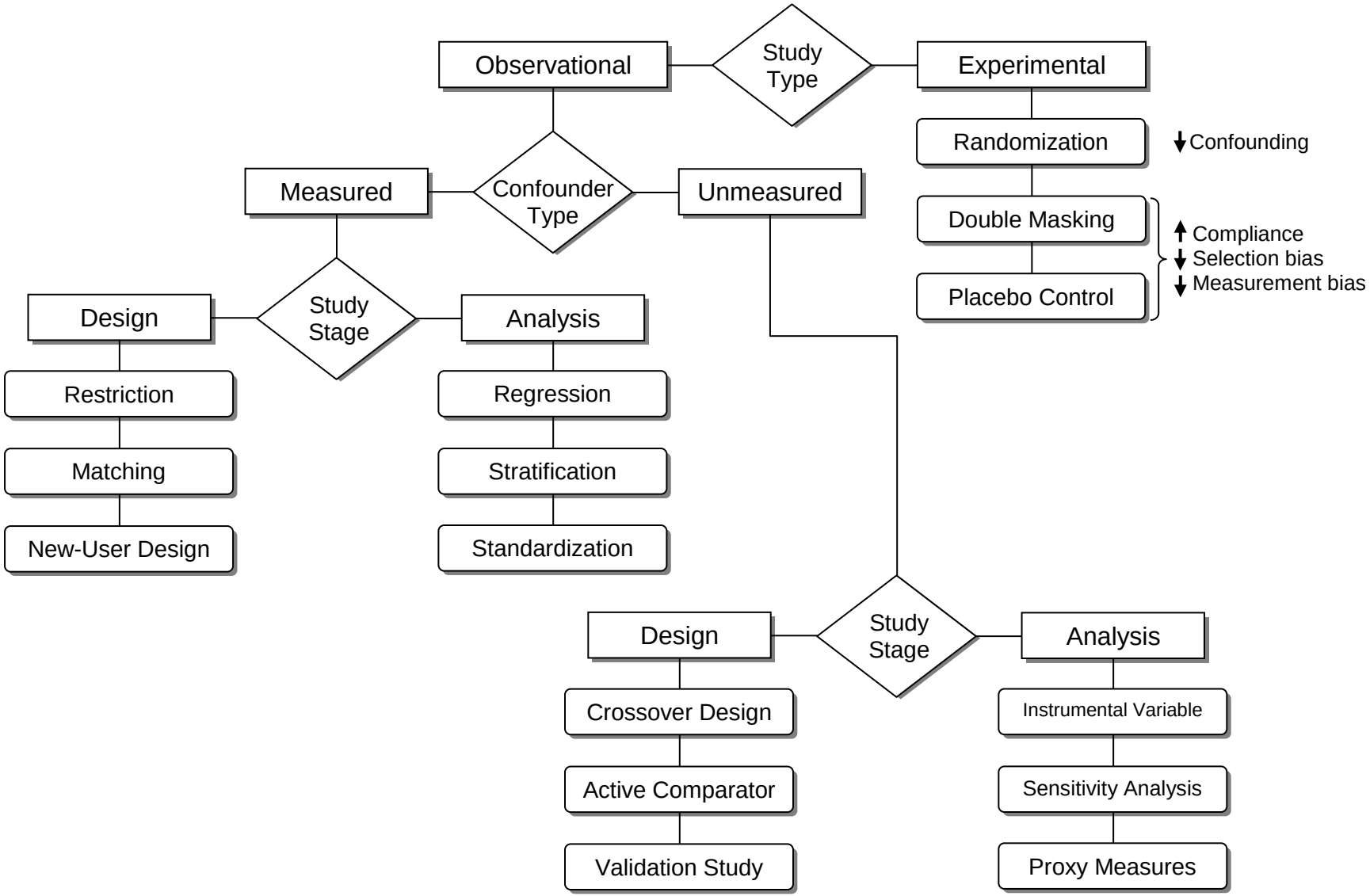


Figure 2-10. Pharmacoepidemiologic approaches to account for bias and confounding

Patient	Time	Status	E	Z
1				
2				
3				
4				
5				
6				
7				
8				

Time: duration of time from the start of follow up until outcome occurrence or last observation (i.e. censoring).

Status: patient status at the recorded time, whether the patient experienced the outcome (1), or was censored (0).

E, Z: exposure and confounder values at the fixed observed time.

(A)

Patient	Start	Stop	Status	E	Z	V
1						
1						
1						
1						
1						
2						
2						
2						

Start, Stop: interval of time (start, stop] in which the status of the patient was observed.

V: time-dependent variable

Multiple records per patient.

(B)

Patient	Time	Status	Time1	Time2	E1	E2	V1	V2	Z
1									
2									
3									
4									
5									
6									
7									
8									

One record per patient.

(C)

Figure 2-11. Data structure for Cox proportional hazards model, A) with fixed covariates, B) time-dependent covariates counting process method and C) time-dependent covariates programming statements method.

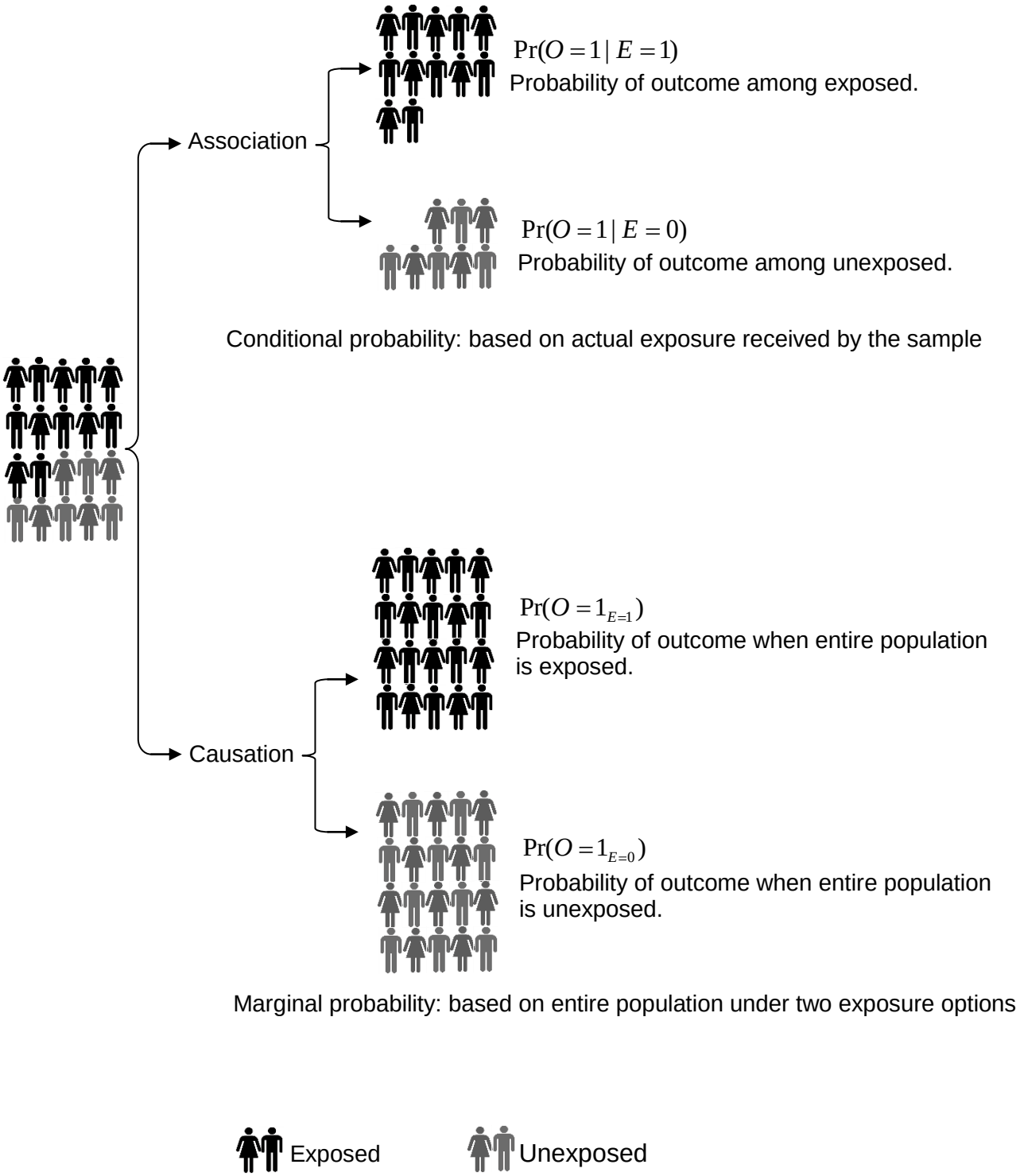
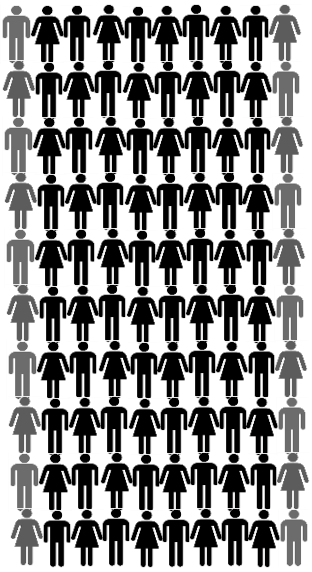


Figure 2-12. Illustration of association versus causation in pharmacoepidemiology

Exposed to treatment ($E = 1$)
n=80

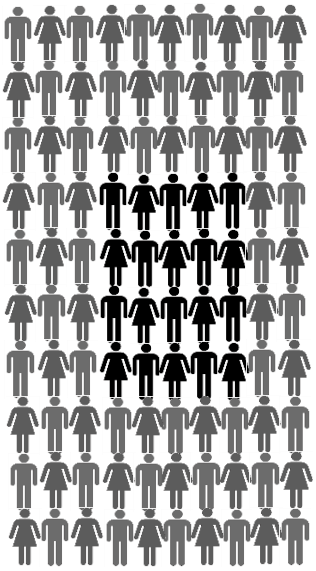


i. $PS = \Pr(E = 1 \mid Z) = 0.8$

ii. $IPTW = \frac{1}{\Pr(E = 1 \mid Z)} = 1.25$

iii. $N = IPTW * n = 100$

Unexposed to treatment ($E = 0$)
n=20



i. $PS = \Pr(E = 0 \mid Z) = 0.2$

ii. $IPTW = \frac{1}{\Pr(E = 0 \mid Z)} = 5$

iii. $N = IPTW * n = 100$

Probability of exposed given  = 0.5 & Probability of unexposed given  = 0.5

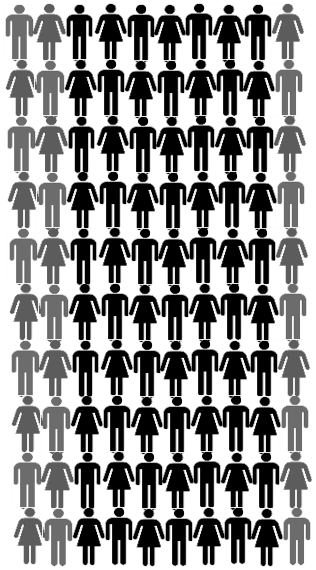
Where  in one group is the counterfactual for  in the other group

Every patient has 50% probability of being a member of an exposure group

(A)

Figure 2-13. Illustration of attaining quasi-randomization by virtue of marginal structural models in a hypothetical population of size N=100 with A) binary exposure and B) multicategory exposure situations. PS, propensity score; IPTW, inverse probability of treatment weighted.

Exposed to treatment A ($E = 1$)
n=70

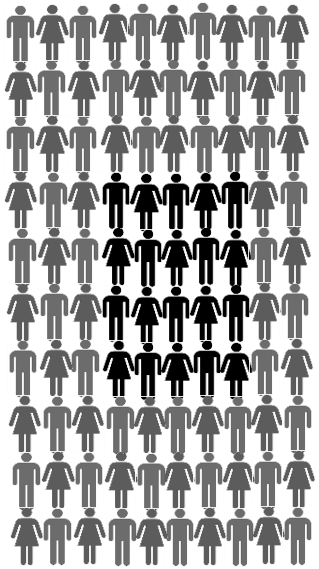


i. $PS = \Pr(E = 1 \mid Z) = 0.7$

ii. $IPTW = \frac{1}{\Pr(E = 1 \mid Z)} = 1.43$

iii. $N = IPTW * n = 100$

Exposed to treatment B ($E = 2$)
n=20

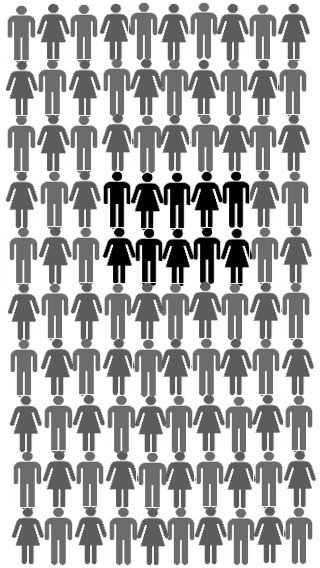


i. $PS = \Pr(E = 2 \mid Z) = 0.2$

ii. $IPTW = \frac{1}{\Pr(E = 2 \mid Z)} = 5$

iii. $N = IPTW * n = 100$

Exposed to treatment C ($E = 3$)
n=10



i. $PS = \Pr(E = 3 \mid Z) = 0.1$

ii. $IPTW = \frac{1}{\Pr(E = 3 \mid Z)} = 10$

iii. $N = IPTW * n = 100$

Probability of exposure to A given  = 0.5, probability of exposure to B given  = 0.5
& probability of exposure to C given  = 0.5

(B)

Figure 2-13. Continued.

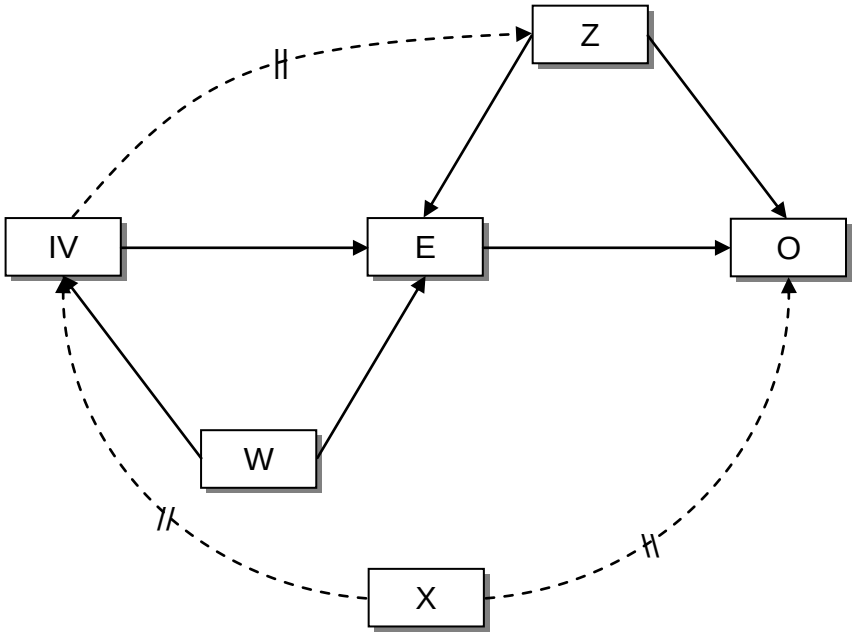


Figure 2-14. Characteristics of an instrumental variable

CHAPTER 3
STUDY AIMS AND SIGNIFICANCE

Study Objective

The broad objective of this study is to assess asthma-related morbidity and mortality in patients exposed to inhaled LABA bronchodilators, as monotherapy, and ICS combination therapy (i.e. ICS/LABA) in the United Kingdom's General Practice Research Database (GPRD) (Figure 3-1).

Research Questions, Specific Aims, and Hypotheses

This study is aimed to answer the following research questions, and to test the corresponding hypotheses:

Research Question No. 1

Is there a difference in the incidence of asthma morbidity in terms of asthma-related accident and emergency (A&E) department visits, asthma-related hospitalizations, and prescribing oral corticosteroids between asthmatic patients exposed to inhaled LABA monotherapy, ICS monotherapy, and ICS/LABA combination therapy in the UK GPRD?

Specific aim no. 1

To examine the association between ICS/LABA combination therapy and asthma morbidity rates compared with inhaled LABA monotherapy, and ICS monotherapy in asthmatic patients in the GPRD.

Hypothesis no. 1

The null hypothesis states that there is no difference in asthma morbidity rates—measured by hazard ratios—between ICS/LABA combination therapy, inhaled LABA monotherapy, and ICS monotherapy in asthmatic patients in the GPRD.

$H_{0A}: HR = 1 \, for$ LABA compared with ICS

$H_{0B}: HR = 1 \, for$ ICS/LABA compared with ICS

$H_{0C}: HR = 1 \, for$ ICS/LABA compared with LABA

The alternative hypothesis states that there is a difference in asthma morbidity rates between ICS/LABA combination therapy, inhaled LABA monotherapy, and ICS monotherapy in asthmatic patients in the GPRD.

$H_{1A}: HR \neq 1 \, for$ LABA compared with ICS

$H_{1B}: HR \neq 1 \, for$ ICS/LABA compared with ICS

$H_{1C}: HR \neq 1 \, for$ ICS/LABA compared with LABA

The null and alternative hypotheses are the same for individual measures of asthma morbidity: A&E department visits for asthma, hospitalizations for asthma, and prescriptions for oral corticosteroids.

Research Question No. 2

Is there a difference in the incidence of asthma deaths between asthmatic patients exposed to inhaled LABA monotherapy, ICS monotherapy, and ICS/LABA combination therapy in the UK GPRD?

Specific aim no. 2

To examine the association between ICS/LABA combination therapy and asthma death rates compared with inhaled LABA monotherapy, and ICS monotherapy in asthmatic patients in the GPRD.

Hypothesis no. 2

The null hypothesis states that there is no difference in asthma death rates between ICS/LABA combination therapy, inhaled LABA monotherapy, and ICS monotherapy in asthmatic patients in the GPRD.

$H_{0A}: HR = 1 \, for$ LABA compared with ICS

$H_{0B}: HR = 1 \, for$ ICS/LABA compared with ICS

$H_{0C}: HR = 1 \, for$ ICS/LABA compared with LABA

The alternative hypothesis states that there is a difference in asthma death rates between ICS/LABA combination therapy, inhaled LABA monotherapy, and ICS monotherapy in asthmatic patients in the GPRD.

$H_{1A}: HR \neq 1 \, for$ LABA compared with ICS

$H_{1B}: HR \neq 1 \, for$ ICS/LABA compared with ICS

$H_{1C}: HR \neq 1 \, for$ ICS/LABA compared with LABA

Research Question No. 3

In asthmatic patients who were exposed to ICS/LABA combination therapy, is there a difference in the incidence of asthma morbidity in terms of asthma-related A&E department visits, asthma-related hospitalizations, and prescribing oral corticosteroids between step-down therapy approaches represented by LABA discontinuation and ICS dose reduction, and continual of original ICS/LABA combination therapy in the UK GPRD?

Specific aim no. 3

To examine the association between ICS/LABA combination therapy and asthma morbidity rates compared with 50% reduced ICS dose in ICS/LABA combination

therapy, and ICS monotherapy due to LABA discontinuation in a subgroup of asthmatic patients who were exposed to ICS/LABA combination therapy for a minimum of 3 months in the GPRD.

Hypothesis no. 3

The null hypothesis states that there is no difference in asthma morbidity rates between ICS/LABA combination therapy (continuers), 50% ICS dose reduced ICS/LABA combination therapy (reducers), and ICS monotherapy (LABA stoppers) in asthmatic patients in the GPRD.

$H_{0A}: HR = 1 \, for$ ICS/LABA 50% reduced ICS dose vs. ICS/LABA original ICS dose

$H_{0B}: HR = 1 \, for$ ICS (LABA stoppers) vs. ICS/LABA original ICS dose incessant

$H_{0C}: HR = 1 \, for$ ICS/LABA 50% ICS dose reducers vs. ICS (LABA stoppers)

The alternative hypothesis states that there is a difference in asthma morbidity rates between ICS/LABA combination therapy continuers, reducers, and LABA stoppers in asthmatic patients in the GPRD.

$H_{1A}: HR \neq 1 \, for$ ICS/LABA reducers vs. ICS/LABA continuers

$H_{1B}: HR \neq 1 \, for$ LABA stoppers vs. ICS/LABA continuers

$H_{1C}: HR \neq 1 \, for$ ICS/LABA reducers vs. LABA stoppers

The null and alternative hypotheses are the same for individual measures of asthma morbidity: A&E department visits for asthma, hospitalizations for asthma, and prescriptions for oral corticosteroids.

Rationale and Significance

The aforementioned specific aims will be achieved by virtue of the application of analytical techniques to account for the time-dependent nature of the variables in real-

life practice settings. The findings will enable us to make “semi-causal” interpretations of the associations between LABA products and asthma related outcomes, and draw informed conclusions regarding the safety profile of inhaled LABA bronchodilators in asthmatic patients. Therefore, the study will serve as a complement to the forthcoming findings from the ongoing clinical trials that are commissioned by the FDA to investigate the effects of LABA discontinuation or ICS/LABA combination therapy on asthma control. The conclusions will inform healthcare professionals, contribute to improved patient care, and further the development of asthma management guidelines.

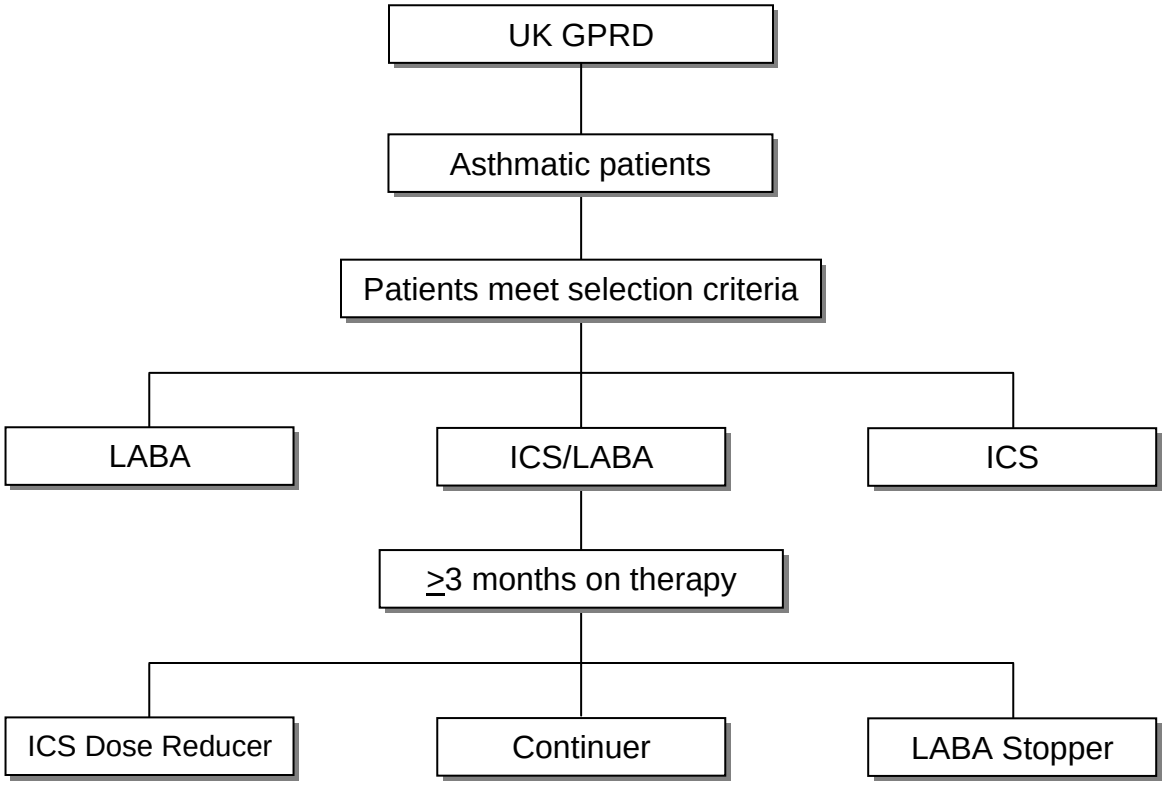


Figure 3-1. Study profile. ICS, inhaled corticosteroids; LABA, long-acting beta-agonists

CHAPTER 4
METHODS

Research Ethics

This research study was reviewed by the Gainesville Health Science Center-Institutional Review Board (IRB) at the University of Florida on July 16, 2007 under protocol number H-311-2007, and the Independent Scientific Advisory Committee (ISAC) of the GPRD on March 22, 2010 under protocol number 10_040R. The research study was approved in writing by the IRB on July 31, 2007 and by the ISAC on June 8, 2010.

Study Type and Design

This study is a population-based retrospective cohort new-user design (inception or incidence cohort) aimed at testing a formal research hypothesis in adherence to the International Society for Pharmacoepidemiology (ISPE) guidelines for good pharmacoepidemiology practices (GPP) (ISPE, 2008), and according to the recommendations from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Research Practices for Comparative Effectiveness Research (Berger, Mamdani, Atkins, & Johnson, 2009; Cox, Martin, Van Staa, Garbe, Siebert, & Johnson, 2009; Johnson et al., 2009). Novel design approaches and advanced statistical analysis methods of causal inference will be applied to account for the limitations in observational designs discussed in chapter 1.

Data Source

The United Kingdom's (UK) General Practice Research Database (GPRD), the UK's Office for National Statistics (ONS) Mortality Data, and the Index of Multiple

Deprivation (IMD) scores are utilized for this study (GPRD, 2011a; Khan, Perera, Harper, & Rose, 2010; NHS, 2010).

The General Practice Research Database (GPRD)

The GPRD is the world's largest database of longitudinal anonymized electronic medical records from public primary healthcare practices in the UK (Wood & Coulson, 2001). The GPRD is a not-for-profit research database that was established in 1987 for the purpose of pharmacoepidemiology and multidisciplinary public health research under the management of the UK's MHRA (Wood & Martinez, 2004). In the UK, general practitioners are the gatekeepers for primary healthcare and referrals. Around 595 participating general practices located throughout the UK, including England, Scotland, Wales, and Northern Ireland, are included in the database with incrementally collected clinical records for approximately 12 million patients from birth to death (GPRD, 2011a). Data collected from participating general practitioners for the GPRD include patient demographics and practice registration details; medical diagnosis, treatment and immunization details; treatment outcomes; patient lifestyle factors; referral details to hospitals or specialties; laboratory tests; and consultation information (Wood & Martinez, 2004). The quality of data in the GPRD is controlled at both patient and practice levels, and specific level-based criteria are required to be met in order to consider the data as apposite for research purposes (Davis, Rietbrock, Rubino, Shah, Williams, & Martinez, 2003). Patient acceptable registration status, demographics, and event recordings are used to consider patients as 'acceptable' for the GPRD research purpose; practice-level criteria include a standard set of conditions related to practice details that are used to derive the Up-to-Standard (UTS) date for each registered

practice in the GPRD. The UTS date is the first date at which the collected data from the individual practice are considered eligible for recording in the GPRD (Wood & Martinez, 2004). As of April 2011, 626 UTS general practices are registered within the GPRD with longitudinal research data for a total of acceptable 11.26 million patients (GPRD, 2011d). The GPRD is a prominent entity in the UK that is active in defining standards and procedures for data quality improvement in primary care. The GPRD subsidizes general practices to facilitate data extraction process; and practices receive feedback concerning data quality from GPRD based on analyses of received practice data (DH, RCGP, & BMA, 2011).

The comprehensiveness, quality, and size of the data make the GPRD a unique tool for population-based longitudinal research designs in pharmacoepidemiology, pharmacovigilance, and outcomes research. In the EU, the GPRD is the most extensively used database in pharmacoepidemiological research (Garcia-Rodríguez & Gutthann, 1998). In addition, the validity of the database for epidemiological research in respiratory system and research in drug safety has been established (Jick, H., Jick, S., & Derby, 1991; Jick, H., Terris, Derby, & Jick, S., 1992; Hansell, Hollowell, Nichols, McNiece, & Strachan, 1999; Soriano, Maier, Visick, & Pride, 2001; Jick, S. et al., 2003). Besides, recording of deaths in the GPRD is complete and consistent with national statistical figures (Meier & Jick, 1997), and the quality of morbidity data for public health and policy research has been evaluated and established (Hollowell, 1997). Furthermore, because prescribers are more motivated to record information pertinent to their patients, the information in medical records database like the GPRD is relatively more accurate and complete in comparison to other types of databases, e.g.

administrative claims database (Jick, S., 2010). Also, it is estimated that about 80% of asthmatic patients in the UK are seen by general practitioners (Vermeire, Rabe, Soriano, & Maier, 2002). All these characteristics make the GPRD an efficient source for the present study topic.

The Office for National Statistics (ONS) Mortality Data

The GPRD is electronically linked to other National Health Service (NHS) databases in an anonymized manner. Currently, the GPRD is linked to a subset of hospitalization records through the Hospital Episode Statistics (HES) database, and death data through the Office for National Statistics (ONS) mortality data. Some disease registries and other census data are also linked to the GPRD (GPRD, 2011b). Deaths registered before January 1, 2001 have the original underlying cause of death and all cause of death mentions coded in the 9th version of the International Classification of Diseases (ICD-9), while deaths registered since January 1, 2001 are coded in the 10th version of the ICD (ICD-10) system (NHS, 2011a). All the mortality records in the current study are registered after January 1, 2001 (until October 20, 2009). The mortality data are for patients in the cohort who are affiliated with the general practices that are participated in the GPRD linkage scheme. This is a subset of the GPRD practices, all in England. Data from 224 of 472 English practices are available. Each practice consents to have their data linked via an external independent third party to external data sources, such as the ONS mortality data for research purposes (Susan Eaton, GPRD, personal communication, September 13, 2010).

The Index of Multiple Deprivation (IMD) Scores

The IMD scores are generated at the practice level, which was provided by the GPRD as a linked dataset of the scores that are categorized into quintiles based on the distribution of the scores within specific UK countries (Khan, Perera, Harper, & Rose, 2010). The scores are constructed by Noble et al. (2000) at Oxford University as a measure of socioeconomic status, which reflects such status based on general practice postcodes. The scores are assigned to each patient at the general practice level and used as a proxy measure for socioeconomic status. The score is calculated differently for each of the four countries of the UK (England, Scotland, Wales, and Northern Ireland). A high score (80) and a high rank (4) indicates the most deprived area. A low score (1) and a low rank (0) indicates the least deprived area (McLennan, Barnes, Noble, Davies, Garratt, & Dibbon, 2011). Most deprived areas correspond to high socioeconomic standings, and the reverse is true for the least deprived areas. These scores were requested from the GPRD, and were not duly supplied; at the meantime, other proxy measures are used to reflect patient's socioeconomic status (patient characteristics section).

Study Population

Patients with asthma who are continuously registered with UTS general practices within the GPRD are identified and randomly selected by GPRD research liaison according to the following selection criteria. Asthma patients were identified using specific Read Clinical Terms, version 3 that are used by the GP to record the diagnosis and follow up for each patient. The GPRD translates Read Clinical Terms to Medical Codes in individual GPRD datasets, which are more user-friendly in data management

process. Asthma diagnosis was defined as having a Medical Code record for asthma in the clinical, referral, or test datasets of the database before the index date of first prescription for the exposure of interest, or during the maximum follow up duration of the study (12 months post index date). The GPRD provides the practitioners with specific guidelines on how to record diagnoses and other clinical and therapeutic events using a specific general practice management software system called Vision (GPRD, 2004).

The following selection criteria are applied to the identified asthmatic patients in the GPRD to construct the exposure cohorts of interest:

Inclusion Criteria

- Patients with records acceptable for research (acceptable patients) who are registered with the UTS general practices in the GPRD during the study period.
- Both male and female sexes.
- All race and ethnic groups.
- Patients aged 13-65 years at index date. Current asthma management guidelines define adult asthmatics as aged greater than 12 years old (BTS, 2009); the prevalence of chronic obstructive pulmonary disease (COPD) is more pronounced in the elderly, particularly those older than 55 (NHLBI, 2003), with higher prevalence among patients older than 60 years of age (GOLD, 2010); and differential diagnosis of asthma from other respiratory disorders is more accurate in individuals aged 5-45 than other age groups (Williams et al., 1998). Nevertheless, including nonsmoker patients aged 40-65 years diminishes asthma misclassification as COPD (Morales, Jackson, Fielding, & Guthrie, 2012).
- Patients with first ever therapy event (prescription) record for one of the study drug classes recorded in the therapy dataset of the database: inhaled LABA, ICS, or both (ICS/LABA). The event date associated with the first prescription will be the index date for the study. For those patients who have both drugs prescribed, the earliest of the first events will be the index date. Therapy events are recorded in the therapy dataset of the GPRD by virtue of the Product Codes.
- Patients with at least two prescriptions for the study drugs in the first 6 months after the index date of first ever prescription.

- Patients with at least 18 months of follow up data prior to the index date are available.

- Patients with at least 12 months of follow up data after the index date are available. This criterion will introduce immortal person-time of 12 months, which will induce measurement bias if not accounted for in the assessment of asthma mortality outcome (specific aim no. 1). Nevertheless, the bias will not be introduced in the assessment of asthma morbidity outcome (specific aims no. 2 and 3); however, this selection criterion might invoke selection bias due to informative censoring. The accounting approach for both issues is discussed in detail in the cohort definition sections that are pertinent to the specific aims of the study.

Exclusion Criteria

- Patients with diagnosis Read Clinical Terms and Medical Codes as medical event records for the following respiratory conditions in the clinical, referral, or test datasets of the database, and Product Codes in the therapy dataset during the baseline year and the follow up year of the study:

1. Chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.

2. Diagnostic and therapeutic respiratory procedures, excluding lung function tests.

3. Lung transplantation, with or without heart.

4. Lung lobectomy.

5. Pneumopathies due to exposure to fumes and chemicals, including occupational lung diseases and pneumoconiosis.

6. Chronic tuberculosis, including respiratory tuberculosis and prescriptions for anti-tuberculosis agents.

7. Bronchopulmonary aspergillosis, including prescriptions for antifungals for aspergillosis.

8. Pneumocystis pneumonia, including prescriptions for anti-pneumocystis pneumonia agents.

9. Respiratory neoplasm, including benign and malignant.

10. Cystic fibrosis.

11. Interstitial (parenchymal) lung disease.

12. Obstructive sleep apnea, including nocturnal dyspnea.

13. Bronchiectasis and atelectasis.

14. Pulmonary hypertension, embolism and edema.

15. Respiratory obstruction by foreign objects.

16. Congenital and structural anomalies of the respiratory system.

17. Congenital heart disease.

18. Congestive heart failure.

19. Pulmonary valvular heart disease.

20. Unspecified and other respiratory diseases, including injuries to the respiratory tract.

- Patients with prescriptions for single-device combination inhaled SABA and muscarinic receptor antagonists (MRA), including ipratropium, oxitropium, tiotropium. Inhaled MRA products are more likely prescribed to patients with COPD than those with asthma (McIvor, Tunks, & Todd, 2011).

- Patients with prescriptions for single-device combination inhaled SABA/ICS, and single-device combination inhaled SABA and mast cell stabilizer (MCS).

- Patients who are current smokers or with a history for smoking. Smoking is associated with COPD, worsens asthma outcomes, and diminishes the response to ICS (Boulet, 2009). Middle age individuals (>40 years old) who are chronic smokers are more likely to develop COPD than nonsmoker counterparts (GOLD, 2010). Patients with prescriptions for smoking cessation therapy are considered current smokers.

- Patients with prescriptions for non-selective beta-adrenoceptor blockers, including ophthalmic formulations and combination antihypertensive products ever recorded during the study period.

- Patients with prescriptions for allergen immunotherapy vaccination.

- Patients with prescriptions for inhaled betamethasone for lack of dosage bioequivalence information to account for ICS strength.

- Patients with prescriptions for the anti-IgE, omalizumab since only one patient was prescribed omalizumab.

- Patients with Read Clinical Terms and corresponding Medical Codes identifying participation in a clinical study, including asthma research.

- Patients with Read Clinical Terms and Medical Codes identifying the use of illicit drugs.
- Patients with indeterminate sex.

Study Duration and Selection of Comparison Groups

Asthma management guidelines were first introduced in the UK in January 1, 1993 (BTS, 1993). The event date associated with the first prescription for the study drug after January 1, 1993 is defined as the index date for the study. Three distinct index dates are defined for the three specific aims, and are discussed below. Study outcomes will be measured during the study follow up period of 12 months post index date (follow up year). The LABA group includes first-user patients to whom a prescription for a LABA inhaler was written; the ICS group includes first-user patients to whom a prescription for an ICS was written; and the ICS/LABA group includes first-users to whom a prescription for either a single-device combination ICS/LABA product was prescribed, or a prescription for separate ICS and LABA inhalers that were written in a single prescription on the same date.

Identified exposure cohorts will be retrospectively followed from the relevant study index date until the end of the follow up year, latest GPRD data recording, patient death, patient transfer out of the general practice, or development of the outcome of interest, whichever date comes first. Besides, patient follow up is continued upon exposure switching to examine the time-varying nature of exposures. Exposure switching is permitted in study aims 1 and 2, and is considered a censoring criterion for study aim 3. When patients switch from one exposure to another, they will contribute exposure person-time to each exposure group during the relevant exposure time-window. To illustrate, a patient who was prescribed an inhaled LABA at the first visit $t = (0-1]$, then

prescribed an ICS at the second visit $t = (1-2]$; she is considered a member of the LABA group during the period between the first visit and the second visit $t = (0-1]$, then a member of the ICS group during the period between the second visit and the subsequent visit $t = (1-2]$, and so on. If she were prescribed an ICS in addition to an inhaled LABA at the second visit, she will be considered a member of the ICS/LABA group during the period from the second visit until the succeeding one $t = (1-2]$. The stepping up or stepping down therapy approach is part of asthma management, and it is partly contributed by the underlying severity and the level of symptomatic control of the disease. Thus, patients could switch from one drug to another based upon their disease severity. However, the statistical approach will account for time-varying exposure and time-dependent confounding that is affected by exposure history.

Exposure Measurement

Study exposures are identified using the Multilex Product Dictionary, which provide GPRD Product Codes and British National Formulary (BNF) Codes. Product Codes reflect product name, active ingredient(s), dosage strength, and dosage formulation (GPRD, 2011c); the BNF Codes reflect the BNF chapter under which the relevant product/drug class is classified (GPRD, 2011c).The GPRD Product Browser tool, Version 1.3.2 (Multilex coding information: August 4, 2011) is utilized to retrieve Product and BNF Codes for study drugs. Inhaled LABA group includes formoterol fumarate, formoterol fumarate dihydrate, and salmeterol xinafoate; ICS group includes beclometasone dipropionate, budesonide, ciclesonide, fluticasone propionate, and mometasone furoate; and single-device combination ICS/LABA group includes budesonide/formoterol fumarate dihydrate, and fluticasone propionate/salmeterol

xinafoate. The ICS/LABA group is defined by the prescription of a single-device combination formulation, or the addition of LABA or ICS as a separate device formulation to a respective ICS or LABA monotherapy.

Exposure to drugs of interest is defined on a monthly basis by virtue of prescription information recorded in the therapy dataset of the GPRD. The patient is considered exposed to the drug of interest when (1) she receives a prescription for that drug in that specific month, or (2) the anticipated end date of the previous prescription exceeds half (>15 days) of that specific month. If neither of these conditions are met, the patient is not considered exposed to the drug of interest at that specific month.

Contingent on the three study specific aims, the following exposure cohort definitions are proposed in an attempt to account for selection and measurement biases that might otherwise arise:

Cohort definition for specific aim no. 1 (morbidity outcome)

For estimating the effect of exposures on asthma morbidity outcomes, patients who were prescribed study drugs are followed for 12 months from the date of the first prescription (index date, month 0), until observing study outcomes or reaching previously discussed censoring criteria (Figure 4-1). Time-dependent confounders and outcome variables are measured during the post-index date follow up year (month 0 to month +12). Baseline, time-independent confounders are measured at the index date and the 12 months preceding period—baseline year (month 0 to -12). The exposure definition in this cohort produces an inception cohort with ICS, inhaled LABA, and ICS/LABA combination therapy initiators, i.e. incident users.

As previously explained, a 12-month immortal person-time was introduced during cohort structure, and although this criterion doesn't directly influence morbidity outcomes, it however might introduce selection bias due to informative censoring, mainly because most of asthma deaths are found to occur before hospitalizations (BTS, 2009) (page 37). To account for this bias and to serve as a sensitivity analysis, the follow up profile for the mortality outcome in the specific aim number 2 was applied to the morbidity outcome in the first specific aim of the study (Figure 4-2).

Cohort definition for specific aim no. 2 (mortality outcome)

Immortal-person time of ≥12 months after the first prescription was introduced during exposure definition and patient selection process (Figure 4-2). To estimate the effect of exposures on asthma mortality outcome, patient follow up (index date, month +12) is started from 12 months after the first prescription and continued for an additional 12 months after the corresponding index date (follow up year) until observing the outcome or reaching any of the censoring criteria mentioned above. Time-dependent confounders and outcome variables are measured during the post index date follow up period of ≥12 months—follow up year (month +12 to +24). Baseline, time-independent confounders are measured at the index date and the 12 months preceding period—baseline year (month 0 to +12). The exposure definition in this cohort produces a prevalence cohort with ICS, inhaled LABA, and ICS/LABA combination therapy prevalent users.

The degree of influence of the immortal-time bias on the point estimate is contingent on the length of the immortal person-time window and the incidence rate for asthma deaths in that window (Zhou, Rahme, Abrahamowicz, & Pilote, 2005). In the

current study, the immortal-person time window is relatively narrow for an outcome which is multifactorial in reason, e.g. asthma severity and patient's behavioral and psychosocial factors (BTS, 2009); if these factors are accounted for at baseline, the magnitude of the bias on asthma deaths is expected to be small in this cohort of incident users who survived for 12 months post first use of LABA or ICS products. Nevertheless, the bias is addressed in the follow up profile discussed above (Figure 4-2).

Per earlier discussion in the methodological challenges section, including prevalent users could induce selection bias, which can be minimized by restricting follow up to those patients who were not exposed to the drug of interest for a period of time, then became exposed after the end of the specific period, when they will be considered drug initiators after being unexposed. Figure 4-3 illustrates the proposed approach that will be used as a sensitivity analysis to previous approach, which will be employed in future work. The effect of exposures on asthma mortality outcome is assessed by following patients for a maximum of 12 months after the index date of (1) 12 months after the first prescription for study drugs (index date, month +12), and (2) 3 months exposure-free period preceding the index date (month +9 to +12), until observing the outcome of interest or reaching any of the censoring criteria stated above. The exposure-free period is defined as the duration of time in which patients exposed to one exposure group (e.g. ICS) are switched to another exposure group (e.g. LABA or ICS/LABA) at the beginning of the exposure-free period (month +9) and continued on the new regimen for three months, then switched back to the penultimate group (ICS) at the end of the exposure-free period (month +12), at which patients are deemed re-initiators of ICS. The same

scenario is applied to the LABA and ICS/LABA groups. Similar to earlier approach, time-dependent confounders and outcome variables are measured during the post index date follow up period of ≥12 months (month +12 to +24), and baseline, time-independent confounders are measured at the index date and the 12 months preceding period (month 0 to +12).

A 3-month period is used in tandem with recommendations from asthma therapeutic guidelines to monitor patients for a minimum of 3 months to evaluate therapeutic response and disease control (NHLBI, 2007; GINA, 2009). Therefore, the immortal-person 12-month period is relatively short to have medication switching among incident users, and such patients are deemed quasi-incident users. Accordingly, the magnitude of the selection bias introduced by the quasi-incident users will be minuscule, and the presented method will serve as a sensitivity analysis to assess this bias. In both scenarios, treatment switching as time-dependent exposure is allowed after index date to fit the proposed analytical models.

Cohort definition for specific aim no. 3 (subgroup morbidity outcome)

To examine the effect of step-down therapy approaches and continuing combination therapy on asthma morbidity, a subgroup of asthmatic patients who meet the following criteria is followed (Figure 4-4):

- Initiators of ICS/LABA combination therapy who have their first prescription of ICS/LABA issued at the index date proposed in specific aim no. 1 (month 0).
- Continued exposure to ICS/LABA as single-device or separate-device combinations for a minimum of 3 months after the first prescription until divergence to the three exposure subgroups (month 0 to +3).
- The divergence point will be the study index date (month +3), at which patients are grouped to three exposure groups:

1. Reduction of the original ICS dose by half and maintenance of inhaled LABA (50%ICS/LABA—dose reducers).

2. Discontinuation of inhaled LABA and maintenance of ICS monotherapy original dose (ICS—LABA stoppers).

3. Maintenance of ICS/LABA combination therapy with original ICS dose (Original ICS/LABA—Incessant).

- Have evidence of asthma control during the immortal person-time period (month 0 to +3) defined by the absence of prescription records for oral corticosteroids, and absence of event records for asthma-related A&E department visits or asthma-related hospitalizations. If this criterion reduces the sample size, these variables will be accounted for as baseline time-independent covariates during the stated period to maintain statistical efficiency.

Patients will be followed for 12 months from index date (month +3 to +15) until observing the outcome of interest or reaching censoring criteria stated above in addition to switching exposure to another exposure category. Thus, exposure switching between the three groups is not permitted as a time-dependent exposure, where patients might step-up therapy from LABA discontinuation to ICS add-on therapy (i.e. ICS/LABA) or from ICS dose reduction to ICS dose escalation.

Time-dependent confounders and outcome variables are measured during the post index date follow up year (month +3 to +15), and the time-independent confounders are measured at the index date and the 3 months prior period (month 0 to +3).

ICS dose quantification. The average daily dose of ICS is calculated from prescribed product strength and usage instructions recorded in the therapy dataset of the database. Exposure group classification according to ICS dosage is based on the estimated equipotent daily doses of ICS according to GINA recommendations in Table 4-1 (GINA, 2009), where the higher-strength class is 50% of the medium-strength class, which is also 50% of the low-strength class. Accordingly, patients within the high- and the medium-strength ICS classes are considered original ICS dose continual

individuals, and when the high-strength class members switch to the medium-strength class and the medium-strength class members switch to the low-strength class, those patients are considered members of the dose reducer group. Table 4-2 lists the commercially available dosage strengths of ICS and ICS/LABA products in the UK.

Outcome Measurement

The outcomes of interest for the study are asthma-related mortality and asthma-related morbidity rates, which are measured during the follow up period after the specified index dates for the corresponding specific aims. Refer to cohort definition sections corresponding to mortality and morbidity outcomes for details on outcome follow up post index dates.

Mortality outcome

Asthma-related mortality is defined as asthma death and identified from the linked ONS Mortality Data, and from the GPRD clinical data files of the medical records. Asthma-related mortality is assessed in two methods. First, for patients who are in general practices that are linked with the ONS Mortality Data, the International Classification of Diseases, tenth version (ICD-10) is used to classify causes of death in the ONS Mortality Data. The following ICD-10 codes for asthma-related mortality are used to identify cases with causes of death that are asthma related: J45 for asthma; J45.0 for predominantly allergic asthma; J45.1 for non-allergic asthma; J45.8 for mixed asthma; J45.9 for unspecified asthma; and J46 for status asthmaticus (WHO, 2007). Non-neonatal causes of deaths are identified in the linked subset of mortality data. The ICD-10 codes in the ONS Mortality data are recorded without the decimal, e.g. J240

instead of J24.0, which are recorded in such manner for technical purposes (ONS, 2009).

The second method includes all general practices using the following algorithm, which involves using the GPRD Medical Browser tool, Version 1.3.2 (Read coding information: November 27, 2009) to extract Read Clinical Terms and corresponding Medical Codes that identify asthma-related codes in clinical, referral, and patient datasets within +/-21 days from the date of death (GPRD, 2011c). The 21-day period reflects the average lag in recording causes of death in medical records by the general practice (Tjeerd van Staa, GPRD, personal communication, May, 9, 2011). Identifying cause of death in the GPRD using this method is representative to the UK national death registry, where about 65% of causes of death retrieved from the GPRD records are found identical to national records (Shah & Martinez, 2004). A study validated asthma deaths in GPRD records versus death certificates, showed that 34 cases of the identified 77 asthma deaths were verified by death certificates (Lanes, Garcia Rodríguez & Huerta, 2002). Yet, the linked ONS mortality dataset improves the corroboration. The linked dataset method will be used as a sensitivity analysis to the records method.

Morbidity outcomes

Asthma-related morbidity reflects poor asthma control, and defined by asthma-related A&E department attendances, asthma-related hospitalizations, and prescriptions for oral corticosteroids (OCS), including short courses for the treatment of asthma exacerbations. The GPRD Medical Browser tool is used to identify relevant Medical Codes for Read Clinical Terms from clinical, consultation, and referral GPRD data files

to reflect asthma A&E visits and asthma hospitalizations. Prescriptions of oral corticosteroids are identified by the Product Codes from therapy datasets using the GPRD Product Browser tool. In addition, an algorithm was developed to identify prescriptions for short-courses of oral corticosteroids based on whether a prescription was part of a repeat schedule or a one-off prescription, where the latter is considered an indicator of a short-course corticosteroids regimen. This algorithm is used as a sensitivity analysis for outcome definition.

Covariate Measurement

Both GPRD Product and Medical Browsers are utilized to respectively identify Product and Medical Codes for the covariates of interest. Table 4-3 serves as a covariate definition exhibit. The following domains and corresponding variables are included in the analysis models as covariates that influence the relationship between study exposures and outcomes:

Patient characteristics

Patient characteristics at index date include the following demographic, behavioral, lifestyle, and socioeconomic factors: patient's age (13-65 years), sex (female; male), and marital status (unmarried; married; and unknown status); duration of registration with the practice, which is defined as the duration in months from registration date until the study index date; patient's exemption status for prescription payment (not exempted; exempted; and unknown status); patient's level of capitation supplement (low; medium; high; not applicable; and unknown status); and patient's baseline weight status, which is determined by a mixture of measures including Read clinical terms and calculated values of the Body Mass Index (BMI) in kg/m^2 categorized according to the

guidelines for the identification of individuals with weight problems (underweight, BMI<18.5, normal weight, BMI=18.5-24.9; overweight, BMI=25-29.9; obese, BMI=30+; and unknown weight status) (NIH, 1998), yet, weight status was classified into obese, non-obese, and unknown status in order to suppress categories with zero values in the non-obese class, which include normal weight, underweight, and overweight statuses. In addition, patient's smoking status at baseline (nonsmoker, former smoker, passive smoker, and unknown smoking status) is included as covariate after excluding patients who were active smokers during the study follow up. Noteworthy, lifestyle information including body weight and smoking are not consistently recorded in the GPRD (Garcia-Rodríguez & Gutthann, 1998), therefore the "unknown" category is added to corresponding variables.

Practice characteristics

There are differences in population demographics, healthcare service utilization, and levels of primary care capitation payment across the four countries of the UK (Rhys, Beerstecher, & Morgan, 2010). Therefore, practice location is included as a covariate (England; Scotland; Wales; Northern Ireland; and unknown location). In addition, consultation length has variable effect on physician's prescribing behavior. Duration of consultation is defined as the length of time in minutes between the opening and closing of the consultation record by the GP. In general, the average duration of consultation in the UK is 9.4 minutes (95%CI, 0.47-18.3) (Deveugele, Derese, van den Brink-Muinen, Bensing, & De Maeseneer, 2002). In another study, the mean duration varied according to patient satisfaction with the GP: highest satisfaction, 9.48 minutes (95%CI, 1.79-20.75); lowest satisfaction, 9.4 minutes (95%CI, 7.92-26.72) (Cape, 2002). Based on

these values, the length of consultation with the patient is categorized to ≤10 minutes and >10 minutes. Moreover, the urgency of patient's visit to the practice is used as a covariate (non-urgent visit; urgent visit; unknown status). Although the visits could be unrelated to asthma, unscheduled emergency visits might influence prescribing behavior.

Asthma severity

As previously discussed, confounding by disease severity and channeling bias are forms of confounding by indication that are commonly presented in chronic disease pharmacoepidemiology, and failure to account for baseline and time-varying severity of asthma could result in casual associations between the exposure of interest and worsened asthma outcomes (Nelson, 2006). The following measures are used to account for asthma severity at baseline and study follow up.

In addition to disease symptoms, spirometry and peak expiratory flow rates (PEFR) are the best measures of asthma severity (Ng, 2000; NHLBI, 2007; BTS, 2009; Kim & Mazza, 2011); however, spirometry information and patient reported outcomes, e.g. symptoms and PEFR are scarcely and inconsistently reported in the GPRD (Garcia-Rodríguez & Gutthann, 1998; Griffin, Lee, Caiado, Kesten, & Price, 2008). Therefore, other proxy measures of asthma severity are utilized, which are applied in similar observational designs (Meier & Jick, 1997; Lanes, Lanza, & Wentworth, 1998; Williams et al., 1998; Lanes, Garcia-Rodríguez, & Huerta, 2002; Anderson et al,, 2005; Blais, Beauchesne, & Forget, 2009; Thomas, von Ziegenweidt, Lee, & Price, 2009; de Vries, Setakis, Zhang, & van Staa, 2010; Guo, Tsai, Kelton, Bian, & Wigle, 2011; Wells, Peterson, Ahmedani, Severson, Gleason-Comstock, & Williams, 2012). Nevertheless,

these designs failed to account for the time-dependent nature of asthma severity, which are predicted by exposure history, and act as predictors of future exposure and outcomes. Although one study (Wells, Peterson, Ahmedani, Severson, Gleason-Comstock, & Williams, 2012) utilized Cox PHREG with SABA prescriptions as time-dependent covariate, the approach inadequately controlled for time-dependent confounding (Suarez, Borràs & Basagaña, 2011).

These measures consist of indicators of drug and healthcare utilization. Drug utilization measures include prescriptions for inhaled SABA; prescriptions for oral corticosteroids within 12 months prior to the index date (baseline year); number of prescriptions for inhaled SABA in the baseline year; and number of prescribed categories of asthma drugs at index date.

When combination products are prescribed in a single-device formulation, the prescription is deemed as for two asthma drug classes, where every ingredient serves as a separate pharmacological entity, e.g. inhaled ICS/LABA. Inhaled SABA and asthma drug category utilization are updated every month as time-dependent confounders in addition to their measurements in the baseline year. SABA utilization is measured as average daily doses of inhaled SABA (Thomas, von Ziegenweidt, Lee, & Price, 2009), and frequently categorized by the average number of canisters prescribed or dispensed (Suissa, Blais & Ernst, 1994), or by the number of refills in a specific time period (Wells, Peterson, Ahmedani, Severson, Gleason-Comstock, & Williams, 2012). The present study will include SABA utilization as a categorical measure that is updated in timely manner similar to the exposure of interest. This approach will minimize the

variation in calculating the average daily doses that are contingent upon the individual SABA product and estimated doses per actuations.

Healthcare utilization measures that reflect asthma severity include asthma-related hospitalization and A&E visits during the baseline year. Hospitalization due to asthma exacerbations in the preceding year predicts the risks for asthma exacerbations, hospitalizations, and asthma mortality in the future (NHLBI, 2007; Omachi, 2009).

Prescribing >2 classes of asthma medications, >2 prescriptions for oral corticosteroids, >6 prescriptions for inhaled SABA, and a hospitalization or an A&E visit for asthma in one year prior to exposure or one year prior to a worsened outcome are recognized risk factors for increased asthma morbidity and mortality (Lanes, Lanza & Wentworth, 1998; Williams et al., 1998; NHLBI, 2007; BTS, 2009; Blais, Beauchesne, & Forget, 2009; Wells, Peterson, Ahmedani, Severson, Gleason-Comstock, & Williams, 2012).

Patients with controlled asthma at baseline are defined as not having more than 2 asthma drug classes or any inhaled SABA as rescue bronchodilators prescribed at the index date, and not having any of the following during 12 months before the index date: prescriptions for oral corticosteroids, more than 6 prescriptions for inhaled SABA, or attending accident and emergency departments or hospitalizations for asthma. An indicator variable for asthma control is included as a covariate in baseline variable pool.

Concurrent asthma drug prescriptions

Concurrent prescriptions for the following asthma medication classes are included as covariates: inhaled SABA; oral leukotriene receptor antagonists (LTRA); oral sustained release methylxanithines; mast cell stabilizers (MCS); and inhaled muscarinic

receptor antagonists (MRA). Oral SABA, the 5-lipoxygenase inhibitor, zileuton; and the anti-IgE, omalizumab are not included as covariates. Oral SABA is not part of asthma treatment in the clinical guidelines, zileuton is not marketed in the UK, and there was only one patient who was prescribed omalizumab who was excluded from the sample.

Other concurrent prescriptions

Prescriptions for the following medication classes could act as effectiveness modifiers and might interfere with asthma outcomes; hence, are included as covariates in the analysis models: oral and parenteral antibiotics for respiratory tract infections (RTI); oral, parenteral and inhalational antivirals for RTI e.g. oseltamivir; nasally administered products, including nasal corticosteroids, nasal MCS, e.g. sodium cromoglicate, nasal antihistamines, and nasal decongestants; antitussives, including expectorants and opioid-based antitussives; selective beta-1-adrenoceptor blockers, including oral and ophthalmic formulations and combination antihypertensive products; all routes non-steroidal anti-inflammatory drugs (NSAIDs); oral and rectal aspirin; oral, rectal, and parenteral acetaminophen (paracetamol); all routes opioid analgesics, including nasal opioids and acetaminophen combination analgesics, excluding codeine-based antitussives, which are included in the antitussive covariate; and oral cholinergic agents, e.g. neostigmine bromide.

Although acetaminophen is not considered an NSAID, the epidemiological and clinical studies suggest an association between exposure to acetaminophen and worsened atopy, including wheezing and asthma (Beasley et al., 2011; McBride, 2011); however, there are arguments against these findings (Chang, Leung, Tam, & Kong,

2011). Therefore, acetaminophen is included as a covariate to account for any potential residual confounding.

Since ophthalmic cholinergic agents (miotics) have small systemic bioavailability, they are not included as covariates. Antihistamines have no effect on lung allergies compared to skin allergies, where loratadine blocked skin allergy but failed to show an effect on the lungs (Town & Holgate, 1990); therefore, they are not considered as covariates. However, nasally administered antihistamines, including combination with nasal corticosteroids are included as covariates because the route of administration might have an effect on triggering asthma exacerbation.

In addition, placebo-controlled clinical trials in asthmatic patients showed contradicting results for the effect of tumor necrosis factor-alpha (TNFα) antagonists, e.g. etanercept on asthma outcomes (Morjaria, Babu, Holgate, & Polosa, 2006; Berry, Brightling, Pavord, & Wardlaw, 2007; Holgate et al., 2011). Large scale studies with longer follow-up duration are recommended to fully understand the role of anti-TNFα in asthma control. In the current study, there were no prescriptions for anti-TNFα at the index date, and only 14 prescriptions during the study follow up. The effect of these agents on asthma remains a matter for future work.

Concomitant immunizations

Influenza vaccination protects against all-cause mortality in COPD patients (GOLD, 2010), and it is recommended in asthmatic patients older than 6 months of age to protect against flu-related complications of asthma (NHLBI, 2007). Pneumococcal polysaccharide vaccination is recommended in COPD patients 65 years and older (GOLD, 2010). However, in June 2008, the US Advisory Committee on Immunization

Practices (ACIP) advised healthcare providers to administer the vaccine to asthmatic adults aged 19-64 years (CDC, 2010, 2012). Immunization information at the time of prescribing study drugs is included as a covariate, which include: prescribed influenza vaccine, including nasal and parenteral preparations; pneumococcal polysaccharide vaccine; and other immunizations regardless of vaccine type.

Comorbid conditions

Various coexisting medication conditions are associated with asthma and could interfere with asthma control and therapy outcomes (Sherrill, Guerra, Bobadilla, & Barbee, 2003; Boulet, 2009; Bush & Zar, 2011). The following comorbid conditions are identified as covariates: atopy, respiratory tract infections (RTI), and psychosocial pathologies. Atopic conditions include allergic rhinosinusitis, allergic conjunctivitis, atopic dermatitis, psoriasis, respiratory allergies, and other allergic conditions, e.g. angioedema and food allergies. RTI include otitis media, pharyngolaryngitis, influenza, acute bronchitis, pneumonia, and other unspecified RTI. Psychosocial pathologies include anxiety, depression, affective personality disorders like schizophrenia and psychosis, and other conditions such as deliberate self-harm; suicidal ideation and attempts; alcohol and drug abuse; learning difficulties; employment, income, marital and legal problem; and social isolation. Psychological problems are further identified by prescriptions for tranquilizers, antidepressants, and antipsychotics. Psychosocial problems put asthmatic patients at risk of fatal or near-fatal asthma (NHLBI, 2007).

Gastroesophageal reflux disease (GERD) was not included as a covariate, since scientific evidence argues against the influence of GERD on asthma symptoms (DiMango et al., 2009), and studies showed that treating GERD with proton-pump

inhibitors had no effect on asthma control in children and adults with coexisting asthma and GERD (ACRC et al., 2009, 2012).

Other factors

The BTS asthma management guidelines were updated approximately eight times from 1993 to 2009 (BTS, 2011); and the Quality and Outcomes Framework (QOF) was implemented by the National Health Service (NHS) in April 1, 2004 as an annual incentive program that rewards general practitioners based on point indicators achieved by managing some chronic conditions, including asthma, in addition to other factors, e.g. level of practice organization; patient experience at the practice; and the availability of additional services that are offered at the practice, e.g. maternity and child health services (NHS, 2011b); it is known that changes in asthma severity are inter-seasonal, and asthma deaths are found to increase in July and August among patients younger than 45 years and in December and January among older patients in the UK (BTS, 2009). Therefore, the influence of seasonality on disease severity and changes in practice guidelines on disease management can be accounted by including calendar time in annual quarters as a covariate in the analyses. An annual quarter is defined as the quarter of the calendar year in which the prescription of study drug was issued, which will be measured at the index date and during the follow-up year, e.g. for a LABA prescription issued on February 12, 2005, and an ICS prescription issued on April 28, 2010, the corresponding quarters are QT1 and QT2, respectively (QT1: January-March; QT2: April-June; QT3: July-September; & QT4: October-December).

The presence of asthma personal management plan (also known as asthma action plan) for well-motivated patients plays a role in reducing asthma hospitalizations and

improving overall asthma control (Toelle & Ram, 2004), and motivating patients to maintain correct inhaler technique (Ovchinikova, Smith, & Bosnic-Anticevich, 2011). Patients without asthma action plans are four times at risk of hospitalization due to asthma attacks than counterparts with asthma action plans (Asthma UK, 2010). Read clinical term signifying the presence or absence of asthma action plans at index date is identified to represent this covariate (Plan unavailable; plan available; & unknown).

In addition, clinical terms reflecting the utilization of humidifying inhalational therapy (unavailable versus available), the level of patient's compliance with asthma medications (regardless of the medication type), and the level of general compliance (satisfactory; unsatisfactory; & unknown) are identified by relevant Read clinical terms and included as covariates at the study index date. No recommendation for humidifying inhalational therapy was made at the index date, thus, the variable is not included in the covariate pool.

The type of inhaler device used to deliver asthma medications into the lungs affects patient adherence, inhaler technique, and asthma clinical outcomes (Takizawa, 2009; Price et al., 2011a, 2011b); likewise, prescribing and utilizing a spacer device in addition to the inhaler product plays a role in patient adherence and subsequent asthma outcomes (Berger, 2009). Therefore, the following variables are included in the covariate pool: Prescription for a compact spacer or holding chamber device at the index date (not issued versus issued); prescription for a nebulizer at the index date (not issued versus issued); and device type at the index date, including pressurized metered-dose inhaler (pMDI); breath-actuated inhaler (BAI), e.g. aerosols; and dry powder inhaler (DPI), e.g. disks and capsules. This information is derived from the

prescribed exposure product and extracting relevant information from the BNF (www.bnf.org) or product's package insert, when available. When the ICS/LABA combination therapy is prescribed in two separate devices with two separate device types, the ICS device type is assigned to the category. Clinical judgment is used to compensate the combination device type with the anti-inflammatory agent, which is the mainstay of asthma therapy. The prescribed device types are classified according to the available formulations in the UK, and are categorized by the study drugs of interest: ICS (pMDI; BAI; & DPI); LABA (pMDI & DPI); & single-device ICS/LABA (pMDI & DPI). Note that BAI formulations are prescribed for ICS products, and in order to efficiently use the device type variable as a covariate across exposure categories, both the pMDI and BAI are merged to form a metered-dose inhaler category (MDI) that will be used as a value for the device type covariate at the index date (MDI versus DPI).

Sample Size and Power Calculations

Assuming similar number of patients in the three exposure groups and the samples are independently selected, the necessary sample sizes to detect the difference at two-sided significance level of (α=0.05) with at least 80% power are summarized in Table 4-4. The calculations did not account for MSM procedure, which permits exposure switching by default; therefore, the estimated sample size is an overestimation of the size required for the MSM.

Statistical Analysis Procedures

Statistical analyses and data presentations are performed using SAS software, Version 9.3 of the SAS System for Windows (2011 SAS Institute Inc., Cary, NC, USA), R software, Version 2.14.1 of the R Environment for Windows (2011 The R Foundation

for Statistical Computing, Vienna, Austria), and Microsoft Office Word software (2010 Microsoft Corporation, Redmond, WA, USA). Two-sided tests with alpha=0.05 a priori level of statistical significance are used throughout the analysis procedures.

Descriptive Statistics

Within each study specific aim, baseline characteristics of the three exposure groups are compared using standard univariate statistical methods. For categorical variables, χ^2 tests are performed to compare the three groups. Alternatively, Fisher's exact test is used to compare categorical variables when the expected frequencies of observations is smaller than 5 (Glantz, 2005). For continuous variables, one-way analysis of variance (ANOVA) is employed for comparing the groups. Categorical variables are described by proportions and respective 95% confidence intervals; means and corresponding standard deviations are reported for continuous variables.

Inferential Statistics

For every specific aim, three regression models are constructed and the unadjusted and adjusted estimates of association between exposure and outcomes are compared across the models. The models include conventional Cox PHREG, time-dependent covariate Cox PHREG, and MSM. In each model, the hazards ratio (HR) and the respective 95% confidence interval (CI) are calculated for the three comparison groups:

- LABA monotherapy vs. ICS monotherapy
- ICS/LABA combination therapy vs. ICS monotherapy
- ICS/LABA combination therapy vs. LABA monotherapy
- Among ICS/LABA combination therapy:

1. ICS dose reducers vs. ICS original dose continuers
2. ICS dose reducers vs. LABA stoppers
3. LABA stoppers vs. ICS original dose continuers

The incidence rates of study outcomes are compared across exposure groups and are calculated in terms of person-time at risk, which defined as the period of time in which the observed individuals are at risk of developing the outcome of interest (Waning & Montagne, 2001; Greenland & Rothman, 2008). The incidence rates are presented as the number of events per 1000 person-month for the four outcomes of interest in the respective study research questions: asthma-deaths, asthma-A&E visits, asthma-hospitalizations, and prescriptions for oral corticosteroids.

Conventional Cox PHREG model

Conventional Cox model doesn't allow testing for time-varying variables; the model in Equation 3-1 will evaluate the degree and extent of exposure association with the outcomes of interest by terminating patient follow up upon exposure switching in addition to other censoring criteria, and all the covariates will be measured at the index date as baseline measures, and in the 12 months prior.

$$\log \lambda_i(t) = \alpha(t) + \beta_i E_i + \beta_i Z_i \qquad (3\text{-}1)$$

Time-dependent covariate Cox PHREG model

Time-dependent Cox model allows for exposure switching and partially accounts for time-dependent confounding and evaluate time-varying nature of exposure on the association between exposure and outcomes. The following two models are tested: The model in Equation 3-2 with setting exposure as time-dependent variable, but all the other covariates as fixed, time-independent variables. These covariates are measured

at the index date, and in the 12 months before. We will call this model *time-dependent exposure and fixed confounders*.

$$\log \lambda_i(t) = \alpha(t) + \beta_i E_i(t) + \beta_i Z_i \quad (3\text{-}2)$$

The variables in the vector Z_i include patient characteristics; practice characteristics; asthma severity measures; asthma co-medications; other co-medications; co-immunizations; comorbidities; annual quarter in which therapy prescriptions are issued; presence of asthma action plan; inhaler device type; and prescription for compact spacer.

The second model in Equation 3-3 involves setting both exposure and covariates as time-dependent factors, except for the baseline covariates that are measured at the index date and during the 12 months prior. We will call this model *time-dependent exposure and confounders*.

$$\log \lambda_i(t) = \alpha(t) + \beta_i E_i(t) + \beta_i Z_i + \beta_i Z_i(t) \quad (3\text{-}3)$$

The variables in the vector Z_i include patient characteristics; practice location; prescription for oral corticosteroids, and number of inhaled SABA prescriptions within 12 months before the index date of exposure prescription; presence of asthma action plan; and prescription for compact spacer.

The variables in the time-dependent vector $Z_i(t)$ include the duration of GP consultation with the patient at every prescribing session; prescription for inhaled SABA; number of prescribed asthma medication classes; asthma co-medications; other co-medications; comorbidities; annual quarter in which the prescription was issued; and inhaler device type.

The time-independent exposure variable in the vector E_i include following patients who were prescribed one exposure group until the development of the outcome of interest, reaching censoring criteria, or switching to another exposure group with a new prescription for the alternative exposure. On the other hand, the time-dependent vector $E_i(t)$ for the exposure involves continuous patient follow up when exposure switching takes place, until the development of the study outcome or reaching censoring criteria.

Marginal structural model

The effect of the exposure on the outcomes of interest are assessed by fitting a MSM that accounts for time-dependent confounding that is affected by time-dependent exposure. Equation 2-16 serves as the final outcome model that includes time-varying exposure and baseline confounders weighted by the influence of time-dependent confounders.

Time-dependent covariates. Time-dependent confounders representing the vector V include the duration of GP consultation with the patient at every prescribing session; prescription for inhaled SABA; number of prescribed asthma medication classes; asthma co-medications; other co-medications; comorbidities; annual quarter in which the prescription was issued; and inhaler device type. These variables are updated on monthly basis.

Time-independent covariates. The fixed confounders representing the vector Z include patient characteristics; practice location; prescription for oral corticosteroids, and number of inhaled SABA prescriptions within 12 months before the index date of

exposure prescription; presence of asthma action plan; and prescription for compact spacer.

Sensitivity Analyses

Sensitivity analyses imply examining the effect of changing study parameters on the results (Greenland, 1996). Sensitivity analyses are conducted to assess the uncertainty of study findings to changes in cohort definition in terms of including patients with COPD diagnosis, characterization of asthma-related outcomes in terms of including selective clinical terms that reflect different asthma definitions, characterization of asthma mortality outcome in the GPRD records for patients not included in the ONS data, characterization of asthma morbidity outcome in terms of hospitalization and A&E visits by including prescriptions for oral corticosteroids as a severity measure instead of an outcome, and testing MSM assumptions of exchangeability (Brumback, Hernán, Haneuse, & Robins, 2004) and positivity (Mortimer, Neugebauer, van der Laan, & Tager, 2005).

Table 4-1. Estimated equipotent daily doses of inhaled corticosteroids for asthmatic adults (>12 years old) according to the GINA 2009 recommendations

Inhaled corticosteroid	Daily dose range (mcg)		
	Low strength	Medium strength	High strength
Beclometasone dipropionate	200-500	501-1000	1001-2000
Budesonide	200-400	401-800	801-1600
Ciclesonide	80-160	161-320	321-1280
Fluticasone propionate	100-250	251-500	501-1000
Mometasone furoate	200-400	401-800	801-1200

GINA, global initiative for asthma

Table 4-2. Dosage strengths of inhaled corticosteroids (ICS) monotherapy and ICS/long-acting beta-agonist (LABA) combination therapy available in the UK

ICS	Strength (mcg/dose)
Beclometasone dipropionate	50, 100, 200, 250, 400
Budesonide	50, 100, 200, 400
Ciclesonide	80, 160
Fluticasone propionate	25, 50, 100, 125, 250, 500
Mometasone furoate	200, 400
ICS/LABA	
Budesonide/Formoterol fumarate dihydrate	100/6, 200/6, 400/12
Fluticasone propionate/Salmeterol xinafoate	50/25, 125/25, 250/25, 100/50, 250/50, 500/50

Table 4-3. Variable definitions

Domain	Variable	Values	Measurement Time
Exposure	Switching during follow up year	0: ICS 1: LABA 2: ICS/LABA	Study aim no. 1 index date & follow up year
	Switching during follow up year	0: ICS 1: LABA 2: ICS/LABA	Study aim no. 2 index date & follow up year
	No switching during follow up year	0: Original dose ICS/LABA 1: 50% ICS dose reducer 2: LABA stopper	Study aim no. 3 index date
Outcome	Prescription for oral corticosteroids	0: Not issued 1: Issued	Study follow up year
	Asthma related visit for accident & emergency dept.	0: Event didn't occur 1: Event occurred	
	Asthma related inpatient hospital attendance	0: Event didn't occur 1: Event occurred	
	Asthma related death	0: Event didn't occur 1: Event occurred	
Asthma severity	Prescription for oral corticosteroids	0: Not issued 1: Issued	Study baseline year
	Asthma related visit for accident & emergency dept.	0: Event didn't occur 1: Event occurred	
	Asthma related inpatient hospital attendance	0: Event didn't occur 1: Event occurred	
	Number of prescriptions for inhaled SABA	>0 prescriptions issued	
	Prescription for inhaled SABA	0: Not issued 1: Issued	Study index date & follow up year
	Number of asthma drug classes prescribed	>0 classes	
Concurrent immunization	Prescription for influenza vaccine	0: Not issued 1: Issued	Study index date & follow up year
	Prescription for pneumoco-ccal polysaccharide vaccine	0: Not issued 1: Issued	
	Prescription for other vaccines	0: Not issued 1: Issued	

Table 4-3. Continued

Domain	Variable	Values	Measurement Time
Concurrent asthma drugs	Prescription for oral leukotriene receptor blocker	0: Not issued 1: Issued	Study index date & follow up year
	Prescription for oral methyl-xanthines	0: Not issued 1: Issued	
	Prescription for inhaled mast cell stabilizer	0: Not issued 1: Issued	
	Prescription for inhaled muscarinic receptor blocker	0: Not issued 1: Issued	
Other co-medications	Prescription for antibiotics for respiratory infections	0: Not issued 1: Issued	Study index date & follow up year
	Prescription for antivirals for respiratory infections	0: Not issued 1: Issued	
	Prescription for nasal corticosteroids	0: Not issued 1: Issued	
	Prescription for nasal mast cell stabilizers	0: Not issued 1: Issued	
	Prescription for nasal antihistamines	0: Not issued 1: Issued	
	Prescription for nasal decongestants	0: Not issued 1: Issued	
	Prescription for antitussives & expectorants	0: Not issued 1: Issued	
	Prescription for oral & ophthalmic selective beta-1-blockers	0: Not issued 1: Issued	
	Prescription for NSAIDs	0: Not issued 1: Issued	
	Prescription for aspirin	0: Not issued 1: Issued	
	Prescription for opioid analgesics	0: Not issued 1: Issued	
	Prescription for oral cholinergics	0: Not issued 1: Issued	
	Prescription for acetaminophen	0: Not issued 1: Issued	
	Prescription for tumor necrosis factor-α blockers	0: Not issued 1: Issued	

Table 4-3. Continued

Domain	Variable	Values	Measurement Time
Concomitant clinical conditions	Atopy	0: Not recorded 1: Recorded	Study index date
	Respiratory infections	0: Not recorded 1: Recorded	
	Psychosocial pathologies	0: Not recorded 1: Recorded	
Patient & practice characteristics	Patient's age	13-65 years	Study index date
	Patient's sex	0: Female 1: Male	
	Patient's marital status	0: Unmarried 1: Married 2: Unknown	
	Patient's weight status	0: Non-obese 1: Obese 2: Unknown	
	Patient's smoking status	0: Nonsmoker 1: Former smoker 2: Passive smoker 3: Unknown	
	Patient exempted from prescription payment	0: Not exempted 1: Exempted 2: Unknown	
	Level of capitation supplement the patient has	0: Low 1: Medium 2: High 3: Not applicable 4: Unknown	
	Duration of patient's registration with the practice	>0 months	
	Duration of practitioner's consultation with patient	0: 10 minutes & shorter 1: Longer than 10 minutes	
	Urgency of patient's visit to the practice	0: Non-urgent visit 1: Urgent visit 2: Unknown	
	General practice location in the UK	0: England 1: Scotland 2: Wales 3: Northern Ireland 4: Unknown	

Table 4-3. Continued

Domain	Variable	Values	Measurement Time
Other factors	Annual quarter in which prescription for exposure of interest was issued	0: 1st, January-March 1: 2nd, April-June 2: 3rd, July-September 3: 4th, October-December	Study index date & follow up year
	Presence of asthma action plan	0: Not available 1: Available 2: Unknown	Study index date
	Humidifying inhalational therapy	0: Not available 1: Available	
	Patient's compliance with asthma medications	0: Satisfactory 1: Unsatisfactory 2: Unknown	
	Patient's level of general compliance	0: Poor 1: Good 2: Unknown	
	Prescription for spacer	0: Not issued 1: Issued	
	Prescription for nebulizer	0: Not issued 1: Issued	
Inhaler device type for exposure of interest	ICS	0: pMDI 1: BAI 2: DPI 3: Unknown	Study index date
	LABA	0: pMDI 1: DPI 2: Unknown	
	ICS/LABA single-device	0: pMDI 1: DPI 2: Unknown	
	Exposure of interest	0: MDI 1: DPI 2: Unknown	

Table 4-4. Estimated sample size of study population

Outcome	Exposure group (incidence, %)		Sample size per group
	LABA	ICS/LABA	
Asthma death	0.067	0.012	20,489
Asthma hospitalization	1.516	0.394	1,179
	ICS	ICS/LABA	
Asthma death	0.016	0.012	--
Asthma hospitalization	1.000	0.394	2,958
	LABA	ICS	
Asthma death	0.067	0.016	25,035
Asthma hospitalization	1.516	1.000	7,323

ICS, inhaled corticosteroids
LABA, long-acting beta-agonists

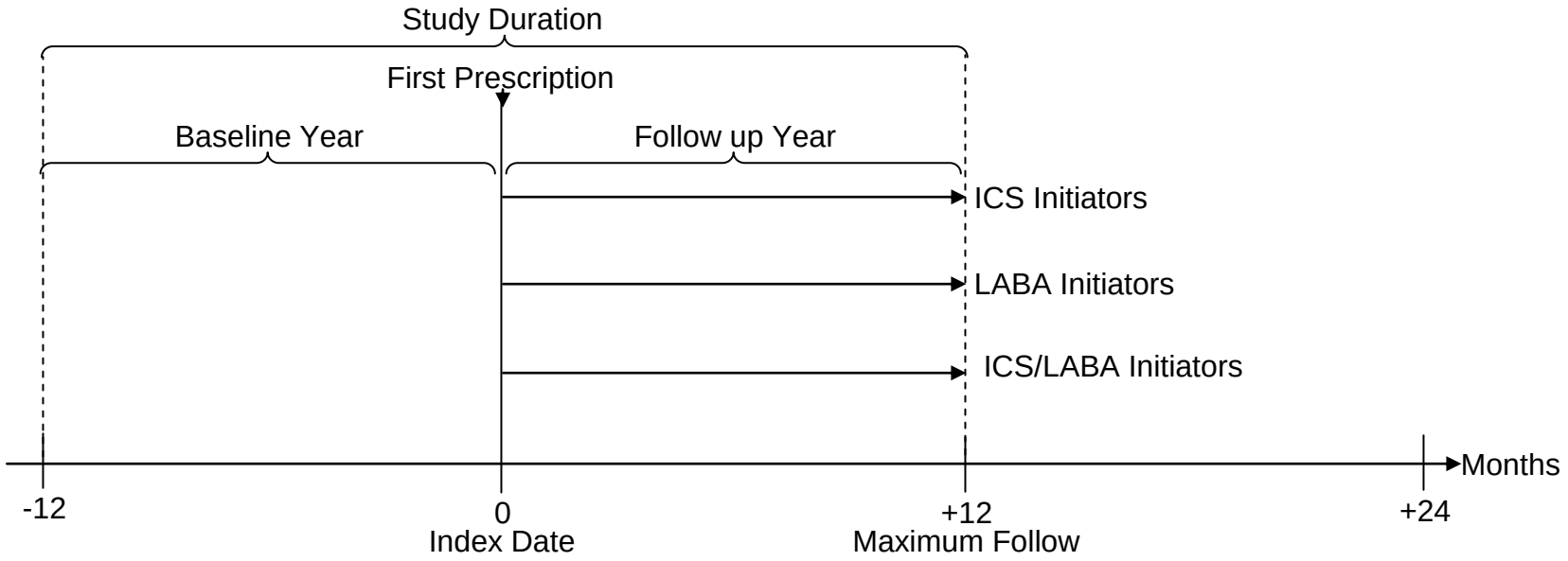


Figure 4-1. Study follow up profile for morbidity outcome (Study Aim No. 1)

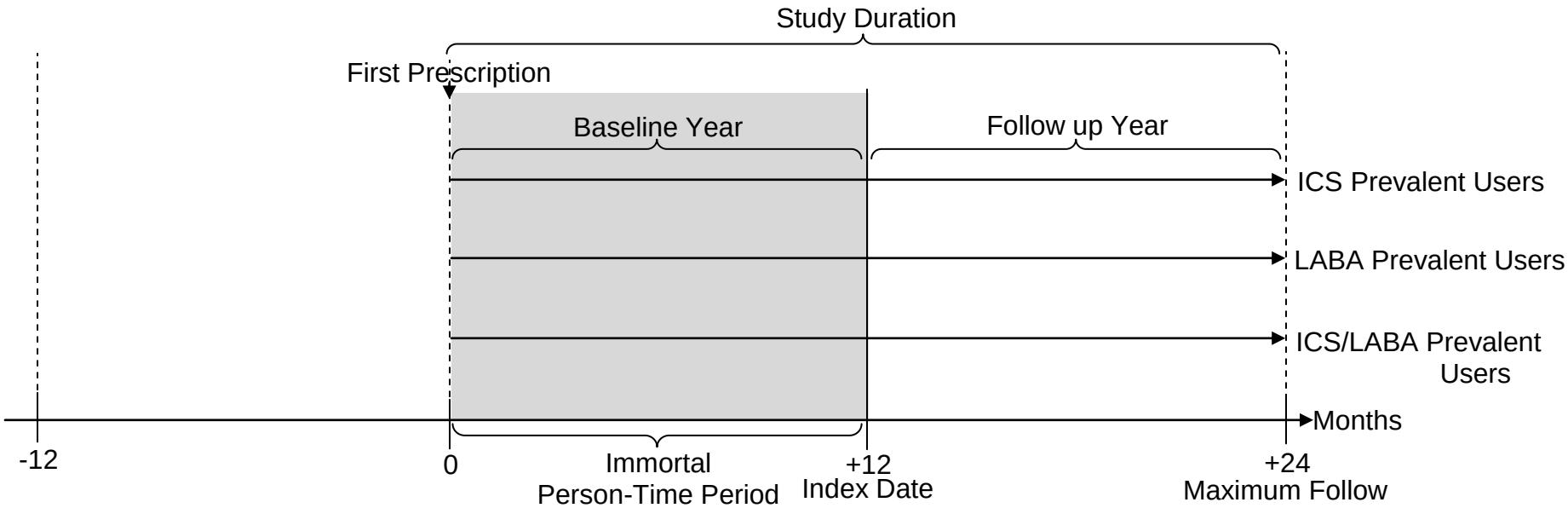


Figure 4-2. Study follow up profile for mortality outcome (Study Aim No. 2)

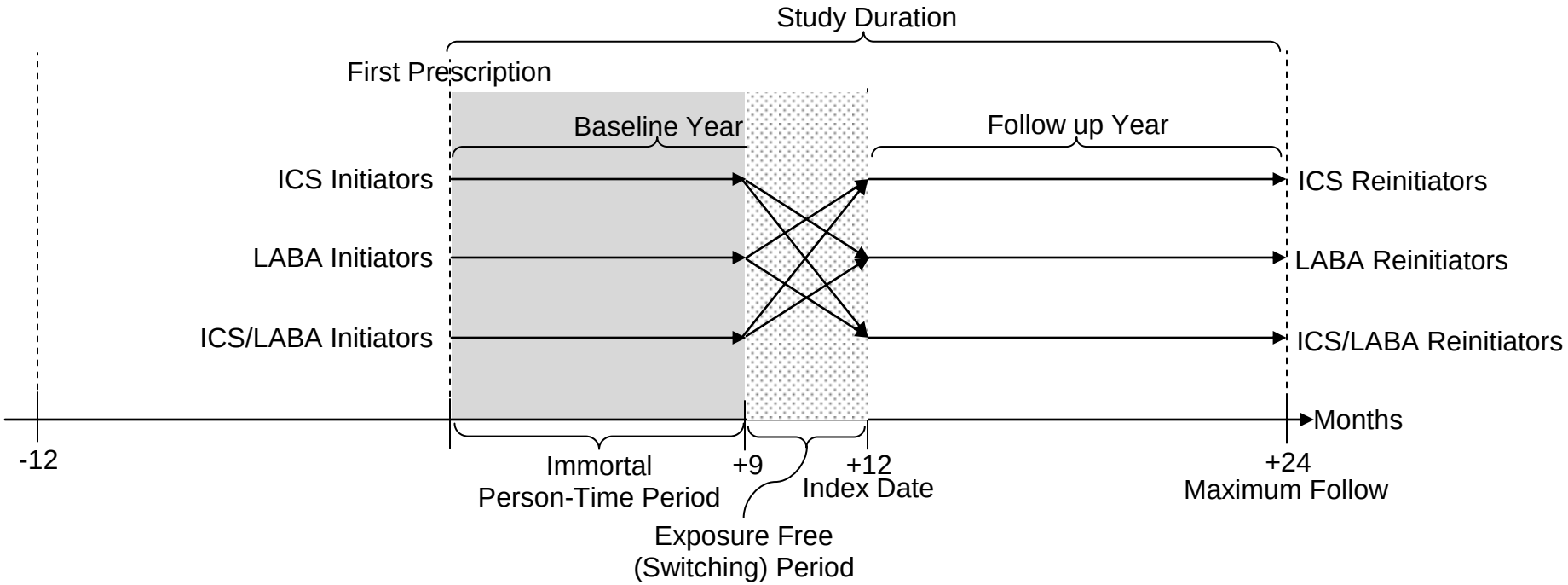


Figure 4-3. Study follow up profile for mortality outcome among prevalent users illustrating the design to adjust for selection bias

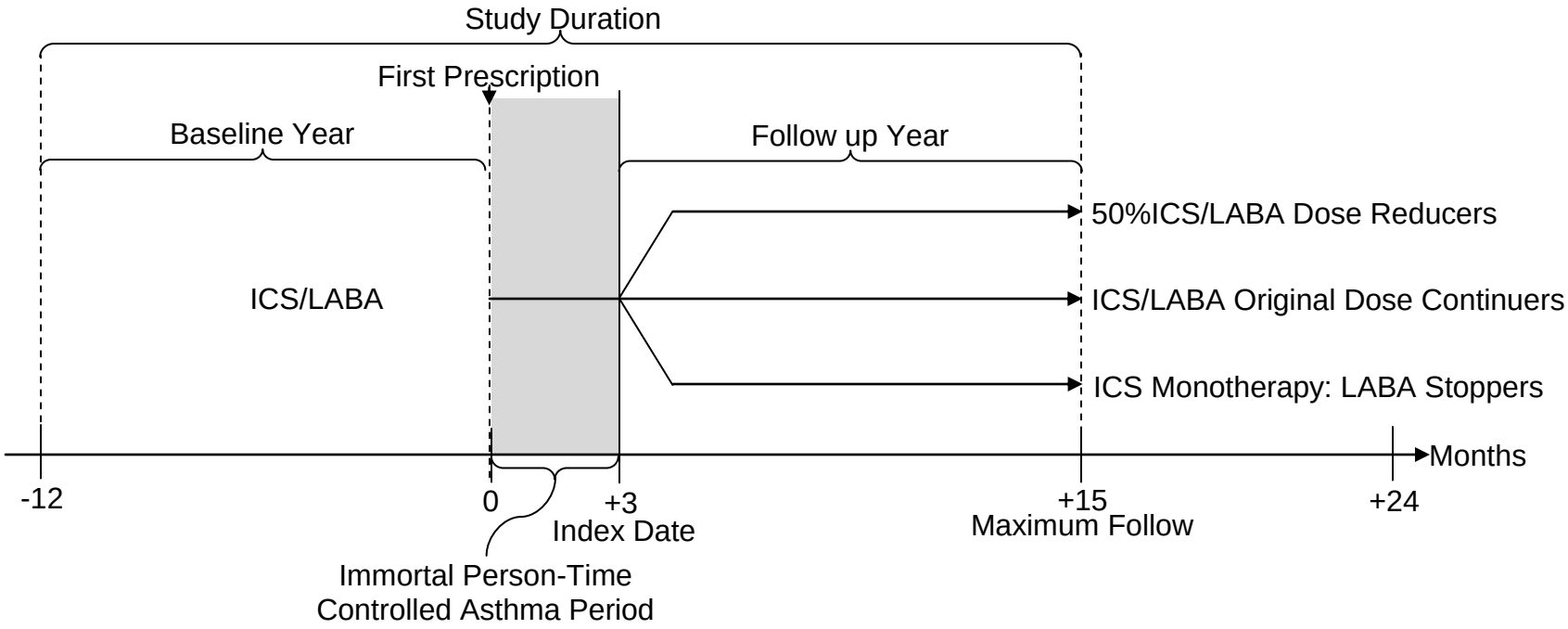


Figure 4-4. Study follow up profile for subgroup analysis for morbidity outcome (Study Aim No. 3)

CHAPTER 5
RESULTS

Descriptive Statistics

Characteristics of study population are described in the following sections of exclusion cohort, original cohort study sample, and step-down therapy subgroup study sample.

Exclusion Cohort

Medical records for patients with asthma are retrieved from the GPRD with 308,839 initiators of the study drugs (inhaled LABA, ICS, or combined ICS/LABA inhalers) who meet the inclusion criteria described above. Patient disposition is shown in figure 5-1 where exclusion numbers in the extension rectangles are mutually not exclusive because patients might have more than one exclusion criterion.

The majority of patients are excluded from the study cohort (257,736). About 10% of the patients received study drugs on or before January 1, 1993. 22.6% of the patients were aged either younger than 13 (12,669) or older than 65 (57,162). Patients with COPD comprised less than fourth of the retrieved records (70,394). Respiratory diagnostic and therapeutic procedures—except lung function tests (5,424), lung transplantation—with or without heart (40), and total or partial removal of lung lobes (830) involved in 2% of the patients. Lung diseases due to occupational exposure to chemicals and fumes, e.g. were reported in 2,482 patients.

Patients with infectious lung diseases accounted for 4.7% of the population, including prescriptions for relevant antibacterial and antifungal agents ever prescribed (5,241 asthmatics with tuberculosis, 9,393 asthmatics with aspergillosis, and 9 patients with pneumocystis pneumonia). Three thousand 250 patients had benign or malignant

neoplasm of the respiratory system, including tumors affecting the larynx, trachea, bronchi, bronchioles, lungs, and pleural cavity. Cystic fibrosis was found in 323 patients, parenchymal lung disease, e.g. pneumoconiosis was found in 537 patients, and obstructive sleep apnea was reported in 4,069 patients. Respiratory insufficiency due to obstruction by foreign objects was recorded in 251 asthmatic patients. Among asthmatics, 5,427 had destruction and widening of the bronchi (bronchiectasis) and partial or complete lung collapse (atelectasis). Congenital and structural anomalies of the respiratory system, including anomalies of the ribs, diaphragm, and intercostal muscles are found in 1,439 patients.

Asthmatics with cardiovascular and respiratory circulatory disorders accounted for 5.3% of the patients: pulmonary hypertension, pulmonary embolism, or pulmonary edema (5,349); congestive heart failure (10,441); congenital heart disease (535); and valvular heart disease affecting the pulmonary valve, e.g. pulmonary atresia (108). Approximately 9% of the patients had unspecified respiratory disorders (26,595), including injuries to the respiratory system, e.g. rib fracture, and conditions other than the ailments specified above. Eight thousand 250 patients were reported to participate in clinical studies, including asthma research.

Nearly half of the patients were active cigarette smokers (152,677), and only 5,430 patients were reported to use recreational drugs and illicit substances, including glue sniffing and marijuana smoking. Patients with prescription-based exclusion criteria comprised approximately 16% of the population. About 7% of asthmatics were prescribed non-selective beta-adrenoceptor blockers, involving ophthalmic products for glaucoma (2,674) and oral products (19,954), including combination antihypertensive

formulations (e.g. diuretics-combined or calcium-channel blocker-combined). Among the population, 8.5% asthmatics were prescribed inhaled SABA single-device combination products, including 23,431 patients with inhaled MRA/SABA; 2,172 patients with inhaled ICS/SABA; and 698 patients with MCS/SABA. Patients with prescriptions for inhaled betamethasone (145), allergen immunotherapy vaccination (27), and omalizumab (1) were excluded. In addition, four asthmatic patients with indeterminate sex were excluded from the study.

Original Cohort

Limiting the GPRD datasets based on the exclusion criteria described above produced a study cohort of 51,103 patients with asthma who have initiated the study drugs between January 4, 1993 and August 20, 2010, and who have survived for at least one year after initiation of study drug (Figure 5-1). The majority of the cohort were prescribed ICS (46,928), followed by ICS/LABA combination products (3,461), and inhaled LABA products (714). Among the combination group, the majority of patients were prescribed single-device combination formulations (2,692) compared to separate-devices (769). Beclomethasone accounted for the majority of ICS monotherapies (n=42,328; 90.2%), followed by budesonide (n=3,097; 6.6%), fluticasone (n=1,361; 2.9%), ciclesonide (n=94; 0.2%), and mometasone (n=47; 0.1%). Salmeterol was prescribed more than formoterol as inhaled LABA (n=674; 94.4% versus n=4; 5.6%). Most of the ICS/LABA combination therapy prescriptions were for fluticasone/salmeterol (n=2,208; 63.8%) compared to budesonide/formoterol (n=1,253; 36.3%).

The study population was followed for an average of 1 year after exposure. During the follow up year, patients received a total of 176,723 ICS prescriptions, 7,468 inhaled

LABA prescriptions, and 33,371 prescriptions for ICS/LABA combination inhalers. There was a consistent distribution of individual products within exposure class, e.g. about 92% of ICS prescriptions were for beclomethasone, 94% of LABA prescriptions were for salmeterol, and 64% of ICS/LABA prescriptions were for fluticasone/salmeterol. However, the distribution of switching products was different across exposure classes. During the follow up year, the majority of ICS initiators continued on ICS monotherapy, and only 15 asthmatics switched to LABA monotherapy as salmeterol (0.03%) compared with 10,371 (22.1%) asthmatics switched to ICS/LABA combination therapy (about 87% as fluticasone/salmeterol). Among LABA monotherapy initiators, 478 (67%) substituted LABA with ICS monotherapy (mostly as beclometasone), 223 (31.2%) patient added ICS (ICS/LABA combination therapy mostly as fluticasone/salmeterol), and only 13 (1.8%) patients continued LABA monotherapy (majority as salmeterol). 2,045 (59.1%) of ICS/LABA combination therapy initiators switched to ICS monotherapy, mainly as beclomethasone and budesonide. About 41% of combination therapy initiators continued on this regimen during the follow up year. There was no stepping down from combination to LABA monotherapy.

Baseline characteristics of exposure groups are shown in table 5-1, which are measured at study index date and baseline year. The mean age for the cohort was 39 years, and patients in the LABA monotherapy and the ICS/LABA combination therapy groups were relatively older than the patients in the ICS monotherapy group (40.4 years, 40.0 years, and 37.2 years, respectively). The majority of the patients in all exposure groups were females with rather similar distribution across the three exposure groups. Among patients with recorded pertinent information, 60% were married at the

time of prescribing study drugs, with about 65%, 62%, and 60% of the LABA, ICS/LABA, and ICS groups were married. Most of the asthmatics were obese (BMI ≥30); however, only one patient at the LABA exposure group had a known weight status, which was obese. About 84% of the ICS exposure group and 78% of the ICS/LABA exposure group were obese at baseline. The majority of the cohort (89%) was non active smoker; about 10% of the patients were reported as former smokers, and only 1% of the patients were classified as passive smokers at the time when exposure drugs are prescribed. The distribution of former smoking status among exposure groups was the highest in the LABA monotherapy group (13.1%), followed by the ICS/LABA combination therapy group (12%), and the ICS monotherapy group (9.6%). On the other hand, passive smoking status was slightly different among exposure groups (ICS, 1%; LABA, 0.7%; and ICS/LABA, 0.6%). The vast majority of asthmatics were exempted from payment for their prescribed medications with low levels of capitation supplements. With minor differences, patients who were prescribed ICS/LABA combination therapy were exempted from payment more than patients who were prescribed monotherapy alternatives (ICS/LABA, 83%; ICS, 80%; LABA, 71%). However, the distribution of capitation supplement was the highest among ICS monotherapy group compared with LABA monotherapy and ICS/LABA combination therapy groups. Yet, most of the patients in each exposure group had low capitation supplements for their prescription payment.

On average, the duration of patient registration with the practice was ten years, and was relatively longer in the combination group compared with the monotherapy groups. About 63% of the visits to the practices during which study drugs were

prescribed were ten minutes or shorter. Approximately 72%, 64%, and 9% of the patients who were respectively prescribed LABA monotherapy, ICS monotherapy, and ICS/LABA combination therapy had ≤10 minute consultation with the general practitioner at the time the corresponding study drugs were prescribed. The preponderance of these visits was classified as not urgent for all asthmatics across all exposure groups. About 79% of the practices were in England, 10% in Wales, 9% in Scotland, and 2% in Northern Ireland. Figure 5-2 depicts the distribution of initiators of ICS and LABA monotherapies, and ICS/LABA combination therapy. Among asthmatics who were prescribed ICS monotherapy, about 80%, 9%, 9%, and 2% received their prescriptions in England, Wales, Scotland, and Northern Ireland, respectively. In the LABA monotherapy group, about 71%, 14%, 12%, and 3% of asthmatics correspondingly received their prescriptions in England, Wales, Scotland, and Northern Ireland. Within the ICS/LABA combination therapy group, about 75%, 13%, 7%, and 5% of the prescriptions were issued in England, Wales, Scotland, and Northern Ireland. Among the cohort, most of the prescriptions in England were for ICS monotherapy. In Scotland and Wales, most prescriptions were issued for LABA monotherapy. Conversely, ICS/LABA combination therapy contributed to the majority of prescriptions for the study exposure of interest in Northern Ireland. The location of practices visited by 125 (0.2%) patients was not recorded in the database, corresponding to 120 patients in the ICS monotherapy group and 5 patients in the ICS/LABA combination group.

Baseline asthma was uncontrolled in the majority of patients (60%); however, that was contributed by the ICS monotherapy group, which had 61% of patients with uncontrolled asthma. Conversely, the disease in 48% of the ICS/LABA combination

therapy and 40% of the LABA monotherapy groups was classified as controlled at the time exposures were prescribed. Only 6% of the whole cohort was prescribed oral corticosteroids and 0.3% attended accident and emergency departments for asthma during the 12 months before receiving prescriptions for the exposure of interest. Only 1 patient was hospitalized for asthma during the 12 months period before receiving a prescription for ICS monotherapy. On average, the cohort received 2.5 prescriptions for inhaled SABA as rescue bronchodilators during the 12 months pre-index date period, which corresponds to 91% of asthmatics received $\leq$6 SABA prescriptions. About 53% of patients were prescribed inhaled SABA concomitantly with the exposure of interest. The mean number of asthma mediation classes prescribed at the index date was 1.7 for the patient; the vast majority of them had one additional asthma medication class prescribed with the exposure of interest at the index date. Merely 3% of asthmatics had more than 2 asthma medication classes prescribed on the same day in which the exposure of interest was prescribed.

Leukotriene receptor antagonists, e.g. montelukast accounted for the majority of asthma medications that were concurrently prescribed with LABA monotherapy and ICS/LABA combination therapy; however, oral methylxanthines, e.g. theophylline accounted for the majority of asthma medications prescribed with ICS monotherapy. Methylxanthines ranked second to LTRA as co-medications prescribed with LABA monotherapy and ICS/LABA combination therapy, followed by inhaled muscarinic receptor antagonists, e.g. ipratropium and inhaled mast cell stabilizers, e.g. nedocromil. Among asthmatics who were prescribed ICS monotherapy, LTRA ranked second to

methylxanthines, followed by inhaled MRA and inhaled MCS as asthma medications that were concurrently prescribed with ICS monotherapy.

Among other medications prescribed on the same day the patients received their study drugs, oral and parenteral antibiotics for respiratory tract infections accounted for about 58% the medications prescribed in the cohort, corresponding to about 59%, 48%, and 50% of the medications concomitantly prescribed with ICS monotherapy, ICS/LABA combination therapy, and LABA monotherapy, respectively. Nasal corticosteroids, e.g. triamcinolone were the second mostly prescribed co-medications at the index date with distributions of 25% of the medications in the ICS/LABA combination group respectively compared with 21% and 22% of the medications in the LABA and ICS monotherapy groups. Opioid analgesics, e.g. morphine accounted for 11% of medications prescribed with ICS/LABA combination inhalers, 10% of medications prescribed with LABA monotherapy inhalers, and 7% of medications prescribed with ICS monotherapy inhalers. About 4% of medications (other than asthma drugs) prescribed together with study drugs were NSAIDs, e.g. ibuprofen. Aspirin and acetaminophen accounted for half of that figure each. Approximately 11% of the medications that were prescribed in tandem with ICS/LABA combination therapy were for NSAIDs compared with 10% and 7% of medications prescribed with ICS and LABA monotherapies. Patients received LABA monotherapy had 6.5% of co-medications as orally or rectally administered aspirin, while aspirin correspondingly accounted for 4% and 2% of co-medications in ICS/LABA combination therapy and ICS monotherapy groups. Antivirals for respiratory tract infections, e.g. oseltamivir; nasally administered antihistamines, e.g. azelastine and decongestants, e.g. oxymetazoline; ophthalmic selective beta-1-blockers, e.g.

betaxolol; and oral cholinergics, e.g. neostigmine bromide were only prescribed in patients received ICS monotherapy prescriptions. Nasally administered MCS, e.g. cromolyn sodium were only prescribed in monotherapy groups, with larger distributions in the LABA group. Expectorants and opioid-based antitussive formulations accounted for 2% of concurrently prescribed medications (other than asthma drugs) for patients in the monotherapy groups, compared with 1.2% of the medications in the ICS/LABA combination group. Orally administered selective beta-1-blockers, e.g. atenolol and atenolol/chlorthalidone accounted for 2% of concomitantly prescribed medications with ICS/LABA combination therapy and LABA monotherapy groups, and 1.5% of co-medications in the ICS monotherapy group.

About 78% of the prescriptions for immunizations that were issued at the index date were for influenza vaccines. Pneumococcal polysaccharide vaccine accounted for about 4% of concomitant vaccines. Other immunizations accounted for the rest of concurrent vaccines that were prescribed on the same date the exposures of interest were prescribed. Patients received LABA monotherapy (n=2) were only prescribed influenza vaccines at baseline. About 78% of the concomitantly prescribed vaccines that were prescribed to asthmatics in the ICS monotherapy and the ICS/LABA combination therapy groups were for influenza. Only 6 patients in the ICS monotherapy group and 3 patients in the ICS/LABA combination group were prescribed pneumococcal polysaccharide vaccine. Other immunizations were tallied to 19% and 13% of all vaccines prescribed to the ICS monotherapy and ICS/LABA combination therapy groups, respectively. The trend of prescribing study drugs in the cohort was similar across the first two and the fourth annual quarters, with most prescriptions in the fourth

quarter; conversely, the third quarter had the least number of prescriptions. This trend was similar across patients prescribed controller medications with ICS monotherapy and ICS/LABA combination therapy; however, inhaled LABA bronchodilator monotherapy was least and most prescribed during the first and fourth quarters of the year, respectively (Figure 5-3).

Atopic conditions in asthmatics accounted for the majority of the selected comorbid conditions (49%), followed by respiratory tract infections (32%) and psychosocial pathologies (19%). Allergic rhinitis and sinusitis, other and unclassified respiratory tract infections, and use of antidepressants were respectively contributed to most of atopies, respiratory infections, and psychosocial problems. The distribution of atopic conditions across exposure groups was similar in ICS monotherapy (3.6%) and ICS/LABA combination therapy groups (3.5%), but was more in the LABA monotherapy group (4.1%). However, the distribution of respiratory tract infections was more prominent in the ICS monotherapy group (2.4%) compared with LABA monotherapy and ICS/LABA combination therapy groups (2.1% & 2.2%, respectively); and psychosocial pathologies were mostly distributed in ICS/LABA combination group (2.4%) compared with the monotherapy groups (ICS, 1.3%; LABA, 2%).

Information about the availability of personalized asthma action plan was only available for about 1% of asthmatics initiated ICS monotherapy and about 2% of patients initiated ICS/LABA combination therapy. All these patients reported having asthma action plans during the study period. Only one patient received ICS monotherapy reported no asthma action plan was available during the study period. Similarly, information about patient's compliance level with prescribed asthma

medications (regardless of the medication class or route of administration) was only available for a small number of asthmatics in the ICS monotherapy and the ICS/LABA combination groups. The distribution between both groups was similar with the majority of patients having satisfactory compared with unsatisfactory compliance levels. Regardless of medication type, good general medication compliance was recorded in about 0.1% of the patients in each of the three exposure groups (one patient in the LABA monotherapy group), and only 7 patients in the ICS monotherapy group reported poor compliance level. The vast majority of the prescribed exposures were in inhaled aerosol forms compared with inhaled dry powders. Aerosols were most prescribed for ICS monotherapy (91%) than LABA monotherapy (74%) or ICS/LABA combination therapy (53%). Conversely, dry powder inhalers were most prescribed for ICS/LABA combination therapy (47%) than monotherapy (ICS, 9%; LABA, 26%). Device type was not determined for about 0.1% of initiators of ICS monotherapy. Most of asthmatics did not receive a spacer or holding chamber at the time when the exposure was prescribed. About 10% of ICS monotherapy initiators had spacer devices prescribed at baseline, compared to 6.6% of ICS/LABA combination therapy and 3.2% of LABA monotherapy initiators. Although most of the patients didn’t receive nebulizers, nebulizers were mostly prescribed to ICS monotherapy initiators, and only one patient in the ICS/LABA combination therapy group was prescribed a nebulizer at baseline. Additionally, patients who initiated LABA monotherapy was not recommended a nebulizer for their inhaled bronchodilator therapy.

The differences in baseline characteristics among exposure groups were statistically significant in age; marital status; smoking status; level of capitation

supplement; consultation duration; urgency of visit; location of practice in the UK; asthma disease control at baseline; asthma severity indicators at index date and baseline year (except for asthma-related hospitalization); concurrent prescriptions for asthma medications; concurrent prescriptions for nasal corticosteroids, nasal mast cell stabilizers, oral and rectal aspirins, and all-routes opioid analgesics; concomitant prescriptions for influenza and pneumococcal polysaccharide vaccines; whether a spacer was prescribed; allergic conjunctivitis among comorbidity with atopic conditions; pneumonia among comorbidity with respiratory tract infections; psychosocial conditions, including prescriptions for tranquilizers and antidepressants; availability of asthma action plan; and the type of inhaler device for the prescribed exposure.

Step-Down Therapy Cohort

Among initiators of ICS/LABA combination products, the effect of step-down therapy approaches are reported according to the daily dosage strength of the ICS in the initiated combination product, whether single-device or separate-devices. The majority of ICS/LABA combination initiators were prescribed medium-dose ICS (2,581) between January 4, 1993 and August 11, 2010 compared to high-dose ICS (645) that were prescribed between January 5, 1993 and July 12, 2010. Among the cohort, 59 initiators of high-dose ICS and 176 initiators of medium-dose ICS had uncontrolled asthma during the three months before initiation date (Figure 5-1). Uncontrolled asthma defined as having prescriptions for oral corticosteroids (n= 56 and 170, respectively), asthma-related attendance to accident and emergency departments (n= 3 and 6, respectively) or hospitalization due to asthma (no event occurred for either group). Those patients were excluded from the cohort. The sample was followed for an average

of 1 year after exposure. During the follow up year, patients received a total of 2,203 prescriptions for high ICS dose ICS/LABA combination therapy inhalers, 5,999 prescriptions for medium ICS dose ICS/LABA combination therapy inhalers, 6,591 prescriptions for low ICS dose ICS/LABA combination therapy inhalers, 43,410 prescriptions for medium dose ICS monotherapy inhalers, and 4,175 prescriptions for low dose ICS monotherapy inhalers. The distribution of baseline characteristics for patients included in the analyses is described below:

Original high-dose ICS initiators

Table 5-2 shows baseline characteristics of patients according to the type of step-down therapy approach among 645 initiators of high-dose ICS combination products. Most of these patients were ICS dose reducers to medium-dose ICS (337), followed by LABA stoppers with original high-dose ICS (172), and continuers of original high-dose ICS strength (136). The mean age of the cohort was 42.1 years. LABA stoppers were relatively older than original and reduced ICS dose combination groups (43.5 versus 41.5 and 41.4, respectively). The majority of patients were females with relatively more distribution among the LABA stoppers compared with the other two groups. Among asthmatics with recorded social and behavioral information, about 65% were married, 86% obese, 87% nonsmokers, 12% former smokers, 85% exempted from prescription payment, and 55% with low capitation supplement. On average, patients were registered with the practices for 9.4 years, with shortest duration among LABA stoppers and longest duration among ICS dose reducers. Most of the visits at which the exposure was prescribed were for ten minutes or less, and the majority was not urgent. Most of the shorter visits were among LABA stoppers, followed by original dose and reduced

dose groups. Visits longer than 10 minutes were mostly for dose reducer patients. Original ICS dose combination group contributed to the majority of urgent visits. About 67% of LABA stoppers, 66% of ICS dose reducers, and 61% of original ICS dose patients were married. Only one patient in the original ICS dose group was classified as non-obese. Most of nonsmoker patients were LABA stoppers; conversely, most of the former smokers were ICS dose reducers, and most of the original ICS dose patients were passive smokers. Payment for prescriptions was mostly exempted with low capitation levels among LABA stoppers compared to ICS/LABA combination groups.

About 78% of the practices were in England, 12% in Wales, 6% in Scotland, and 4% in Northern Ireland. Figure 5-4 depicts the distribution of initiators of original high dose ICS and reduced medium dose ICS ICS/LABA combination therapies, and LABA stopper (high dose ICS monotherapy). Among asthmatics who were prescribed high dose ICS combination therapy, about 77%, 14%, 5%, and 4% received their prescriptions in England, Wales, Scotland, and Northern Ireland, respectively. In the reduced medium dose ICS combination therapy group, about 77%, 12%, 6%, and 5% of asthmatics correspondingly received their prescriptions in England, Wales, Scotland, and Northern Ireland. Within the LABA stopper group, about 80%, 9%, 8%, and 3% of the prescriptions were issued in England, Wales, Scotland, and Northern Ireland. Among the cohort, most of the prescriptions in England and Scotland were for high dose ICS monotherapy (LABA Stoppers). In Wales, most prescriptions were issued for high dose ICS combination therapy. Conversely, medium dose ICS combination therapy contributed to the majority of exposure prescriptions in Northern Ireland. Practice

location for one patient in the reduced ICS dose combination group was not recorded in the database.

Approximately 44% of asthmatics received prescriptions for SABA rescue inhalers, corresponding to 52% LABA stoppers, 43% medium dose ICS combination therapy patients, and 39% high dose ICS combination therapy patients. The mean number of asthma medication classes prescribed at index date for the cohort was 2.2, with the least number among LABA stoppers. The vast majority of asthmatics received one additional asthma medication class to their exposure of interest. Nearly 1 in 3 patients had more than two asthma medication classes prescribed at the index date. The vast majority of prescriptions issued to LABA stoppers had $\leq$2 asthma medication classes (99%), compared with 58% of original high dose ICS and 56% of reduced medium dose ICS combination groups. Most of the prescriptions with >2 asthma medication classes were issued for reduced ICS dose combination group, followed by the original high dose ICS combination group. Only one LABA stopper had >2 asthma medication classes prescribed on the same date LABA was withdrawn and high dose ICS was continued. The majority of asthma medications prescribed at baseline was LTRA (45.4%), followed by oral methylxanthines (27.3%), inhaled MRA (25.8%), and inhaled MCS (1.5%). Anti-inflammatory LTRA medications and inhaled MRA bronchodilators were mostly prescribed to high dose ICS combination therapy patients, and least prescribed to high dose ICS monotherapy patients (LABA stoppers). Equally, oral xanthines were more prescribed with high dose ICS combination therapy compared with medium dose ICS combination therapy and high dose ICS monotherapy.

Among the cohort, about 38%, 22%, and 11% of prescriptions issued for concomitant medications at baseline (other than asthma drugs) were respectively for RTI antibiotics, nasal corticosteroids, and opioid analgesics. Antibiotics and nasal corticosteroids were mostly prescribed to high dose ICS groups (combination and monotherapy) and least prescribed to medium dose ICS combination therapy (dose reducers). Conversely, opioid analgesics were mostly prescribed to dose reducers than original dose patients or LABA stoppers. About 5%, 3%, and 2% of the concurrent medications prescribed to the cohort were for NSAIDs, aspirin, and acetaminophen, respectively. Most of the NSAIDs prescriptions were issued to high dose ICS groups compared to medium dose ICS group. On the other hand, aspirin and acetaminophen were mostly prescribed to medium dose ICS combination therapy group, followed by LABA stoppers and high dose ICS combination therapy group. Approximately 1.7%, 1.2% of concomitant prescriptions were issued for orally administered selective beta blockers and antitussives, respectively. Oral selective beta blockers were least prescribed to LABA stoppers compared with other two groups; antitussives were least prescribed to dose reducers. Only one patient in the LABA stopper group received a prescription for nasally administered MCS. No patient in this step-down therapy cohort received prescriptions for RTI antivirals, nasal antihistamines, nasal decongestants, ophthalmic selective beta blockers, or oral cholinergics.

Influenza vaccines accounted for the majority of the prescriptions of concurrent immunizations at the time exposures of interest were prescribed, which was mainly contributed by patients in the ICS dose reducer combination therapy group (n= 4). Only one prescription for influenza vaccine was prescribed to high dose ICS combination

therapy patients, one prescription for pneumococcal polysaccharide vaccine and one prescription for other vaccines were issued to dose reducer group, and one prescription for other vaccines was issued to the LABA stopper group.

About 27% of the prescriptions were issued to the cohort in the fourth quarter of the year; the distribution of prescriptions was relatively equivalent across the other three quarters. Most of the high dose ICS combination therapy prescriptions were issued during the second quarter, whereas the step-down approaches (dose reducers and LABA stoppers) were mostly prescribed during the fourth quarter (Figure 5-6, A).

Approximately 45% of the identified comorbidities in the cohort were classified as atopic conditions, and 55% were evenly distributed between respiratory tract infections and psychosocial pathologies. Atopies accounted for the majority of comorbid conditions in original ICS dose combination group; conversely, psychosocial pathologies and respiratory infections accounted for the majority of comorbidities in the step-down therapy approaches (dose reducers and LABA stoppers, respectively). Most of atopic conditions in these asthmatics were allergic rhinitis and sinusitis. Unclassified respiratory tract infections accounted for the majority of RTI in the cohort. Utilization of antidepressants contributed to most of psychosocial problems identified in the cohort.

Personalized asthma action plan was available in 2 original high ICS dose users, 6 medium ICS dose reducers, and 1 LABA stoppers. Only one patient in the dose reducer group had unsatisfactory compliance level with any prescribed asthma medications, compared to four patients in the same group had satisfactory compliance with asthma medications and one patient had good compliance with any medication prescribed regardless of the class or indication. Only one patient in the original ICS dose group had

satisfactory asthma drug compliance and two patients in the same group had good compliance with any medication prescribed. No compliance-related information was recorded in the LABA stopper group. Nearly two third prescribed exposures were in form of aerosols (pMDI and BAI) and one third was in form of dry powder inhalers. Aerosols were mainly prescribed to the original high ICS dose ICS/LABA combination group, followed by the LABA stopper and ICS dose reducer groups. On the other hand, dry powder inhalers were mainly prescribed to the ICS dose reducer ICS/LABA combination group, followed by the LABA stopper and original high ICS dose ICS/LABA combination groups. At baseline, only 8% of asthmatics had a spacer or a holding chamber device prescribed, corresponding to about 10% of original ICS dose users, 8% of LABA stoppers, and 7% of ICS dose reducers. One patient in the ICS dose reducer group received a prescription for nebulizer.

Baseline differences across the groups were statistically significant in the following characteristics: Age; smoking status; capitation supplement level; consultation duration; prescription for SABA rescue inhaler; number of asthma medication classes prescribed; LTRA and methylxanthines concomitant asthma medications prescribed; respiratory tract infections as concurrent clinical conditions; and inhaler device type for the exposure of interest.

Original medium-dose ICS initiators

Table 5-3 describes baseline characteristics of patients by the type of step-down therapy approach among 2,581 initiators of medium-dose ICS combination products. The majority of these patients were LABA stoppers with original medium-dose ICS (1,742), followed by ICS dose reducers to low-dose ICS (519), and continuers of original

medium-dose ICS strength (320). The mean age of the cohort was 40.3 years. LABA stoppers and original ICS dose combination group were relatively older than reduced ICS dose combination group (41.3 and 41.4 versus 38.2, respectively). The majority of patients were females with relatively more distribution among the low ICS dose reducers compared with the other two groups. Among asthmatics with recorded social and behavioral information, about 67% were married, 92% obese, 88% nonsmokers, 11% former smokers, 77% exempted from prescription payment, and 56% with low capitation supplement. On average, patients were registered with the practices for 9.6 years, with longest duration among LABA stoppers and shortest duration among ICS dose reducers. Similar to the previous step-down cohort, most of the visits at which the exposure was prescribed were for ten minutes or less, and the majority was not urgent. Most of the shorter visits were among LABA stoppers, followed by reduced dose and original dose groups. Visits longer than 10 minutes were mostly for original medium ICS dose ICS/LABA combination therapy patients. Combination therapy groups contributed to the majority of urgent visits. About 69% of LABA stoppers, and 66% of original ICS dose patients, and 58% of ICS dose reducers were married. Only one patient in the LABA stopper group was classified as non-obese. Most of nonsmoker and passive smoker patients were LABA stoppers; conversely, most of the former smokers were in the original medium dose ICS group. Payment for prescriptions was mostly exempted among original medium dose ICS combination group compared to step-down therapy groups. However, most of the low capitation supplements were in the step-down therapy groups, especially among LABA stoppers.

About 76% of the practices were in England, 11% in Wales, 9% in Scotland, and 4% in Northern Ireland. Figure 5-5 illustrates the distribution of initiators of original medium dose ICS and reduced low dose ICS ICS/LABA combination therapies, and LABA stopper (medium dose ICS monotherapy). Among asthmatics who were prescribed medium dose ICS combination therapy, about 77%, 12%, 6%, and 5% received their prescriptions in England, Wales, Scotland, and Northern Ireland, respectively. In the reduced low dose ICS combination therapy group, about 77%, 12%, 7%, and 4% of asthmatics correspondingly received their prescriptions in England, Wales, Scotland, and Northern Ireland. Within the LABA stopper group, 76%, 10%, about 10%, and 4% of the prescriptions were issued in England, Wales, Scotland, and Northern Ireland. Among the cohort, most of the prescriptions in Northern Ireland and Wales were for medium dose ICS and low dose ICS combination therapy groups, compared to LABA stoppers with least distribution in both countries. The distribution of exposure prescriptions issued in England was virtually equal across exposure groups. Conversely, most of the prescriptions issued in Scotland were for medium dose ICS monotherapy (LABA stoppers). Practice location for 5 patients was not recorded in the database, corresponding to one patient in the original ICS dose group, and 1 and 4 patients in the step-down therapy approach groups (ICS dose reducers and LABA stoppers, respectively).

Approximately 49% of asthmatics received prescriptions for SABA rescue inhalers, corresponding to 53% LABA stoppers, 39% low dose ICS combination therapy patients, and 43% medium dose ICS combination therapy patients. The mean number of asthma medication classes prescribed at index date for the cohort was 2.1, with the least

number among LABA stoppers. The vast majority of asthmatics received one additional asthma medication class to their exposure of interest. About 14% of patients had more than two asthma medication classes prescribed at the index date. The vast majority of prescriptions issued to LABA stoppers had ≤2 asthma medication classes (99%), compared with 60% of reduced low dose ICS and 56% of original medium dose ICS combination groups. Most of the prescriptions with >2 asthma medication classes were issued for reduced ICS dose combination group, followed by the original medium dose ICS combination group. Only 1% of LABA stoppers had >2 asthma medication classes prescribed on the same date LABA was withdrawn and medium dose ICS was continued. In contrast to the previous step-down therapy cohort, the majority of asthma medications prescribed at baseline was oral methylxanthines (33.6%), followed by oral LTRA (30.5%), inhaled MRA (29%), and inhaled MCS (7%). Anti-inflammatory LTRA medications and inhaled MRA bronchodilators were mostly prescribed to medium dose ICS combination therapy patients, and least prescribed to medium dose ICS monotherapy patients (LABA stoppers). Equally, oral xanthines were more prescribed with ICS/LABA combination therapies than ICS monotherapy.

Among the cohort, about 54%, 23%, and 10% of prescriptions issued for concomitant medications at baseline (other than asthma drugs) were respectively for RTI antibiotics, nasal corticosteroids, and opioid analgesics. Antibiotics were mostly prescribed to LABA stoppers. Conversely, nasal corticosteroids were least prescribed to LABA stoppers. Opioid analgesics were mostly prescribed to original medium dose ICS ICS/LABA combination group compared. About 4%, 3%, and 2% of the concurrent medications prescribed to the cohort were for NSAIDs, aspirin, and acetaminophen,

respectively. Most of the NSAIDs prescriptions were issued to ICS dose reducers compared to original medium dose ICS groups (combination and monotherapies). On the other hand, aspirin and acetaminophen were mostly prescribed to original dose ICS combination therapy group, and least prescribed to LABA stopper group. Approximately 2% of concomitant prescriptions were issued for orally administered selective beta blockers and additional 2% for antitussives. Oral selective beta blockers were mostly prescribed to original medium dose ICS combination group than other two groups. Equally, antitussives were mostly prescribed to LABA stoppers. Like the previous step-down therapy cohort, only one patient in the LABA stopper group received a prescription for nasally administered MCS. Yet, three patients in this group received prescriptions for nasally administered antihistamines. No patient in this step-down therapy cohort received prescriptions for RTI antivirals, nasal decongestants, ophthalmic selective beta blockers, or oral cholinergics.

Influenza vaccines accounted for the majority of the prescriptions of concurrent immunizations at baseline, which was mainly contributed by patients in the ICS dose reducer combination therapy group. Influenza vaccine and other types of vaccines were least prescribed to LABA stoppers compare to combination therapy users. Only two prescriptions for pneumococcal polysaccharide vaccine were issued to the cohort, one in the original medium dose group and another in the LABA stopper group.

About 26% of the prescriptions were issued to the cohort in the fourth quarter of the year; unlike the other step-down therapy cohort, the distribution of prescriptions was not similar across the other three quarters. About 26%, 25%, and 23% of prescriptions were correspondingly issued in the first, second, and third quarters. Most of the medium

dose ICS prescriptions (original combination therapy and LABA stoppers monotherapy) were issued during the fourth quarter, whereas the low dose ICS combination prescriptions (dose reducers) were mostly prescribed during the first quarter (Figure 5-6, B).

Approximately 25% of the identified comorbidities in the cohort were classified as atopic conditions, and 32% and 22% were respiratory tract infections and psychosocial pathologies, respectively. Atopies accounted for the majority of comorbid conditions in all the three groups; however, psychosocial pathologies ranked the second mostly encountered comorbidities in the medium ICS dose groups (combination and monotherapies), whereas respiratory infections accounted for the second most comorbidities in the low reduced dose ICS combination group. Similar to other step-down therapy cohort, most of atopic conditions in these asthmatics were allergic rhinitis and sinusitis, and unclassified respiratory tract infections accounted for the majority of RTI in the cohort. Likewise, utilization of antidepressants contributed to most of the psychosocial problems identified in the cohort.

Personalized asthma action plan was available in 6 original medium ICS dose users, 14 low ICS dose reducers, and 10 LABA stoppers. Only one patient in the original medium dose ICS group and one patient in the reduced low dose ICS group had unsatisfactory compliance level with any prescribed asthma medications, compared to four and 2 patients in the same groups had satisfactory compliance with asthma medications. Additionally, three LABA stoppers had satisfactory compliance with asthma medications, and only one patient in the same group had poor general compliance level. One original ICS dose user, 2 ICS dose reducers, and 4 LABA

stoppers had good overall compliance with medications regardless of medication type or clinical indication. Approximately 73% of prescribed exposures were aerosol formulations and 37% were dry power disk inhalers. Unlike other step-down therapy cohort, aerosols were mainly prescribed to LABA stoppers (low dose ICS monotherapy), followed by the combination groups (original medium dose ICS and reduced low dose ICS). Dry powder inhalers were mainly prescribed to low dose ICS reducers; followed by original medium ICS dose groups (original combination and LABA stoppers). Only 9.5% of asthmatics had a spacer or a holding chamber device prescribed at baseline, corresponding to about 11% of LABA stoppers, 7% of original ICS dose users, and 6% of ICS dose reducers. One original ICS dose user and one LABA stopper received a prescription for nebulizer.

Baseline differences across the groups were statistically significant in the following characteristics: Age; sex; marital status; smoking status; capitation supplement level; consultation duration; practice location in the UK; prescription for SABA rescue inhaler; number of asthma medication classes prescribed; LTRA, antibiotics for RTI, acetaminophen, and opioids as concomitant medications; concurrently prescribed influenza vaccines; psychosocial pathologies as concurrent clinical conditions; presence of asthma action plan; asthma medication compliance; inhaler device type for the exposure of interest; and whether a spacer was prescribed.

Inferential Statistics

The results of testing study hypotheses are described in the following sections of asthma-related morbidity outcomes for original cohort and step-down therapy subgroups, and asthma-related and all-cause mortality outcomes for original cohort.

Asthma-related Morbidity

Asthma-related morbidity rates are identified by prescription rates for oral corticosteroids and asthma-related accident and emergency department attendance rates. No asthma-related hospitalization was recorded in the sample during the 1-year study follow up, and no asthma-related A&E department visits for initiators of high-dose ICS combination therapy step-down cohort; thus, these outcomes were not included in outcome assessment for the corresponding original cohort and the relevant step-down therapy cohort. Table 5-4 shows the incidence rates of prescriptions for oral corticosteroids and A&E department visits for asthma exacerbations during study follow up after exposure initiation. Table 5-5 gives the incidence rates of prescribing short courses OCS for asthma exacerbations. Among the original cohort, initiators of LABA monotherapy had higher incidence rates for asthma-related morbidity than ICS monotherapy and ICS/LABA combination therapy initiators. Among step-down therapy cohorts, continuers of high-dose ICS and continuers of medium-dose ICS combination therapies had higher incidence rates for asthma-related morbidity than dose reducers or LABA stoppers.

Prescriptions for oral corticosteroids

The study population received a total of 7,108 prescriptions for oral corticosteroids during the 1-year follow-up, 91.4% of which were for short courses to treat asthma exacerbations. The distribution of prescriptions for OCS and short courses of OCS in the original cohort was 4,597 and 4,197, respectively for ICS monotherapy initiators; 326 and 310, respectively for LABA monotherapy initiators; 2,185 and 1,988, respectively for ICS/LABA combination therapy initiators. Among high-dose ICS step-

down subgroup, the number of prescriptions for OCS and short courses of OCS prescribed during the 1-year follow up was 286 and 265 for original dose continuers; and 465 and 310 for dose reducers. LABA stoppers received 171 OCS prescriptions that all classified as short courses. On the other hand, the distribution of prescriptions for OCS and short courses of OCS among medium-dose subgroup was as following: original dose continuers (862 and 690, respectively); dose reducers (856 and 568, respectively); and LABA stoppers (1,317 and 1,219, respectively) (Tables 5-4 and 5-5).

Main cohort. During the first year after exposure to study drugs, the incidence rate of prescribing relatively long courses of OCS was higher in LABA monotherapy initiators (19.9 per 100 person-yrs, 95%CI, 13.8-28.6) than ICS/LABA combination therapy initiators (17.7 per 100 person-yrs, 95%CI 14.9-20.9) or ICS monotherapy initiators (10.6 per 100 person-yrs, 95%CI 10.0-11.2). Likewise, initiators of LABA monotherapy had higher incidence rates of prescribing short courses of OCS for asthma exacerbations (18.5 per 100 person-yrs, 95%CI 12.7-27.0) compared to ICS/LABA combination therapy initiators (14.8 per 100 person-yrs, 95%CI 12.4-17.8) or ICS monotherapy initiators (9.8 per 100 person-yrs, 95%CI 9.3-10.4).

Table 5-8 lists the distribution of mean time-to-event for outcomes of interest stratified by exposure type. On average, initiators of LABA monotherapy had the shortest mean time to receive prescriptions of long or short courses OCS for asthma exacerbations (11.3 months) compared with initiators of ICS monotherapy (11.7 months) and ICS/LABA combination therapy (11.4 months). Figure 5-7 shows a statistically significant difference in the probability of receiving long and short courses of OCS among initiators of ICS, LABA or ICS/LABA. Also, Bonferroni correction for

multiple comparisons showed statistically highly significant differences between all the three comparison groups; yet, comparing survival probability between LABA monotherapy and ICS/LABA combination therapy yielded statistically not significant results (Bonferroni p-value 0.1247).

High-dose ICS step-down subgroup. Continuers of ICS/LABA combination therapy with high-dose ICS had higher incidence rates for prescribing long and short courses of OCS (respectively: 28.9 per 100 person-yrs, 95%CI, 19.2-43.5 and 27.7 per 100 person-yrs, 95%CI, 18.2-42.0) compared with initiators of reduced medium-dose ICS combination therapy (21.9 per 100 person-yrs, 95%CI, 16.0-29.9 and 17.9 per 100 person-yrs, 95%CI, 12.7-25.4) and LABA stoppers who are continuing high-dose ICS monotherapy (respectively: 19.3 per 100 person-yrs, 95%CI, 11.8-31.5 and 15.1 per 100 person-yrs, 95%CI, 12.9-17.5). The trend of incidence rates was similar for original dose continuers between long and short OCS courses. However, the figure was reversed between step-down therapy approaches, where high-dose ICS monotherapy users had the lowest incidence rate of prescribing long courses; in contrast, medium-dose ICS combination therapy users had the lowest incidence rate of prescribing short courses.

Asthmatics who withdrew LABA and continued high-dose ICS as monotherapy had the shortest average time to receive prescriptions of long or short courses OCS for asthma exacerbations (3.8 months) compared with asthmatics who continued LABA while reducing ICS dose to medium as a combination therapy (8 months) and asthmatics who continued ICS/LABA combination therapy with original high-dose ICS (5.4 months). However, no statistically significant difference was observed between

exposure groups in terms of prescribing long (Long-rank test p-value 0.2118) or short courses of OCS (Long-rank test p-value 0.1421), and Bonferroni adjustment failed to show statistically significant results for the three comparisons (Table and Figure 5-8).

Medium-dose ICS step-down subgroup. Continuers of ICS/LABA combination therapy with medium-dose ICS had higher incidence rates for prescribing long and short courses of OCS (respectively: 21.9 per 100 person-yrs, 95%CI, 16.0-29.9 and 17.9 per 100 person-yrs, 95%CI, 12.7-25.4) compared with initiators of reduced low-dose ICS combination therapy (12.0 per 100 person-yrs, 95%CI, 8.9-16.1 and 10.9 per 100 person-yrs, 95%CI, 8.1-14.9) and LABA stoppers who are continuing medium-dose ICS monotherapy (respectively: 15.5 per 100 person-yrs, 95%CI, 13.4-17.9 and 15.1 per 100 person-yrs, 95%CI, 12.9-17.5). Unlike the previous step-down cohort, the trend of incidence rates was similar across exposure groups between long and short OCS courses regardless of the step-down therapy approach.

Unlike patients started ICS/LABA combination therapy with high-dose ICS, asthmatics who started combination therapy with medium-dose ICS had the shortest time to receive prescriptions for OCS (8 months) compared with counterparts who had any of the two step-down approaches (11.6 months). However, in tandem with patients commenced high-dose ICS, there was no statistically significant differences between exposure groups in terms of OCS prescribing (Table and Figure 5.8).

Asthma-related A&E visits

During one year of patient follow-up, a total of 100 A&E department visits for asthma exacerbations were recorded for the cohort, corresponding to 68 events for ICS monotherapy initiators, 16 events for LABA monotherapy initiators, and 16 events for

ICS/LABA combination therapy initiators. Among medium-dose step-down cohort, low ICS dose reducers encountered 19 asthma-related A&E visits compared to 7 visits for low dose ICS monotherapy (LABA stoppers). No asthma-related A&E visits were reported in the original medium-dose continuers in medium-dose step-down cohort or among asthmatics in high-dose step-down cohort (Table 5-4).

Main cohort. Asthmatics who started LABA monotherapy had higher annual incidence rates for A&E department visits for asthma exacerbations (0.5 per 100 person-yrs, 95%CI, 0.08-3.9) than counterparts who started ICS monotherapy (0.1 per 100 person-yrs, 95%CI, 0.08-0.2) or ICS/LABA combination therapy (0.3 per 100 person-yrs, 95%CI, 0.08-1.3). Compared to ICS-based therapy approaches, patients who started LABA monotherapy had the shortest time to be admitted to A&E department for asthma exacerbations (about 1 week versus 11-12 months). However, there was no statistically significant difference between therapy approaches in terms of asthma-related A&E department visits (log-rank test p-value 0.2185), and Bonferroni test did not show any significant difference for all three comparisons (Table and Figure 5-8).

Medium-dose ICS step-down subgroup. No asthma-related visits to A&E departments were reported for initiators of high-dose ICS step-down therapy cohort. Among initiators of medium-dose ICS step-down therapy, no similar events were reported for continuers of medium-dose ICS combination therapy. Among the step-down therapy approaches, patients who reduced ICS dose to low-dose while continuing LABA had higher incidence rates for asthma-related A&E visits (0.3 per 100 person-yrs, 95%CI, 0.05-2.4) than patients who withdrew LABA and continued medium-dose ICS

monotherapy (0.2 per 100 person-yrs, 95%CI, 0.04-0.7). Patients who continued LABA as ICS/LABA combination therapy while reducing ICS dose to low had, on average, one day after exposure to be admitted to A&E department for asthma exacerbations compared with patients who withdrew LABA and continued medium-dose ICS monotherapy (6.4 months). Similar to original cohort, log-rank and Bonferroni tests showed no statistically significant difference between exposure groups (Table and Figure 5-8).

Asthma-related Mortality

Incidence rates for asthma-related mortality are calculated among initiators of study drugs in general practices that are linked to the ONS mortality database (n=117), and among initiators of study drugs in general practices that are part of the ONS mortality database linkage scheme, i.e. algorithm-based (n=50,986). All the linked practices were in England, while the unlinked practices were spread across all four UK countries with the majority in England (79%), followed by Wales (10%), Scotland (9%), and Northern Ireland (2%). Table 5-6 shows the incidence rates of mortality outcomes during study follow up after exposure initiation (from the beginning of second year after first prescription of study exposure—Figure 4-2). Among the algorithm-derived asthma-death practices, initiators of LABA monotherapy had higher incidence rates for asthma-deaths (0.6 per 100 person-yrs, 95%CI, 0.2-1.5) compared with ICS/LABA combination therapy (0.5 per 100 person-yrs, 95%CI, 0.3-0.7) and ICS monotherapy initiators (0.1 per 100 person-yrs, 95%CI, 0.1-0.2). Among the ONS mortality linked practices, only 5 cases of asthma-related deaths were identified, and all were initiators of ICS monotherapy with uncontrolled asthma at baseline and mean age of 31 years. The

majority of those asthmatics were nonsmoker males initiated their ICS in the form of aerosols during the first quarter of the year (Table 5-7). The ONS-derived incidence rate of asthma-related mortality among initiators of ICS monotherapy was 5.0 per 100 person-yrs (95%CI, 2.1-12.0).

Furthermore, among study sample, initiators of ICS/LABA combination therapy had higher incidence rates for all-cause deaths (1.1 per 100 person-yrs, 95%CI, 0.8-1.5), followed by LABA monotherapy (0.7 per 100 person-yrs, 95%CI, 0.3-1.7) and ICS monotherapy initiators (0.5 per 100 person-yrs, 95%CI, 0.4-0.6). Although the average time to asthma mortality and all-cause mortality was identical across exposure groups (12 months after the end of first year following issuing first prescription for ICS, LABA, or ICS/LABA), there was statistically significant difference between exposure groups and between all the three comparisons (log-rank test p-value <0.0001; Bonferroni p-value <0.001 for all comparisons).

Comparison of Models

Tables 5-9 to 5-14 gives hazard ratios of asthma-related morbidity, asthma-related mortality, and all-cause mortality stratified by regression models and exposure group comparisons.

Conventional Cox PHREG models. Unadjusted Cox regression models showed that the hazard of receiving prescriptions for OCS for LABA initiators is 2.92 times the hazard for ICS monotherapy initiators; the hazard for ICS/LABA combination therapy initiators is 9.87 times the hazard for ICS monotherapy initiators, and 1.32 times the hazard for LABA monotherapy initiators. The hazard trend was relatively similar for short courses OCS. However, adjusting the model for time-independent covariates,

including variables measured during the baseline year and index date accounted for the variation in the unadjusted hazard ratios. Initiators of LABA monotherapy had 78% more likelihood of receiving prescriptions for OCS than initiators of ICS monotherapy (HR, 1.78; 95% CI, 1.17-2.54), initiators of ICS/LABA combination therapy had 54% higher likelihood of receiving OCS than initiators of ICS monotherapy (HR, 1.54; 95%CI, 1.30-1.86); however, they were 5% less likely to receive OCS prescriptions than initiators of LABA monotherapy (HR, 0.95; 95%CI, 0.63-1.41). Similarly, prescribing short courses OCS was 71% more likely to initiators of LABA than ICS monotherapies (HR, 1.71; 95%CI, 1.16-2.49), 40% more likely to initiators of combination therapy than ICS monotherapy (HR, 1.4; 95%CI, 1.15-1.70), and 15% less likely to initiators of combination therapy than LABA monotherapy (HR, 0.85; 95%CI, 0.56-1.30). Comparisons including ICS monotherapy were statistically significant, compared to ICS/LABA versus LABA monotherapy, and the adjusted models fitted better than the unadjusted models (unadjusted model Akaike information criterion—AIC, 30568.065; baseline-adjusted model AIC, 28127.583) (Table 5-9).

Unadjusted models showed LABA initiators had 4.04 times the hazard of asthma-related A&E department visits for ICS initiators; ICS/LABA initiators had 2.25 times the hazard for ICS initiators; and ICS/LABA initiators were about 1% more likely to be admitted to A&E departments for asthma exacerbations than LABA initiators. On the other hand, adjusting for baseline time-independent covariates yielded statistically not significant estimates of increased risks for asthma-related A&E department attendance by initiators of LABA monotherapy compared to initiators of ICS monotherapy (HR, 3.96; 95%CI, 0.4-30), and decreased risks by initiators of ICS/LABA combination therapy than

initiators of LABA monotherapy (HR, 0.78; 95%CI, 0.2-6.04). The hazard of A&E department visits between ICS/LABA combination therapy and ICS monotherapy initiators was not different (HR, 0.99; 95%CI, 0.21-7.14). The baseline-adjusted model did not fit better than the unadjusted model for predicting A&E department visits (unadjusted model AIC, 349.218; baseline-adjusted model AIC, 381.544) (Table 5-12).

Among asthmatics in practices that are unlinked to ONS-mortality database, the unadjusted estimates showed LABA monotherapy and ICS/LABA combination therapy initiators had higher risks for asthma-related deaths than ICS monotherapy initiators, and combination therapy initiators had higher asthma mortality risks than LABA monotherapy initiators. Adjusting for baseline characteristics showed the hazard of asthma deaths for LABA initiators was 3.2 times the hazard for ICS initiators (HR, 3.2; 95%CI, 1.65-8.92), and the hazard for ICS/LABA initiators was 5.1 times the hazard for ICS initiators (HR, 5.1; 95%CI, 1.01-5.02) and 1.62 times the hazard for LABA initiators (HR, 1.62; 95%CI, 0.1-22.1). Compared to the unadjusted model, the baseline-adjusted was better fitted (unadjusted model AIC, 1782.478; baseline-adjusted model AIC, 1697.062). The comparisons between LABA and ICS monotherapies were statistically significant, while the comparisons between combination therapy and ICS monotherapy were borderline significant, compared with the not significant comparisons between combination therapy and LABA monotherapy (Table 5-13). With regard to all-cause mortality outcome, the unadjusted model showed that LABA-based therapies had higher risks for all-cause deaths than ICS monotherapy, and ICS/LABA combination therapy had higher risks than LABA monotherapy regimens. Likewise, the direction was similar across the estimates after adjusting for baseline time-independent covariates. The

hazard of all-deaths for LABA initiators was 32% higher than the hazard of all-deaths for ICS initiators (HR, 1.32; 95%CI, 0.49-5.95); the hazard of all-deaths for ICS/LABA initiators was 77% higher than the hazard for ICS initiators (HR, 1.77; 95%CI, 0.71-4.0); and the hazard for ICS/LABA initiators was 39% higher than the hazard for LABA initiators (HR, 1.39; 95%CI, 0.44-4.34). The adjusted model was better fitted than the unadjusted one (unadjusted model AIC, 5504.828; baseline-adjusted AIC, 5191.972), but the estimates lacked statistical significance (Table 5-14).

Among asthmatics who initiated high-dose ICS in ICS/LABA combination therapy, the unadjusted models showed relatively no difference in the hazard of receiving long or short courses of OCS prescriptions for ICS dose reducers compared with the hazard for continuers of original high-dose ICS combination therapies, or the hazard for LABA stoppers compared with dose reducers. However, the models showed that LABA stoppers (high-dose ICS monotherapy) were 37-39% less likely to receive long or short courses OCS than continuers of original high-dose ICS/LABA combination therapy. After adjusting for baseline covariates, initiators of medium-dose ICS/LABA combination therapy (dose reducers) were 21% less likely to receive OCS prescriptions than continuers of original high-dose ICS/LABA combination therapy (HR, 0.79; 95%CI, 0.68-1.07). Prescriptions of OCS were 64% and 59% less likely to be issued for initiators of high-dose ICS monotherapy (LABA stoppers) than continuers of original high-dose ICS/LAAB combination therapy (HR, 0.36; 95%CI, 0.08-1.17) or initiators of medium-dose ICS/LABA combination therapy (HR, 0.41; 95%CI, 0.12-1.07), respectively. Likewise, relative rates and corresponding confidence intervals were similar across comparisons involving short courses of OCS. Compared to the unadjusted model, the

baseline-adjusted model fits well (Unadjusted model AIC, 1080,772; baseline-adjusted model AIC, 974.684); however, none of the comparisons were statistically significant (Table 5-10).

Among initiators of medium-dose ICS/LABA combination therapy, unadjusted models showed relatively no difference in the hazards for prescribing long or short courses of OCS for dose reducers than continuers of original ICS dose combination therapies; yet, continuers of original medium-dose ICS monotherapy (LABA stoppers) were 8-10% more likely to receive prescriptions for short or long courses OCS than medium-dose ICS/LABA combination therapy initiators (continuers), and 2.24-2.26 times more likely to receive short or long OCS prescriptions than low-dose ICS/LABA combination therapy initiators (dose reducers). Adjusting for baseline covariates yielded no difference in the hazard of prescribing long courses OCS between dose reducers and continuers of original ICS dose, but showed that low-dose ICS reducers were 17% less likely to receive short courses OCS than continuers of original medium-dose ICS combination therapies. Similarly, initiators of medium-dose ICS monotherapy (LABA stoppers) were 2% more likely to receive long-courses OCS than continuers of medium-dose ICS combination therapy (HR, 1.02; 95%CI, 0.32-3.23), but 39% less likely to receive short-courses OCS than continuers of medium-dose ICS combination therapy (HR, 0.61; 95%CI, 0.39-0.94). Prescribing long-courses OCS for LABA stoppers was 52% more likely than reducers of ICS dose combination therapy (HR, 1.52; 95%CI, 1.14-7.0), and prescribing short-courses OCS for LABA stoppers was 36% more likely than dose reducers (HR, 1.36; 95%CI, 0.97-6.37). Statistical significance was observed between LABA stoppers and dose reducers in terms of prescribing long-courses OCS,

and between LABA stoppers and continuers of original dose in terms of prescribing short-courses OCS. Relative to the unadjusted model, the baseline-adjusted model fitted better (unadjusted model AIC, 4321.999; baseline-adjusted model AIC, 4066.097) (Table 5-11).

Crude estimates showed initiators of medium-dose ICS monotherapy (LABA stoppers) had 2.53 times the hazard of asthma-related attendance to A&E departments for initiators of low-dose ICS as ICS/LABA combination therapy. Adjusting for baseline covariates showed LABA stoppers were 21% more likely to be admitted to A&E departments for asthma exacerbations than dose reducers (HR, 1.21; 95%CI, 0.07-13.2). The prediction model did not fit well in comparison to the unadjusted model (unadjusted model AIC, 51.318; baseline-adjusted model AIC, 128.0) (Table 5-12).

Time-dependent Cox PHREG models. Adjusting the model for time-dependent covariates in addition to baseline variables showed initiators of LABA monotherapy were 34% more likely to receive prescriptions for long-courses OCS than initiators of ICS monotherapy (HR, 1.34%; 95%CI, 1.27-2.02); and initiators of ICS/LABA combination therapy are 17% more likely to receive long-courses of OCS than initiators of ICS monotherapy (HR, 1.17; 95%CI, 1.04-2.3), and 30% less likely to receive OCS than initiators of LABA monotherapy (HR, 0.7; 95%CI, 0.4-1.64). Also, LABA initiators were 47% more likely to receive short-courses OCS for asthma exacerbations than ICS initiators (HR, 1.47; 95%CI, 1.22-2.44); there was no difference in prescribing short-course OCS between combination therapy initiators and ICS monotherapy initiators (HR, 1.0; 95%CI, 0.66-2.1); however, ICS/LABA initiators were 9% less likely to receive short courses OCS for asthma exacerbations than LABA monotherapy initiators (HR,

0.91; 95%CI, 0.81-1.35). Statistical significance was observed in comparisons between LABA and ICS initiators. Compared to baseline-adjusted model, time-dependent covariate-adjusted model had AIC values of 72818.935 for OCS and 70778.622 for short course OCS (Table 5-9).

In addition, LABA initiators were 4% more likely to be admitted to A&E departments for asthma exacerbations compared to ICS initiators (HR, 1.04; 95%CI, 0.32-15). On the other hand, initiators of combination therapy are less likely to visit A&E departments for asthma exacerbations compared to ICS monotherapy initiators (HR, 0.72; 95%CI, 0.08-5.01) and LABA monotherapy initiators (HR, 0.56; 95%CI, 0.11-4.12). Statistical significance was not attained in the regression model (AIC, 7631.89) (Table 5-12).

The model for predicting asthma-related deaths among general practices that are not part of the ONS-mortality database linkage scheme showed statistically significant differences between initiators of monotherapies by LABA and ICS (HR, 2.67; 95%CI, 1.44-4.93; model AIC, 2408.12). Initiators of combination therapy were more likely to experience asthma deaths than initiators of ICS monotherapy (HR, 4.2; 95%CI, 0.32-54.4) or LABA monotherapy (HR, 1.58; 95%CI, 0.11-21.8) (Table 5-13). Conversely, there was no statistically significant difference for all-cause deaths between comparison groups (model AIC, 8575.759), where LABA monotherapy initiators had 26% increase in the risk of death from any cause compared with ICS monotherapy initiators (HR, 1.26; 95%CI, 0.83-1.92); and combination therapy initiators were less likely to die from any cause than ICS monotherapy initiators (HR, 0.61; 95%CI, 0.21-1.74) or LABA monotherapy initiators (HR, 0.48; 95%CI, 0.16-1.46).

Among initiators of high-dose ICS/LABA combination therapy, statistical significance was observed between all comparison groups for OCS prescribing (model AIC, 2334.382) (Table 5-10). The hazard of receiving prescriptions for OCS for asthmatics on medium-dose ICS combination therapy (dose reducers) is 78% of the hazard for asthmatics continued high-dose ICS combination therapy (original dose continuers) (HR, 0.78; 95%CI, 0.6-0.95); the hazard of prescribing OCS to asthmatics who withdrew LABA and continued high-dose ICS monotherapy is 34% of the hazard for original dose continuers (HR, 0.34; 95%CI, 0.07-0.55); and the hazard of issuing OCS prescriptions to LABA stoppers is 33% the hazard for dose reducers (HR, 0.33; 95%CI, 0.07-0.52). The patterns for hazard ratios and corresponding confidence intervals for prescribing short courses OCS were relatively similar to the patterns of prescribing long courses OCS with model AIC value of 1973.53.

Among asthmatics who initiated medium-dose ICS/LABA combination therapy, statistical significance was not observed in comparing OCS prescribing rates between asthmatics reduced ICS dose to low-dose ICS/LABA combination therapy and continuers of original medium-dose ICS/LABA combination therapy (HR, 0.85; 95%CI, 0.67-1.07). Initiators of medium-dose ICS monotherapy (LABA stoppers) were 79% less likely to receive prescriptions for OCS than continuers of medium-dose ICS/LABA combination therapy (HR, 0.21; 95%CI, 0.09-0.52); and LABA stoppers were 28% more likely to receive OCS prescriptions than dose reducers (HR, 1.28; 95%CI, 1.09-5.08). Model AIC equals to 8708.432 (Table 5-11). Short courses OCS for asthma exacerbations were less likely prescribed to low-dose ICS/LABA than medium-dose ICS/LABA combination therapies (HR, 0.75; 95%CI, 0.59-0.97). Consistent with

prescribing long courses OCS, LABA stoppers were less likely to receive short courses OCS than original dose continuers (HR, 0.19; 95%CI, 0.1-0.38), but more likely to receive short courses OCS than dose reducers (HR, 1.24; 95%CI, 1.07-5.01). Model AIC value equals to 7661.84 (Table 5-11). Moreover, asthmatics who discontinued LABA and continued medium-dose ICS as monotherapy had 3% more likelihood to be admitted to A&E departments for asthma exacerbations than asthmatics who reduced the dose of ICS to low-dose while maintaining LABA as an alternative step-down therapy approach (HR, 1.03; 95%CI, 0.04-7.02; model AIC, 432.701) (Table 5-12).

Marginal structural models. In the original cohort, LABA initiators were 14% more likely to receive OCS than ICS initiators (HR, 1.14; 95%CI, 1.03-1.22. Conversely, combination therapy initiators were less likely to receive OCS than ICS initiators (HR, 0.91; 95%CI, 0.41-1.0) or LABA initiators (HR, 0.23, 95%CI, 0.1-0.34). Compared to previous model, MSM model was better fitted (Cox AIC, 72818.935; MSM AIC, 62275.601) and statistical significance was borderline between combination therapy and ICS monotherapy comparisons. Likewise, initiators of LABA monotherapy had 10% higher risk of receiving prescriptions for short courses OCS than initiators of ICS monotherapy (HR, 1.10; 95%CI, 1.07-1.18). Prescribing short courses OCS for asthma exacerbations was 62% less likely in ICS/LABA combination therapy initiators than ICS monotherapy initiators (HR, 0.38; 95%CI, 0.12-0.66) and 50% less likely in combination therapy initiators than LABA monotherapy initiators (HR, 0.5; 95%CI, 0.14-0.78). Compared to previous Cox model, MSM model for predicting short courses OCS was better fitted (Cox AIC, 70778.622; MSM AIC, 59429.489). Comparisons between combination therapy and LABA monotherapy groups were statistically significant (Table

5-9). Additionally, the hazard of visiting A&E departments for asthma exacerbations for LABA monotherapy initiators is 1% of the hazard for ICS monotherapy initiators (HR, 1.01; 95%CI, 0.05-8.02). Combination therapy initiators were less likely to have asthma-related visits to A&E departments compared to ICS monotherapy initiators (HR, 0.41; 95%CI, 0.03-3.14) or LABA monotherapy initiators (HR, 0.31; 95%CI, 0.05-2.06). Noticeably, none of the A&E visit estimates were statistically significant, although the model was better fitted compared with the previous Cox model (Cox AIC, 7631.89; MSM AIC, 6899.302) (Table 5-12).

In tandem with time-dependent Cox model, MSM showed statistical significance differences in asthma-deaths between LABA monotherapy initiators and ICS monotherapy initiators (HR, 1.25; 95%CI, 1.11-3.01; MSM AIC, 2089.231). Combination therapy initiators were more likely to experience asthma-deaths than ICS monotherapy counterparts (HR, 2.12; 95%CI, 0.13-35.9) or LABA monotherapy initiators (HR, 1.2; 95%CI, 0.04-15.3) (Table 5-13). Nevertheless, the model did not detect statistically significant differences between exposure groups in terms of all-cause mortality (MSM AIC, 7911.483) (Table 5-14), where LABA initiators had 15% more likelihood of death regardless the cause compared to ICS initiators (HR, 1.15; 95%CI, 0.63-1.78). On the other hand, ICS/LABA combination therapy initiators had less likelihood of dying from any reason than ICS monotherapy initiators (HR, 0.4; 95%CI, 0.15-1.52) or LABA monotherapy initiators (HR, 0.31; 95%CI, 0.1-1.31).

Model selection. Unadjusted models are not useful to consider given the nature of observational data, and models adjusted for baseline covariates do not adequately control for variations contributed by time-dependent covariates and exposures.

Estimates from marginal structural models and Cox models with time-dependent covariates are compared and contrasted in terms of AIC values for model fit evaluations, and graphically to determine if time-dependent confounding was present. For all models, MSM had lower AIC values than time-dependent Cox models, indicating better fit. With regard to models in step-down therapy approaches, AIC values were higher in time-dependent Cox models than baseline-adjusted models, an expected finding since AIC penalizes models with larger number of covariates. Figures 5-13 and 5-14 depicts hazard ratios and corresponding confidence intervals of OCS, short course of OCS, A&E visits, asthma-deaths, and all-cause deaths classified by exposure group comparisons and regression models. In general, confidence intervals for estimates derived by MSM were narrower than corresponding confidence intervals derived by time-dependent Cox models. Interestingly, MSM confidence intervals overlapped with outcome-specific intervals derived by Cox models for mortality outcomes and A&E department visits, but did not overlap for prescribing OCS outcomes, suggesting the presence of time-dependent confounding with regard to exposure effect on prescribing OCS, and absence of such confounding on deaths and A&E department visits.

Sensitivity Analyses

Prescriptions for oral corticosteroids were included as a covariate instead of an outcome to account for asthma severity, and HR estimates were not significantly different in terms of asthma-related A&E department visits. Time-dependent Cox model: LABA vs. ICS (HR, 1.05; 95%CI 0.29-16.1); ICS/LABA vs. ICS (HR, 0.71; 95%CI, 0.1-4.91); and ICS/LABA vs. LABA (HR, 0.61; 95%CI, 0.06-6.89). MSM: LABA vs. ICS (HR, 1.0; 95%CI 0.03-6.71); ICS/LABA vs. ICS (HR, 0.39; 95%CI, 0.04-3.0); and ICS/LABA

vs. LABA (HR, 0.28; 95%CI, 0.06-1.98). However, there was a noticeable difference in terms of asthma-related mortality, where MSM estimates had narrower confidence intervals and weaker HR estimates and the statistical significance between LABA initiators and ICS initiators was disappeared. However, Cox model estimates did not change significantly, suggesting prescribing OCS can be a time-dependent confounder when asthma mortality is the outcome of interest. MSM: LABA vs. ICS (HR, 1.04; 95%CI, 0.95-2.0); ICS/LABA vs. ICS (HR, 1.07; 95%CI, 0.08-3.01); and ICS/LABA vs. LABA (HR, 0.95; 95%CI, 0.02-5.61). Cox model: LABA vs. ICS (HR, 2.59; 95%CI 1.31-4.01); ICS/LABA vs. ICS (HR, 3.99; 95%CI, 0.28-50); and ICS/LABA vs. LABA (HR, 1.41; 95%CI, 0.08-19.1).

Moreover, the addition of patients with coexisting COPD did not impart significant changes to morbidity or mortality estimates, where the direction and the magnitude of HR were similar to estimates obtained in original cohort with excluded COPD patients; however, some estimates gained statistical significance in MSM models: prescribing OCS for ICS/LABA vs. ICS (HR, 0.82; 95%CI, 0.32-0.92); ICS/LABA vs. LABA (HR, 0.21; 95%CI, 0.1-0.33); LABA vs. ICS (HR, 1.11; 95%CI, 0.98-1.19). Asthma A&E visits: LABA vs. ICS (HR, 0.91; 95%CI 0.1-2.38); ICS/LABA vs. ICS (HR, 0.32; 95%CI, 0.11-0.57); ICS/LABA vs. LABA (HR, 0.28; 95%CI, 0.17-1.08). These findings suggest LABA products have beneficial effects on COPD outcomes. Asthma deaths: LABA vs. ICS (HR, 1.19; 95%CI, 1.05-2.05); ICS/LABA vs. ICS (HR, 1.97; 95%CI, 0.1-21.4); ICS/LABA vs. LABA (HR, 1.1; 95%CI, 0.1-9.14).

Figure 5-15 illustrates the distribution of stabilized weights over study follow up year by every month of exposure measurement. On average, the weights have a mean

of 1.02 (min, 0.36; max, 2.66) compared to unstabilized weights (mean, 2.33; min, 1.13; max, 3.32) indicating model satisfaction with positivity assumption.

In addition, there was no tangible differences in MSM-derived morbidity outcomes when patient follow up changed to 12 months after first prescriptions of study drugs (i.e. study index date for morbidity outcome followed index date for mortality outcome—Figure 4-2). Prescribing OCS: LABA vs. ICS (HR, 1.08; 95%CI, 0.99-1.18); ICS/LABA vs. ICS (HR, 0.87; 95%CI, 0.37-0.98); and ICS/LABA vs. LABA (HR, 0.18; 95%CI, 0.07-0.21). Asthma-related A&E department visits: LABA vs. ICS (HR, 0.97; 95%CI, 0.03-6.7); ICS/LABA vs. ICS (HR, 0.37; 95%CI, 0.03-3.0); and ICS/LABA vs. LABA (HR, 0.28; 95%CI, 0.05-1.9).

Table 5-1. Patient characteristics for original study cohort stratified by exposure type (January 4, 1993-August 20, 2010)

Characteristic	Exposure group, n=51,103			p-value*
	ICS 46,928 (91.8)	LABA 714 (1.4)	ICS/LABA 3,461 (6.8)	
Age (years)	37.2 (15.3)	40.4 (15.2)	40.0 (14.7)	<0.001
Sex (Female)	26,641 (56.8)	404 (56.6)	1,989 (57.5)	0.7197
Marital status				0.0191
Unmarried	4,537 (9.7)	70 (9.8)	342 (9.9)	
Married	6,843 (14.6)	127 (17.8)	556 (16.1)	
Unknown	35,548 (75.7)	517 (72.4)	2,563 (74.0)	
Weight status				0.6454
Non-obese	12 (0.03)	0	2 (0.06)	
Obese	63 (0.1)	1 (0.1)	7 (0.2)	
Unknown	46,853 (99.8)	713 (99.9)	3,452 (99.7)	
Smoking status				<0.001
Nonsmoker	40,798 (87.0)	599 (83.9)	2,957 (85.4)	
Former smoker	4,385 (9.3)	91 (12.7)	406 (11.7)	
Passive smoker	473 (1.0)	5 (0.7)	20 (0.6)	
Unknown	1,272 (2.7)	19 (2.7)	78 (2.3)	
Prescription payment				0.1265
Not exempted	133 (0.3)	2 (0.3)	11 (0.3)	
Exempted	521 (1.1)	5 (0.7)	54 (1.6)	
Unknown	46,274 (98.6)	707 (99.0)	3,396 (98.1)	
Capitation supplement level				<0.001
Low	334 (0.7)	4 (0.6)	21 (0.6)	
Medium	222 (0.5)	2 (0.3)	14 (0.4)	
High	80 (0.2)	1 (0.1)	5 (0.1)	
Not applicable	21,396 (45.6)	239 (33.5)	1,264 (36.5)	
Unknown	24,896 (53)	468 (65.5)	2,157 (62.4)	
Registration duration (months)	n=46,039 119.8 (123.7)	n=691 117.0 (133.0)	n=3,436 120.6 (131.0)	0.7837
Consultation duration				<0.001
≤10 minutes	29,819 (63.5)	515 (72.1)	2,028 (58.6)	
>10 minutes	17,075 (36.4)	196 (27.5)	1,426 (41.2)	
Unknown	34 (0.1)	3 (0.4	7 (0.2)	
Urgency of visit to practice				<0.001
Not urgent visit	46,493 (99.1)	710 (99.5)	3,423 (98.9)	
Urgent visit	401 (0.8)	1 (0.1)	31 (0.9)	
Unknown	34 (0.1)	3 (0.4)	7 (0.2)	
General practice location				<0.001
England	37,393 (79.7)	507 (71.0)	2,581 (74.6)	
Scotland	4,082 (8.7)	84 (11.8)	256 (7.4)	
Wales	4,393 (9.3)	99 (13.8)	440 (12.7)	
Northern Ireland	940 (2.0)	24 (3.4)	179 (5.2)	
Unknown	120 (0.3)	0	5 (0.1)	

Table 5-1. Continued

Characteristic	Exposure group, n=51,103			p-value*
	ICS 46,928 (91.8)	LABA 714 (1.4)	ICS/LABA 3,461 (6.8)	
Asthma severity 12 months prior to index date				
Prescription for OCS	2,673 (5.7)	46 (0.1)	257 (0.5)	<0.001
A&E department visit	126 (0.3)	2 (0.3)	20 (0.6)	0.0048
Hospitalization	1 (<0.1)	0	0	0.9565
No. of SABA prescriptions	2.2 (7.7)	3.2 (12.0)	2.2 (9.8)	0.0042
≤6	42,717 (91)	637 (89.2)	3,179 (91.9)	0.0575
>6	4,211 (9.0)	77 (10.8)	282 (8.1)	
Asthma severity at index date				
Prescription for SABA	25,500 (54.3)	219 (30.7)	1,339 (38.7)	<0.001
No. of asthma drug classes	1.5 (0.5)	1.3 (0.5)	2.4 (0.5)	<0.001
≤2	46,698 (99.5)	703 (98.5)	2,083 (60.2)	<0.001
>2	230 (0.5)	11 (1.5)	1,378 (39.8)	
Asthma controlled at baseline	18,293 (39.0)	429 (60.1)	1,787 (51.6)	<0.001
Concurrent asthma medications				
LTRA	86 (0.2)	14 (2.0)	53 (1.5)	<0.001
Oral methylxanthines	99 (0.2)	6 (0.8)	24 (0.7)	<0.001
Inhaled MCS	64 (0.1)	4 (0.6)	2 (0.06)	0.0042
Inhaled MRA	94 (0.2)	5 (0.7)	24 (0.7)	<0.001
Other concurrent medications				
Antibiotics for RTI	4,509 (9.6)	54 (7.6)	306 (8.8)	0.0658
Antivirals for RTI	6 (0.01)	0	0	0.7657
Nasal CS	1,686 (3.6)	23 (3.2)	164 (4.7)	0.002
Nasal MCS	15 (0.03)	2 (0.3)	0	<0.001
Nasal antihistamines	17 (0.04)	0	0	0.4693
Nasal decongestants	17 (0.04)	0	0	0.4693
Antitussives	161 (0.3)	2 (0.3)	8 (0.2)	0.5285
Selective beta-1-blockers	116 (0.2)	2 (0.3)	13 (0.4)	0.3508
Oral	115 (0.2)	2 (0.3)	13 (0.4)	0.3355
Ophthalmic	1 (<0.1)	0	0	0.9565
NSAIDs	288 (0.6)	5 (0.7)	32 (0.9)	0.0830
Aspirin	145 (0.3)	7 (1.0)	26 (0.7)	<0.001
Acetaminophen	191 (0.4)	2 (0.3)	21 (0.6)	0.1810
Opioid analgesics	546 (1.2)	11 (1.5)	73 (2.1)	<0.001
Oral cholinergics	1 (<0.1)	0	0	0.9565
Concurrent immunizations				
Influenza vaccine	154 (0.3)	2 (0.3)	24 (0.7)	0.0021
Pneumococcal PS vaccine	6 (0.01)	0	3 (0.1)	0.0063
Other vaccines	37 (0.1)	0	4 (0.1)	0.5701
Annual quarter at index date				0.2568
1st (January-March)	11,635 (24.8)	160 (22.4)	902 (26.1)	
2nd (April-June)	12,230 (26.0)	176 (24.7)	876 (25.3)	
3rd (July-September)	10,767 (23.0)	182 (25.5)	779 (22.5)	
4th (October-December)	12,296 (26.2)	196 (27.4)	904 (26.1)	

Table 5-1. Continued

Characteristic	Exposure group, n=51,103			p-value*
	ICS 46,928 (91.8)	LABA 714 (1.4)	ICS/LABA 3,461 (6.8)	
Comorbidities				
Atopic conditions	1,697 (3.6)	29 (4.1)	120 (3.5)	0.7315
Allergic rhinosinusitis	968 (2.1)	13 (1.8)	66 (2.0)	0.7492
Allergic conjunctivitis	25 (0.05)	2 (0.3)	2 (0.06)	0.0411
Atopic dermatitis	282 (0.6)	4 (0.5)	18 (0.5)	0.8307
Psoriasis	26 (0.06)	1 (0.1)	2 (0.06)	0.6410
Respiratory allergies	7 (0.01)	0	0	0.7324
Other allergies	448 (1.0)	10 (1.4)	35 (1.0)	0.4612
Respiratory tract infections	1,139 (2.4)	15 (2.1)	76 (2.2)	0.5998
Otitis media	31 (0.07)	0	0	0.2516
Pharyngolaryngitis	148 (0.3)	3 (0.4)	11 (0.3)	0.8849
Influenza	53 (0.1)	1 (0.1)	1 (0.03)	0.3348
Bronchitis	3 (0.01)	0	0	0.8751
Pneumonia	4 (0.01)	0	2 (0.06)	0.0342
Other infections	610 (1.3)	8 (1.1)	44 (1.3)	0.9076
Psychosocial pathologies	618 (1.3)	14 (2.0)	83 (2.4)	<0.001
Anxiety	15 (0.03)	0	2 (0.06)	0.6417
APD	1 (0.01)	0	0	0.8751
Depression	129 (0.3)	1 (0.1)	14 (0.4)	0.2945
Other conditions	21 (0.04)	1 (0.1)	4 (0.1)	0.1158
Tranquilizer use	65 (0.1)	3 (0.4)	11 (0.3)	0.0067
Antipsychotic use	32 (0.07)	0	5 (0.1)	0.2105
Antidepressant use	484 (1.0)	10 (1.4)	65 (1.9)	<0.001
Asthma action plan				<0.001
Available	564 (1.2)	0	74 (2.1)	
Not available	1 (<0.1)	0	0	
Unknown	46,363 (98.8)	714 (100)	2,287 (97.9)	
Asthma medication compliance				0.7359
Satisfactory	101 (0.2)	0	8 (0.2)	
Unsatisfactory	27 (0.1)	0	2 (0.1)	
Unknown	46,800 (99.7)	714 (100)	3,451 (99.7)	
General compliance level				0.7208
Good	40 (0.1)	1 (0.1)	5 (0.1)	
Poor	7 (0.01)	0	0	
Unknown	46,881 (99.9)	713 (99.9)	3,456 (99.9)	
Inhaler device type for exposure				<0.001
pMDI	37,230 (79.3)	527 (73.8)	1,088 (31.4)	
BAI	5,433 (11.6)	n/a	n/a	
DPI	4,158 (8.9)	187 (26.2)	1,517 (43.8)	
Unknown	107 (0.2)	0	856 (24.8)	
Aerosol	42,696 (91.0)	527 (73.8)	1,823 (52.7)	<0.001
Powder	4,169 (8.9)	187 (26.2)	1,638 (47.3)	
Unknown	63 (0.1)	0	0	
Spacer was prescribed	4,944 (10.5)	23 (3.2)	230 (6.6)	<0.001
Nebulizer was prescribed	36 (0.08)	0	1 (0.03)	0.4622

ICS, inhaled corticosteroids; LABA, long-acting beta-agonists
OCS, oral corticosteroids; A&E, accident and emergency
SABA, inhaled short-acting beta-agonists
LTRA, leukotriene receptor antagonists
MCS, mast cell stabilizers
MRA, muscarinic receptor antagonists
RTI, respiratory tract infections
NSAIDs, non-steroidal anti-inflammatory drugs
PS, polysaccharide
APD, affective personality disorders
pMDI, pressurized metered dose inhaler
BAI, breath actuated inhaler
DPI, dry powder inhaler
*Chi-squared test or Fisher's exact test are used for categorical characteristics, and analysis of variance (ANOVA) test is used for continuous characteristics
Numbers and percentages are reported for categorical factors, and means and corresponding standard deviations are reported for continuous factors

Table 5-2. Patient characteristics for step-down therapy cohort stratified by approach type among original high ICS/LABA dose initiators (January 5, 1993-July 12, 2010)

Characteristic	Exposure group[+], n=645			p-value[*]
	Original dose 136 (21.1)	Dose reducer 337 (52.2)	LABA stopper 172 (26.7)	
Age (years)	41.5 (13.6)	41.4 (14.0)	43.5 (13.3)	0.021
Sex (Female)	76 (55.9)	190 (56.4)	98 (56.9)	0.966
Marital status				0.1704
Unmarried	14 (10.3)	29 (8.6)	12 (7.0)	
Married	22 (16.2)	58 (17.2)	24 (14.0)	
Unknown	100 (73.5)	250 (74.2)	136 (79.0)	
Weight status				0.3736
Non-obese	1 (0.7)	0	0	
Obese	1 (0.7)	4 (1.2)	1 (0.6)	
Unknown	134 (98.6)	333 (98.8)	171 (99.4)	
Smoking status				0.0246
Nonsmoker	115 (84.5)	287 (85.1)	154 (89.5)	
Former smoker	17 (12.5)	45 (13.3)	13 (7.6)	
Passive smoker	2 (1.5)	2 (0.6)	2 (1.2)	
Unknown	2 (1.5)	3 (1.0)	3 (1.7)	
Prescription payment				0.7881
Not exempted	1 (0.7)	3 (0.9)	3 (1.7)	
Exempted	3 (2.2)	8 (2.4)	5 (2.9)	
Unknown	132 (97.1)	326 (97.7)	164 (95.3)	
Capitation supplement level				<0.001
Low	2 (1.5)	5 (1.5)	3 (1.7)	
Medium	0	1 (0.3)	0	
High	1 (0.7)	2 (0.6)	1 (0.7)	
Not applicable	42 (30.9)	125 (37.1)	105 (61.0)	
Unknown	91 (66.9)	204 (62.5)	63 (36.6)	
Registration duration (months)	n=121 112.5 (144.5)	n=307 116.1 (134.4)	n=153 109.0 (131.5)	0.6382
Consultation duration				<0.001
≤10 minutes	90 (66.2)	189 (56.1)	140 (81.4)	
>10 minutes	46 (33.8)	148 (43.9)	31 (18.0)	
Unknown	0	0	1 (0.6)	
Urgency of visit to practice				0.061
Not urgent visit	132 (97.0)	334 (99.1)	171 (99.4)	
Urgent visit	4 (3.0)	3 (0.9)	1 (0.6)	
Unknown	0	0	0	
General practice location				0.1186
England	105 (77.2)	258 (76.6)	138 (80.2)	
Scotland	7 (5.1)	20 (6.0)	14 (8.1)	
Wales	19 (14.0)	41 (12.2)	15 (8.7)	
Northern Ireland	5 (3.6)	17 (5.0)	5 (3.0)	
Unknown	0	1 (0.2)	0	

Table 5-2. Continued

Characteristic	Exposure group[+], n=645			p-value[*]
	Original dose 136 (21.1)	Dose reducer 337 (52.2)	LABA stopper 172 (26.7)	
Asthma severity at index date				
Prescription for SABA	53 (39.0)	145 (43.0)	89 (51.7)	<0.001
No. of asthma drug classes	2.5 (0.6)	2.5 (0.6)	1.5 (0.5)	<0.001
≤2	79 (58.0)	189 (56.0)	171 (99.4)	<0.001
>2	57 (42.0)	148 (44.0)	1 (0.6)	
Concurrent asthma medications				
LTRA	6 (4.4)	5 (1.5)	1 (0.6)	<0.001
Oral methylxanthines	3 (2.2)	2 (0.6)	1 (0.6)	0.0485
Inhaled MCS	1 (0.7)	0	0	0.1547
Inhaled MRA	2 (1.4)	3 (0.9)	2 (1.1)	0.1237
Other concurrent medications				
Antibiotics for RTI	14 (10.3)	26 (7.7)	18 (10.4)	0.1476
Antivirals for RTI	0	0	0	n/a
Nasal CS	8 (6.0)	15 (4.4)	9 (5.2)	0.4448
Nasal MCS	0	0	1 (0.6)	0.2505
Nasal antihistamines	0	0	0	n/a
Nasal decongestants	0	0	0	n/a
Antitussives	1 (0.7)	1 (0.3)	1 (0.6)	0.9321
Selective beta-1-blockers	2 (1.4)	4 (1.2)	1 (0.6)	0.7361
Oral	2 (1.4)	4 (1.2)	1 (0.6)	0.7361
Ophthalmic	0	0	0	n/a
NSAIDs	2 (1.4)	3 (0.9)	3 (1.7)	0.1675
Aspirin	2 (1.4)	3 (0.9)	1 (0.6)	0.7878
Acetaminophen	1 (0.7)	2 (0.6)	1 (0.6)	0.5083
Opioid analgesics	4 (3.0)	10 (3.0)	3 (1.7)	0.2192
Oral cholinergics	0	0	0	n/a
Concurrent immunizations				
Influenza vaccine	1 (0.7)	3 (0.9)	0	0.1155
Pneumococcal PS vaccine	0	1 (0.3)	0	0.6338
Other vaccines	0	1 (0.3)	1 (0.6)	0.657
Annual quarter at index date				0.8884
1st (January-March)	33 (24.3)	82 (24.3)	40 (23.2)	
2nd (April-June)	37 (27.2)	84 (25.0)	42 (24.4)	
3rd (July-September)	30 (22.0)	81 (24.0)	42 (24.4)	
4th (October-December)	36 (26.5)	90 (26.7)	48 (28.0)	

Table 5-2. Continued

Characteristic	Exposure group[+], n=645			p-value[*]
	Original dose 136 (21.1)	Dose reducer 337 (52.2)	LABA stopper 172 (26.7)	
Comorbidities				
Atopic conditions	6 (4.4)	13 (3.8)	5 (3.0)	0.1258
Allergic rhinosinusitis	3 (2.2)	7 (2.0)	3 (1.7)	0.3672
Allergic conjunctivitis	0	0	0	n/a
Atopic dermatitis	2 (1.5)	2 (0.6)	1 (0.6)	0.2768
Psoriasis	0	0	0	n/a
Respiratory allergies	0	0	0	n/a
Other allergies	1 (0.7)	4 (1.2)	2 (1.1)	0.4383
Respiratory tract infections	6 (4.4)	5 (1.5)	6 (3.5)	0.0175
Otitis media	0	0	1 (0.6)	0.2505
Pharyngolaryngitis	2 (1.4)	1 (0.3)	0	0.1386
Influenza	0	0	0	n/a
Bronchitis	0	0	0	n/a
Pneumonia	1 (0.7)	0	0	0.1547
Other infections	3 (2.2)	4 (1.2)	5 (3.0)	0.0898
Psychosocial pathologies	6 (4.4)	15 (4.4)	8 (4.6)	0.5838
Anxiety	0	0	1 (0.6)	0.2505
APD	0	0	0	n/a
Depression	1 (0.7)	3 (0.9)	2 (1.1)	0.7389
Other conditions	0	1 (0.3)	1 (0.6)	0.6685
Tranquilizer use	2 (1.4)	1 (0.3)	0	0.2660
Antipsychotic use	0	1 (0.3)	1 (0.6)	0.6685
Antidepressant use	3 (2.2)	9 (2.6)	3 (1.7)	0.3227
Asthma action plan				0.1991
Available	2 (1.5)	6 (1.8)	1 (0.6)	
Not available	0	0	0	
Unknown	134 (98.5)	331 (98.2)	171 (99.4)	
Asthma medication compliance				0.5606
Satisfactory	1 (0.7)	4 (1.2)	0	
Unsatisfactory	0	1 (0.3)	0	
Unknown	135 (99.3)	332 (98.5)	172 (100)	
General compliance level				0.1386
Good	2 (1.4)	1 (0.3)	0	
Poor	0	0	0	
Unknown	134 (98.6)	336 (99.7)	172 (100)	
Inhaler device type for exposure				<0.001
Aerosol (pMDI & BAI)	115 (84.6)	209 (62.0)	114 (66.3)	
Powder (DPI)	21 (15.4)	128 (38.0)	58 (33.7)	
Unknown	0	0	0	
Spacer was prescribed	14 (10.3)	24 (7.1)	14 (8.1)	0.1401
Nebulizer was prescribed	0	1 (0.1)	0	0.6338

ICS, inhaled corticosteroids
LABA, long-acting beta-agonists
OCS, oral corticosteroids
A&E, accident and emergency

SABA, inhaled short-acting beta-agonists
LTRA, leukotriene receptor antagonists
MCS, mast cell stabilizers
MRA, muscarinic receptor antagonists
RTI, respiratory tract infections
NSAIDs, non-steroidal anti-inflammatory drugs
PS, polysaccharide
APD, affective personality disorders
pMDI, pressurized metered dose inhaler
BAI, breath actuated inhaler
DPI, dry powder inhaler
*Chi-squared test or Fisher's exact test are used for categorical characteristics, and analysis of variance (ANOVA) test is used for continuous characteristics
Numbers and percentages are reported for categorical factors, and means and corresponding standard deviations are reported for continuous factors
+Original dose users are patients with ICS/LABA combination therapy with high dose ICS, dose reducers are patients who step down to ICS/LABA combination therapy with medium dose ICS, and LABA stoppers are high dose ICS monotherapy users

Table 5-3. Patient characteristics for step-down therapy cohort stratified by approach type among original medium ICS/LABA dose initiators (January 4, 1993-August 11, 2010)

Characteristic	Exposure group[+], n=2,581			p-value[*]
	Original dose 320 (12.4)	Dose reducer 519 (20.1)	LABA stopper 1,742 (67.5)	
Age (years)	41.4 (14.0)	38.2 (15.0)	41.3 (14.0)	<0.001
Sex (Female)	181 (56.5)	301 (58.0)	944 (54.2)	0.0264
Marital status				0.0034
Unmarried	28 (8.7)	55 (10.6)	136 (7.8)	
Married	56 (17.5)	78 (15.0)	307 (17.6)	
Unknown	236 (73.8)	386 (74.4)	1,299 (74.6)	
Weight status				0.1629
Non-obese	0	0	1 (0.05)	
Obese	4 (1.3)	1 (0.2)	6 (0.3)	
Unknown	316 (98.7)	518 (99.8)	1,735 (99.6)	
Smoking status				0.0006
Nonsmoker	272 (85.0)	447 (86.1)	1,512 (86.8)	
Former smoker	43 (13.4)	53 (10.2)	188 (10.8)	
Passive smoker	2 (0.6)	3 (0.6)	14 (0.8)	
Unknown	3 (1.0)	16 (3.1)	28 (1.6)	
Prescription payment				0.5353
Not exempted	1 (0.3)	3 (0.6)	2 (0.1)	
Exempted	10 (3.1)	6 (1.1)	24 (1.4)	
Unknown	309 (96.6)	510 (98.3)	1,716 (98.5)	
Capitation supplement level				<0.001
Low	2 (0.6)	3 (0.6)	12 (0.7)	
Medium	1 (0.3)	2 (0.4)	7 (0.4)	
High	1 (0.3)	1 (0.2)	2 (0.1)	
Not applicable	118 (36.8)	177 (34.1)	927 (53.2)	
Unknown	198 (62.0)	336 (64.7)	794 (45.5)	
Registration duration (months)	n=317 116.2 (134.4)	n=503 108.2 (117.1)	n=1,697 121.6 (136.2)	0.0021
Consultation duration				<0.001
≤10 minutes	179 (56.0)	303 (58.4)	1,261 (72.4)	
>10 minutes	140 (43.8)	215 (41.4)	479 (27.5)	
Unknown	1 (0.2)	1 (0.2)	2 (0.1)	
Urgency of visit to practice				0.8892
Not urgent visit	317 (99.1)	514 (99.0)	1,730 (99.3)	
Urgent visit	2 (0.6)	4 (0.8)	10 (0.6)	
Unknown	1 (0.3)	1 (0.2)	2 (0.1)	
General practice location				0.0003
England	245 (76.5)	398 (76.7)	1,324 (76.0)	
Scotland	19 (6.0)	36 (7.0)	171 (9.8)	
Wales	39 (12.2)	63 (12.1)	174 (10.0)	
Northern Ireland	16 (5.0)	21 (4.0)	70 (4.0)	
Unknown	1 (0.3)	1 (0.2)	3 (0.2)	

Table 5-3. Continued

Characteristic	Exposure group[+], n=2,581			p-value[*]
	Original dose 320 (12.4)	Dose reducer 519 (20.1)	LABA stopper 1,742 (67.5)	
Asthma severity at index date				
Prescription for SABA	137 (42.8)	201 (38.7)	923 (53.0)	<0.001
No. of asthma drug classes	2.5 (0.5)	2.4 (0.5)	1.5 (0.5)	<0.001
≤2	179 (56.0)	310 (59.7)	1,724 (99.0)	<0.001
>2	141 (44.0)	209 (40.3)	18 (1.0)	
Concurrent asthma medications				
LTRA	5 (1.5)	6 (1.1)	3 (0.2)	<0.001
Oral methylxanthines	2 (0.6)	3 (0.6)	9 (0.5)	0.9353
Inhaled MCS	0	1 (0.2)	2 (0.1)	0.3509
Inhaled MRA	3 (1.0)	2 (0.4)	7 (0.4)	0.4335
Other concurrent medications				
Antibiotics for RTI	24 (7.5)	40 (7.7)	174 (10.0)	0.0087
Antivirals for RTI	0	0	0	n/a
Nasal CS	14 (4.4)	24 (4.6)	64 (3.7)	0.1617
Nasal MCS	0	0	1 (0.06)	0.7857
Nasal antihistamines	0	0	3 (0.2)	0.485
Nasal decongestants	0	0	0	n/a
Antitussives	3 (1.0)	3 (0.6)	10 (0.6)	0.577
Selective beta-1-blockers	4 (1.2)	5 (1.0)	10 (0.6)	0.8571
Oral	4 (1.2)	5 (1.0)	10 (0.6)	0.8571
Ophthalmic	0	0	0	n/a
NSAIDs	2 (0.6)	4 (0.8)	10 (0.6)	0.6331
Aspirin	4 (1.2)	3 (0.6)	7 (0.4)	0.088
Acetaminophen	3 (1.0)	3 (0.6)	5 (0.3)	0.0098
Opioid analgesics	10 (3.1)	8 (1.5)	24 (1.4)	0.003
Oral cholinergics	0	0	0	n/a
Concurrent immunizations				
Influenza vaccine	7 (2.2)	15 (3.0)	13 (0.7)	0.0004
Pneumococcal PS vaccine	1 (0.3)	0	1 (0.1)	0.2495
Other vaccines	1 (0.3)	2 (0.4)	3 (0.2)	0.6445
Annual quarter at index date				0.1734
1st (January-March)	78 (24.3)	147 (28.3)	437 (25.1)	
2nd (April-June)	79 (24.7)	121 (23.3)	439 (25.2)	
3rd (July-September)	77 (24.1)	114 (22.0)	409 (23.5)	
4th (October-December)	86 (26.9)	137 (26.4)	457 (26.2)	

Table 5-3. Continued

Characteristic	Exposure group[+], n=2,581			p-value[*]
	Original dose 320 (12.4)	Dose reducer 519 (20.1)	LABA stopper 1,742 (67.5)	
Comorbidities				
Atopic conditions	12 (3.8)	17 (3.3)	52 (3.0)	0.3428
Allergic rhinosinusitis	6 (2.0)	9 (1.7)	28 (1.6)	0.5968
Allergic conjunctivitis	0	1 (0.2)	1 (0.06)	0.2941
Atopic dermatitis	2 (0.6)	3 (0.6)	9 (0.5)	0.8352
Psoriasis	0	1 (0.2)	1 (0.08)	0.6919
Respiratory allergies	0	0	1 (0.08)	0.7857
Other allergies	4 (1.2)	3 (0.6)	12 (0.7)	0.2131
Respiratory tract infections	4 (1.2)	11 (2.1)	42 (2.4)	0.0923
Otitis media	0	0	0	n/a
Pharyngolaryngitis	1 (0.3)	2 (0.4)	3 (0.2)	0.5477
Influenza	0	0	1 (0.06)	0.485
Bronchitis	0	0	1 (0.06)	0.7857
Pneumonia	0	1 (0.2)	1 (0.06)	0.5424
Other infections	3 (1.0)	8 (1.5)	36 (2.0)	0.5309
Psychosocial pathologies	8 (2.5)	13 (2.5)	19 (1.1)	<0.001
Anxiety	0	1 (0.2)	0	0.019
APD	0	0	0	n/a
Depression	2 (0.6)	2 (0.4)	5 (0.3)	0.3171
Other conditions	1 (0.3)	1 (0.2)	1 (0.06)	0.0571
Tranquilizer use	1 (0.3)	2 (0.4)	3 (0.2)	0.5271
Antipsychotic use	1 (0.3)	1 (0.2)	1 (0.06)	0.2963
Antidepressant use	3 (1.0)	6 (1.1)	9 (0.5)	<0.001
Asthma action plan				<0.001
Available	6 (1.8)	14 (2.7)	10 (0.6)	
Not available	0	0	0	
Unknown	314 (98.2)	505 (97.3)	1732 (99.4)	
Asthma medication compliance				0.0088
Satisfactory	4 (1.3)	2 (0.4)	3 (0.2)	
Unsatisfactory	1 (0.3)	1 (0.2)	0	
Unknown	315 (98.4)	516 (99.4)	1,739 (99.8)	
General compliance level				0.9302
Good	1 (0.3)	2 (0.4)	4 (0.2)	
Poor	0	0	1 (0.05)	
Unknown	319 (99.7)	517 (99.6)	1,737 (99.7)	
Inhaler device type for exposure				<0.001
Aerosol (pMDI & BAI)	198 (61.9)	252 (48.5)	1,432 (82.2)	
Powder (DPI)	122 (38.1)	267 (51.5)	308 (17.7)	
Unknown	0	0	2 (0.1)	
Spacer was prescribed	22 (7.0)	32 (6.2)	192 (11.0)	<0.001
Nebulizer was prescribed	1 (0.3)	0	1 (0.06)	0.2495

ICS, inhaled corticosteroids
LABA, long-acting beta-agonists
OCS, oral corticosteroids
A&E, accident and emergency

SABA, inhaled short-acting beta-agonists
LTRA, leukotriene receptor antagonists
MCS, mast cell stabilizers
MRA, muscarinic receptor antagonists
RTI, respiratory tract infections
NSAIDs, non-steroidal anti-inflammatory drugs
PS, polysaccharide
APD, affective personality disorders
pMDI, pressurized metered dose inhaler
BAI, breath actuated inhaler
DPI, dry powder inhaler
*Chi-squared test or Fisher's exact test are used for categorical characteristics, and analysis of variance (ANOVA) test is used for continuous characteristics
Numbers and percentages are reported for categorical factors, and means and corresponding standard deviations are reported for continuous factors
+Original dose users are patients with ICS/LABA combination therapy with medium dose ICS, dose reducers are patients who step down to ICS/LABA combination therapy with low dose ICS, and LABA stoppers are medium dose ICS monotherapy users

Table 5-4. Incidence rates of morbidity outcomes among initiators of study drugs

Exposure	Outcome			
	Oral corticosteroid prescription		Asthma A&E department visit	
	No. of cases	Rate (95%CI)[+]	No. of cases	Rate (95%CI)[+]
Original cohort				
ICS monotherapy	1,321	10.6 (10.0-11.2)	15	0.1 (0.08-0.2)
LABA monotherapy	29	19.9 (13.8-28.6)	1	0.5 (0.08-3.9)
ICS/LABA combination therapy	138	17.7 (14.9-20.9)	2	0.3 (0.08-1.3)
Step-down therapy cohort				
High dose ICS combination therapy	23	28.9 (19.2-43.5)	0	n/a
Medium dose ICS combination therapy	39	21.9 (16.0-29.9)	0	n/a
High dose ICS monotherapy	16	19.3 (11.8-31.5)	0	n/a
Medium dose ICS combination therapy	39	21.9 (16.0-29.9)	0	n/a
Low dose ICS combination therapy	45	12.0 (8.9-16.1)	1	0.3 (0.05-2.4)
Medium dose ICS monotherapy	178	15.5 (13.4-17.9)	2	0.2 (0.04-0.7)

[+] cases per 100person-years
A&E, accident and emergency
ICS, inhaled corticosteroids
LABA, long-acting beta-agonists
n/a, not applicable

Table 5-5. Incidence rates of prescriptions for short courses of oral corticosteroids for asthma exacerbations among initiators of study drugs

Exposure	Short course oral corticosteroids	
	No. of cases	Rate (95%CI)[+]
Original cohort		
ICS monotherapy	1,226	9.8 (9.3-10.4)
LABA monotherapy	27	18.5 (12.7-27.0)
ICS/LABA combination therapy	116	14.8 (12.4-17.8)
Step-down therapy cohort		
High dose ICS combination therapy	22	27.7 (18.2-42.0)
Medium dose ICS combination therapy	32	17.9 (12.7-25.4)
High dose ICS monotherapy	16	19.3 (11.8-31.5)
Medium dose ICS combination therapy	32	17.9 (12.7-25.4)
Low dose ICS combination therapy	41	10.9 (8.1-14.9)
Medium dose ICS monotherapy	173	15.1 (12.9-17.5)

[+] cases per 100 person-years
A&E, accident and emergency
ICS, inhaled corticosteroids
LABA, long-acting beta-agonists

Table 5-6. Incidence rates of mortality outcomes among initiators of study drugs

Exposure	Outcome			
	Asthma death		All-cause death	
	No. of cases	Rate (95%CI)[+]	No. of cases	Rate (95%CI)[+]
ONS linked practices				
ICS monotherapy	5	5.0 (2.1-12.0)		
LABA monotherapy	0	n/a		
ICS/LABA combination therapy	0	n/a		
ONS unlinked practices[++]				
ICS monotherapy	63	0.1 (0.1-0.2)		
LABA monotherapy	4	0.6 (0.2-1.5)		
ICS/LABA combination therapy	16	0.5 (0.3-0.7)		
Original cohort				
ICS monotherapy			215	0.5 (0.4-0.6)
LABA monotherapy			5	0.7 (0.3-1.7)
ICS/LABA combination therapy			36	1.1 (0.8-1.5)

[+] cases per 100 person-years
[++] algorithm-derived outcome
ICS, inhaled corticosteroids
LABA, long-acting beta-agonists
ONS, office for national statistics
n/a, not applicable

Table 5-7. Characteristics of asthmatics died of asthma that are identified in the ONS Mortality linked database

Characteristic	No. (%)
Initiators of inhaled corticosteroids monotherapy	5 (100)
>2 asthma medication classes prescribed at index date	5 (100)
>6 inhaled SABA prescriptions issued in preceding year	5 (100)
Asthma status uncontrolled at index date	5(100)
Age (year), Mean (SD)	31 (17.3)
13	2 (40)
35	1 (20)
44	1 (20)
50	1 (20)
Sex	
Female	1 (20)
Male	4 (80)
Marital status	
Unmarried	1 (20)
Married	1 (20)
Unknown	3 (60)
Smoking status	
Nonsmoker	3 (60)
Unknown	2 (40)
Concomitant medications at index date	
Inhaled short-acting beta-agonists	5 (100)
Antibiotics for respiratory infections	1 (20)
Aspirin	1 (20)
Consultation duration (minute)	
$\leq$10	4 (80)
>10	1 (20)
Inhaler device type for inhaled corticosteroids	
Aerosols	3 (60)
Dry powder	2 (40)
Capitation supplement level	
Not applicable	4 (80)
Unknown	1 (20)
Annual quarter at index date	
1st (January-March)	2 (40)
2nd (April-June)	1 (20)
3rd (July-September)	1 (20)
4th (October-December)	1 (20)

SABA, short-acting beta-agonist
SD, standard deviation

Table 5-8. Distribution of average time-to-event among exposure groups

Exposure	Time-to-event in days, Mean (SD) Outcome				
	OCS	OCS short course	A&E visit	Asthma-death	All-cause death
ICS	351.2 (0.4)	352.1 (0.4)	335.0 (0.05)	365 (0)	364 (0.01)
LABA	340.2 (5.1)	341.3 (5.0)	7.0 (n/a)	365 (0)	365 (0)
ICS/LABA	343.5 (2.0)	347.4 (1.8)	365.0 (0.1)	365 (0)	365 (0)
High-dose ICS/LABA	163.0 (3.0)	164.0 (2.7)			
Medium-dose ICS/LABA	240.4 (2.6)	243.7 (2.3)			
High-dose ICS[+]	113.6 (1.2)	113.6 (1.2)			
Medium-dose ICS/LABA	240.4 (2.6)	243.7 (2.3)	n/a		
Low-dose ICS/LABA	349.2 (2.6)	351.0 (2.4)	1.0 (n/a)		
Medium-dose ICS[+]	347.4 (1.4)	348.0 (1.4)	191.0 ()		

[+] LABA stopper
A&E, accident and emergency
ICS, inhaled corticosteroids
LABA, long-acting beta-agonists
OCS, oral corticosteroids
n/a, not applicable
SD, standard deviation

Table 5-9. Hazard ratios of oral corticosteroid prescriptions among original cohort

Model	Outcome	Exposure Comparison	HR	95%CI	AIC
Unadjusted	OCS	LABA vs. ICS	2.92	2.54 – 3.36	30568.065
		ICS/LABA vs. ICS	9.87	7.05 – 13.8	
		ICS/LABA vs. LABA	1.32	1.14 – 1.52	
	Short course OCS	LABA vs. ICS	2.71	2.40 – 3.02	28127.583
		ICS/LABA vs. ICS	8.83	6.19 – 12.0	
		ICS/LABA vs. LABA	1.29	1.08 – 1.43	
Adjusted conventional Cox PHREG[+]	OCS	LABA vs. ICS	1.78	1.17 – 2.54	29763.723
		ICS/LABA vs. ICS	1.54	1.30 – 1.86	
		ICS/LABA vs. LABA	0.95	0.63 – 1.41	
	Short course OCS	LABA vs. ICS	1.71	1.16 – 2.49	27505.543
		ICS/LABA vs. ICS	1.40	1.15 – 1.70	
		ICS/LABA vs. LABA	0.85	0.56 – 1.30	
Adjusted time-dependent Cox PHREG[++]	OCS	LABA vs. ICS	1.34	1.27 – 2.02	72818.935
		ICS/LABA vs. ICS	1.17	1.04 – 2.30	
		ICS/LABA vs. LABA	0.70	0.40 – 1.64	
	Short course OCS	LABA vs. ICS	1.47	1.22 – 2.44	70778.622
		ICS/LABA vs. ICS	1.00	0.66 – 2.10	
		ICS/LABA vs. LABA	0.91	0.81 – 1.35	
Marginal structural model[+++]	OCS	LABA vs. ICS	1.14	1.03 – 1.22	62275.601
		ICS/LABA vs. ICS	0.91	0.41 – 1.00	
		ICS/LABA vs. LABA	0.23	0.09 – 0.34	
	Short course OCS	LABA vs. ICS	1.10	1.07 – 1.18	59429.489
		ICS/LABA vs. ICS	0.38	0.12 – 0.66	
		ICS/LABA vs. LABA	0.50	0.14 – 0.78	

[+] adjusted for baseline-year and index-date covariates
[++] adjusted for baseline-year, index-date and time-dependent covariates
[+++] adjusted for all covariates, including time-dependent confounders

AIC, Akaike information criterion
CI, confidence interval
ICS, inhaled corticosteroids
HR, hazard ratio
LABA, long-acting beta-agonists
OCS, oral corticosteroids

Table 5-10. Hazard ratios of oral corticosteroid prescriptions among step-down cohort with high-dose ICS/LABA initiators

Model	Outcome	Exposure Comparison	HR	95%CI	AIC
Unadjusted	OCS	Reducer vs. Original	1.00	0.72 – 1.68	1082.443
		Stopper vs. Original	0.63	0.39 – 1.67	
		Stopper vs. Reducer	1.03	0.57 – 1.89	
	Short course OCS	Reducer vs. Original	0.98	0.70 – 1.68	974.846
		Stopper vs. Original	0.61	0.39 – 1.66	
		Stopper vs. Reducer	1.01	0.55 – 1.84	
Adjusted conventional Cox PHREG[+]	OCS	Reducer vs. Original	0.79	0.68 – 1.07	1080.772
		Stopper vs. Original	0.36	0.08 – 1.17	
		Stopper vs. Reducer	0.41	0.12 – 1.07	
	Short course OCS	Reducer vs. Original	0.78	0.68 – 1.04	974.684
		Stopper vs. Original	0.35	0.07 – 1.16	
		Stopper vs. Reducer	0.39	0.08 – 1.03	
Adjusted time-dependent Cox PHREG[++]	OCS	Reducer vs. Original	0.78	0.60 – 0.95	2334.382
		Stopper vs. Original	0.34	0.07 – 0.55	
		Stopper vs. Reducer	0.33	0.07 – 0.52	
	Short course OCS	Reducer vs. Original	0.71	0.60 – 0.90	1973.530
		Stopper vs. Original	0.32	0.06 – 0.50	
		Stopper vs. Reducer	0.35	0.06 – 0.51	

[+] adjusted for baseline-year and index-date covariates
[++] adjusted for baseline-year, index-date and time-dependent covariates
AIC, Akaike information criterion
CI, confidence interval
HR, hazard ratio
OCS, oral corticosteroids

Table 5-11. Hazard ratios of oral corticosteroid prescriptions among step-down cohort with medium-dose ICS/LABA initiators

Model	Outcome	Exposure Comparison	HR	95%CI	AIC
Unadjusted	OCS	Reducer vs. Original	1.01	0.44 – 4.11	4378.684
		Stopper vs. Original	1.10	0.76 – 1.35	
		Stopper vs. Reducer	2.26	2.02 – 8.85	
	Short course OCS	Reducer vs. Original	0.94	0.41 – 3.07	4117.586
		Stopper vs. Original	1.08	0.75 – 1.14	
		Stopper vs. Reducer	2.24	1.90 – 2.71	
Adjusted conventional Cox PHREG[+]	OCS	Reducer vs. Original	0.99	0.78 – 2.01	4321.999
		Stopper vs. Original	1.02	0.32 – 3.23	
		Stopper vs. Reducer	1.52	1.14 – 7.00	
	Short course OCS	Reducer vs. Original	0.83	0.26 – 2.65	4066.097
		Stopper vs. Original	0.61	0.39 – 0.94	
		Stopper vs. Reducer	1.36	0.97 – 6.37	
Adjusted time-dependent Cox PHREG[++]	OCS	Reducer vs. Original	0.85	0.67 – 1.07	8708.432
		Stopper vs. Original	0.21	0.09 – 0.52	
		Stopper vs. Reducer	1.28	1.09 – 5.08	
	Short course OCS	Reducer vs. Original	0.75	0.59 – 0.97	7661.840
		Stopper vs. Original	0.19	0.10 – 0.38	
		Stopper vs. Reducer	1.24	1.07 – 5.01	

[+] adjusted for baseline-year and index-date covariates
[++] adjusted for baseline-year, index-date and time-dependent covariates
AIC, Akaike information criterion
CI, confidence interval
HR, hazard ratio
OCS, oral corticosteroids

Table 5-12. Hazard ratios of asthma-related accident and emergency department visits among original cohort and step-down cohort with medium-dose ICS/LABA initiators

Model	Outcome	Exposure Comparison	HR	95%CI	AIC
Unadjusted	Asthma A&E visit	LABA vs. ICS	4.04	0.52 – 35.7	349.218
		ICS/LABA vs. ICS	2.25	0.51 – 9.87	
		ICS/LABA vs. LABA	1.01	0.33 – 7.27	
		Stopper vs. Reducer	2.53	0.21 – 22.0	51.318
Adjusted conventional Cox PHREG[+]	Asthma A&E visit	LABA vs. ICS	3.96	0.40 – 30.0	381.544
		ICS/LABA vs. ICS	0.99	0.21 – 7.14	
		ICS/LABA vs. LABA	0.78	0.20 – 6.04	
		Stopper vs. Reducer	1.21	0.07 – 13.2	128.000
Adjusted time-dependent Cox PHREG[++]	Asthma A&E visit	LABA vs. ICS	1.04	0.32 – 15.0	7631.890
		ICS/LABA vs. ICS	0.72	0.08 – 5.01	
		ICS/LABA vs. LABA	0.56	0.11 – 4.12	
		Stopper vs. Reducer	1.03	0.04 – 7.02	432.701
Marginal structural model[+++]	Asthma A&E visit	LABA vs. ICS	1.01	0.05 – 8.02	6899.302
		ICS/LABA vs. ICS	0.41	0.03 – 3.14	
		ICS/LABA vs. LABA	0.32	0.05 – 2.06	

[+] adjusted for baseline-year and index-date covariates
[++] adjusted for baseline-year, index-date and time-dependent covariates
[+++] adjusted for all covariates, including time-dependent confounders
A&E, accident and emergency
AIC, Akaike information criterion
CI, confidence interval
ICS, inhaled corticosteroids
HR, hazard ratio
LABA, long-acting beta-agonists

Table 5-13. Hazard ratios of asthma-deaths among original cohort in practices unlinked to ONS-mortality database

Model	Outcome	Exposure Comparison	HR	95%CI	AIC
Unadjusted	Asthma death	LABA vs. ICS	4.18	1.52 – 11.5	1782.478
		ICS/LABA vs. ICS	5.47	2.01 – 6.01	
		ICS/LABA vs. LABA	1.83	0.28 – 42.49	
Adjusted conventional Cox PHREG[+]	Asthma death	LABA vs. ICS	3.20	1.65 – 8.92	1697.062
		ICS/LABA vs. ICS	5.10	1.01 – 5.02	
		ICS/LABA vs. LABA	1.62	0.09 – 22.1	
Adjusted time-dependent Cox PHREG[++]	Asthma death	LABA vs. ICS	2.67	1.44 – 4.93	2408.120
		ICS/LABA vs. ICS	4.20	0.32 – 54.4	
		ICS/LABA vs. LABA	1.58	0.11 – 21.8	
Marginal structural model[+++]	Asthma death	LABA vs. ICS	1.25	1.11 – 3.01	2089.231
		ICS/LABA vs. ICS	2.12	0.13 – 35.9	
		ICS/LABA vs. LABA	1.20	0.04 – 15.3	

[+] adjusted for baseline-year and index-date covariates
[++] adjusted for baseline-year, index-date and time-dependent covariates
[+++] adjusted for all covariates, including time-dependent confounders
AIC, Akaike information criterion
CI, confidence interval
ICS, inhaled corticosteroids
HR, hazard ratio
LABA, long-acting beta-agonists

Table 5-14. Hazard ratios of all-cause deaths among original cohort

Model	Outcome	Exposure Comparison	HR	95%CI	AIC
Unadjusted	All-cause death	LABA vs. ICS	1.54	0.63 – 6.01	5504.828
		ICS/LABA vs. ICS	2.23	1.57 – 4.77	
		ICS/LABA vs. LABA	1.45	0.57 – 4.98	
Adjusted conventional Cox PHREG[+]	All-cause death	LABA vs. ICS	1.32	0.49 – 5.95	5191.972
		ICS/LABA vs. ICS	1.77	0.71 – 4.00	
		ICS/LABA vs. LABA	1.39	0.44 – 4.34	
Adjusted time-dependent Cox PHREG[++]	All-cause death	LABA vs. ICS	1.26	0.83 – 1.92	8575.759
		ICS/LABA vs. ICS	0.61	0.21 – 1.74	
		ICS/LABA vs. LABA	0.48	0.16 – 1.46	
Marginal structural model[+++]	All-cause death	LABA vs. ICS	1.15	0.63 – 1.78	7911.483
		ICS/LABA vs. ICS	0.40	0.15 – 1.52	
		ICS/LABA vs. LABA	0.31	0.09 – 1.31	

[+] adjusted for baseline-year and index-date covariates
[++] adjusted for baseline-year, index-date and time-dependent covariates
[+++] adjusted for all covariates, including time-dependent confounders
AIC, Akaike information criterion
CI, confidence interval
ICS, inhaled corticosteroids
HR, hazard ratio
LABA, long-acting beta-agonists

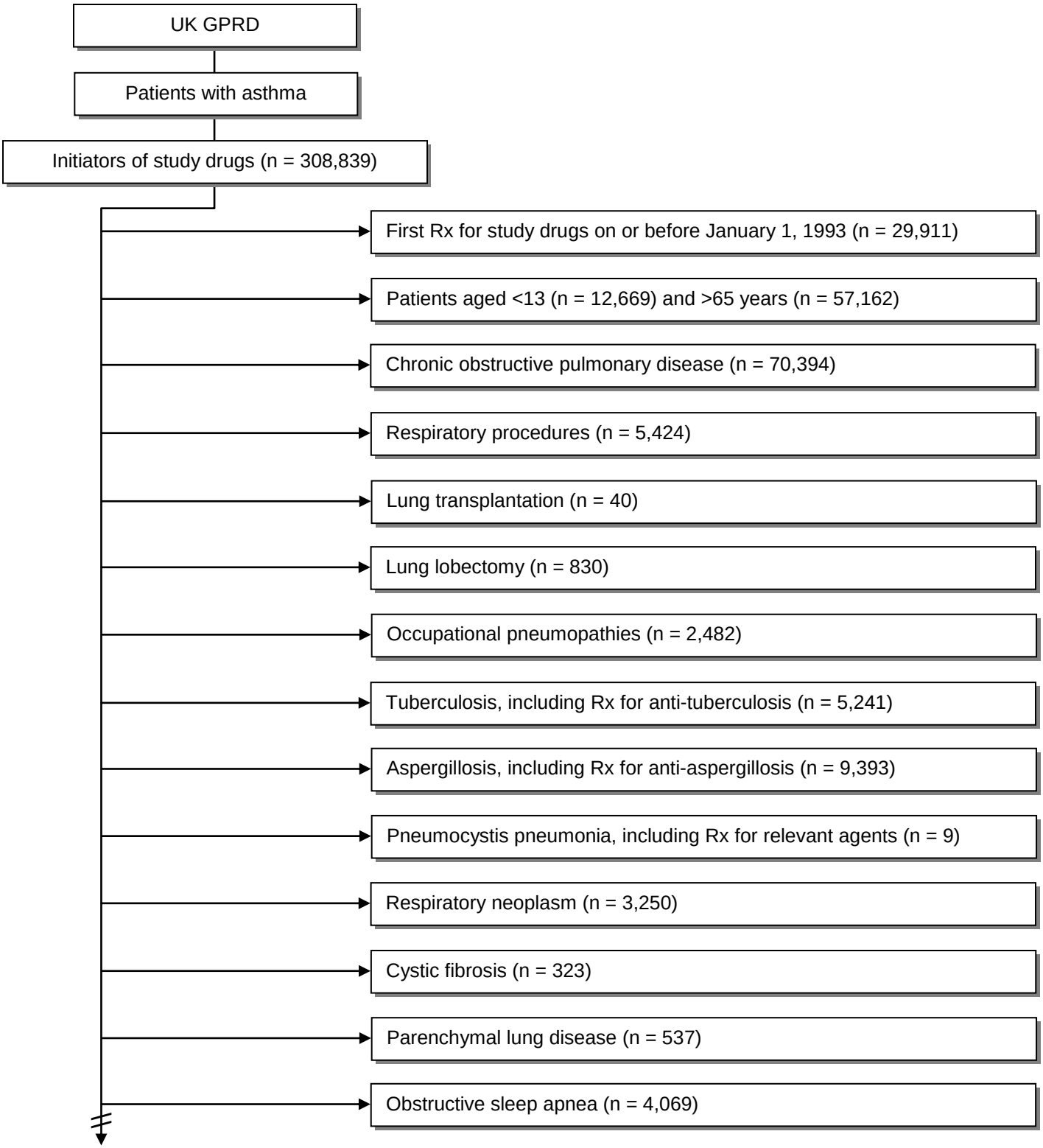


Figure 5-1. Cohort sample disposition. ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; Rx, Prescription. Exclusion numbers are mutually not exclusive, where patients might have more than one criterion.

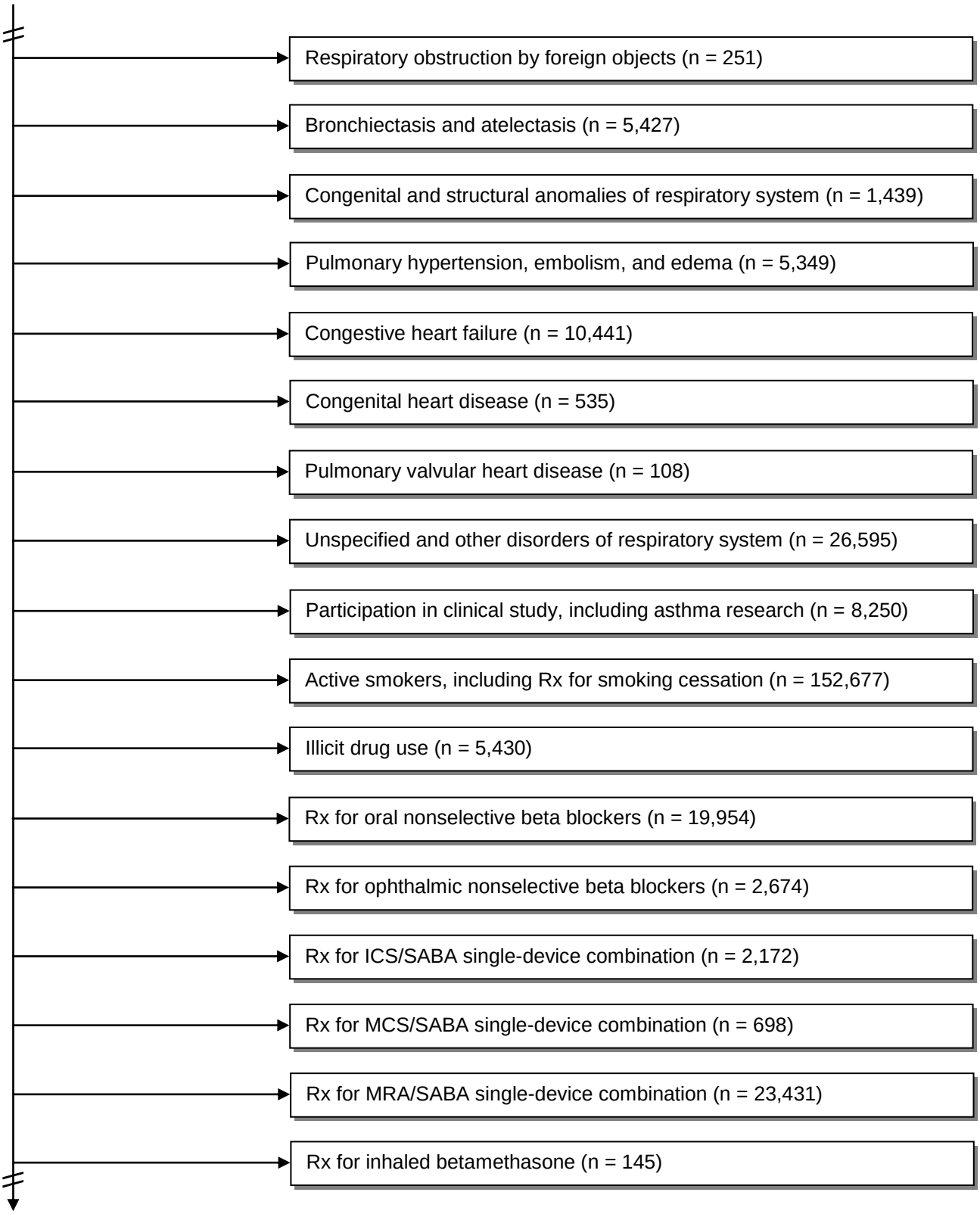


Figure 5-1. Continued

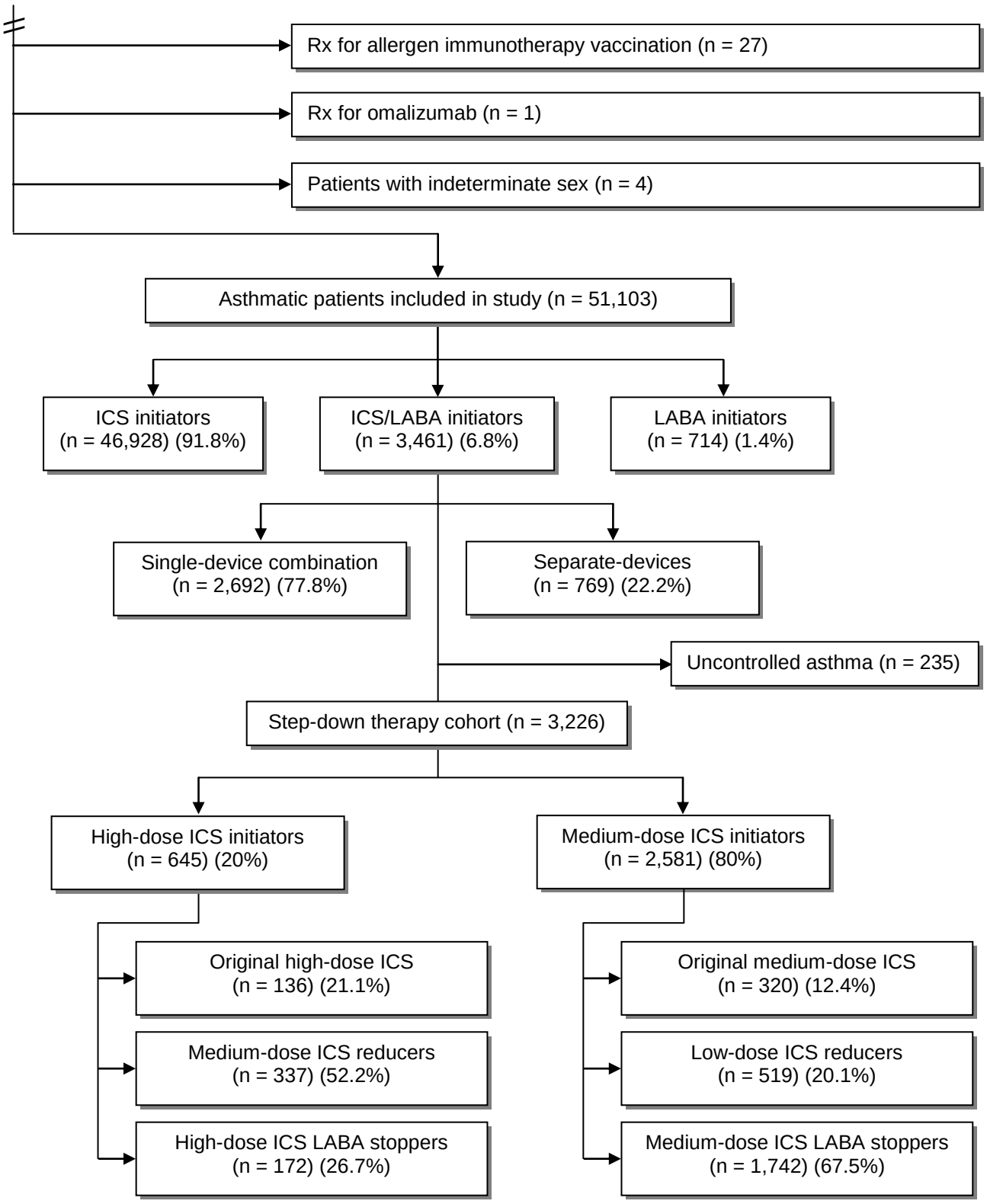


Figure 5-1. Continued

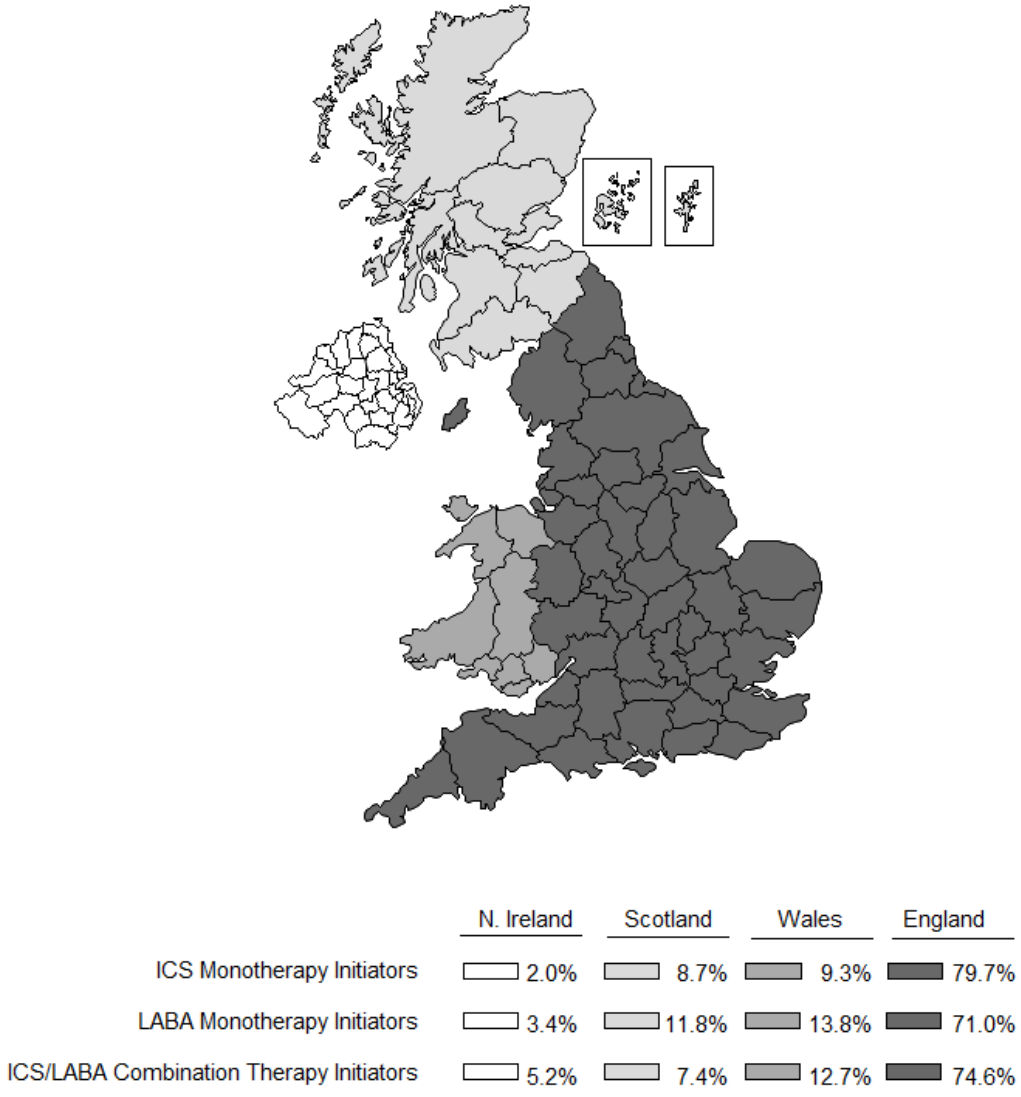


Figure 5-2. Distribution of exposure initiators across UK countries. ICS, inhaled corticosteroids; LABA, long-acting beta-agonists.

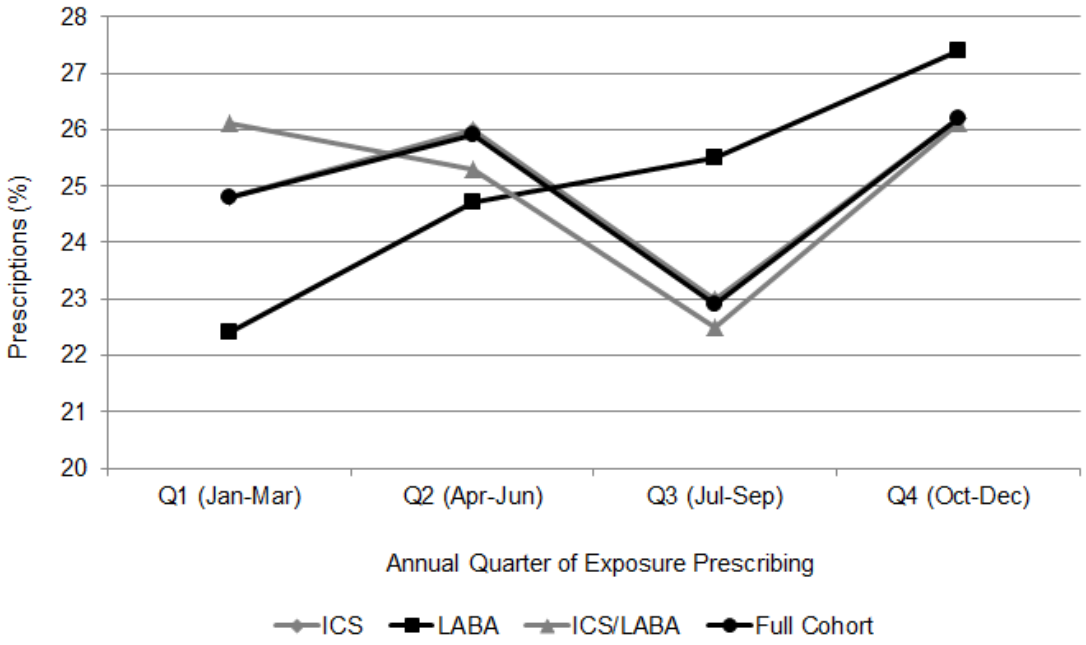


Figure 5-3. Prescribing trend of study exposures. ICS, inhaled corticosteroids; LABA, long-acting beta-agonists.

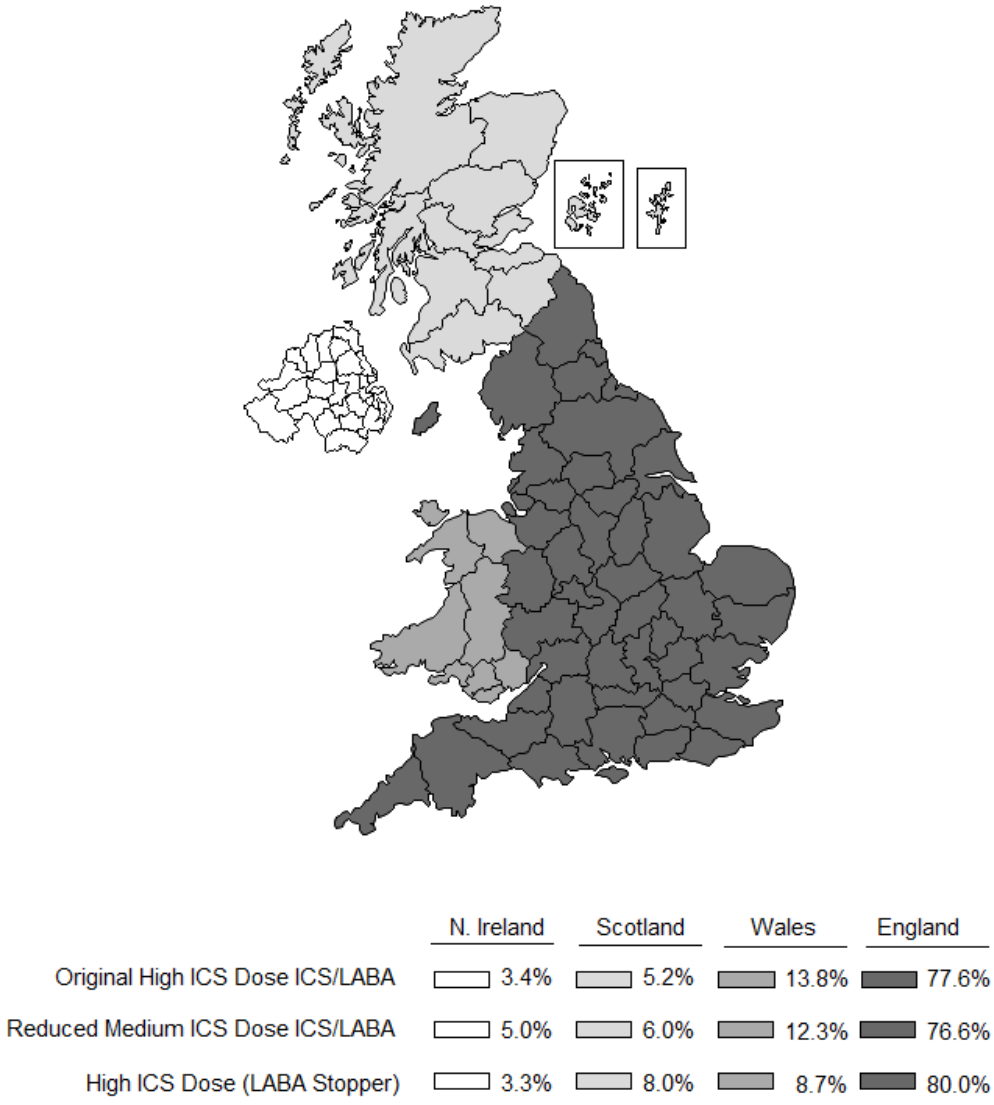


Figure 5-4. Distribution of prescriptions in the step-down therapy cohort with original high ICS/LABA dose initiators. ICS, inhaled corticosteroids; LABA, long-acting beta-agonists

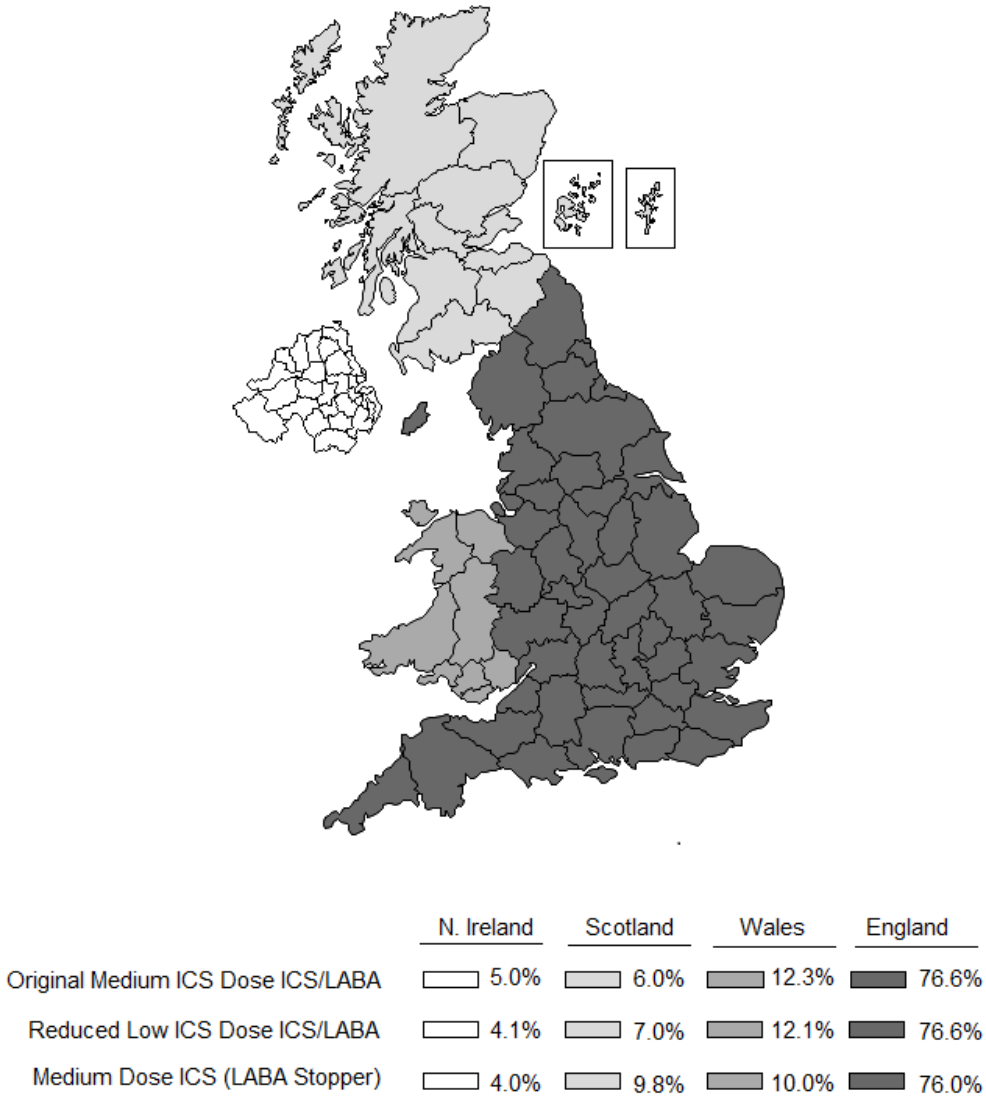
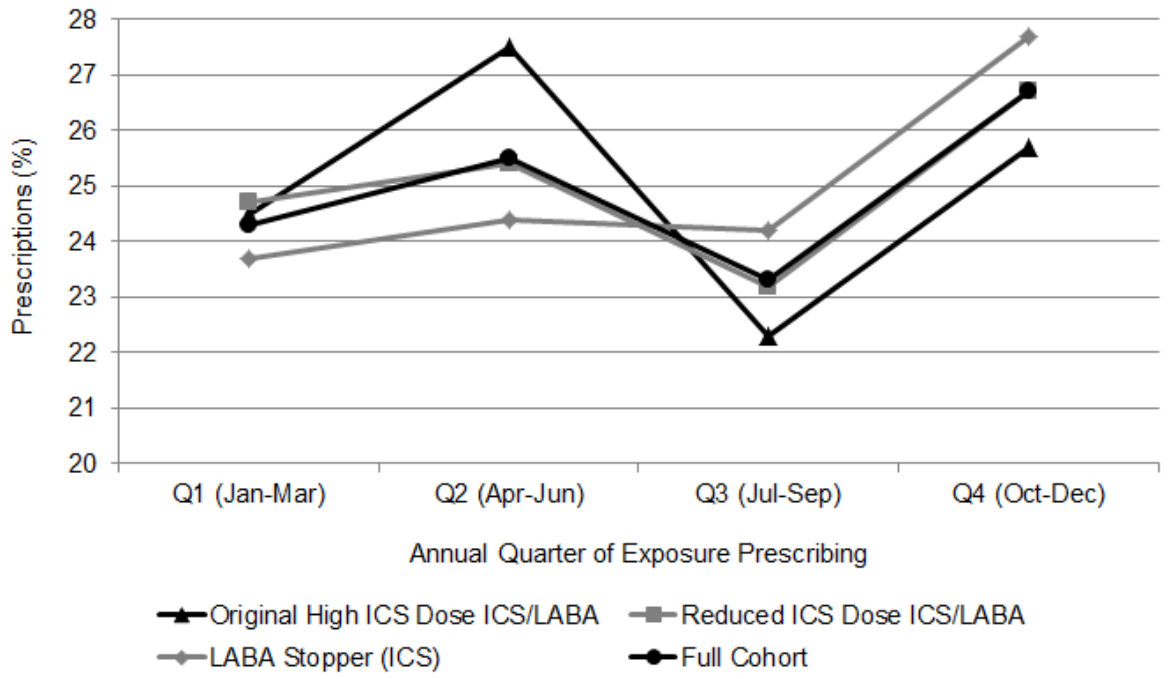
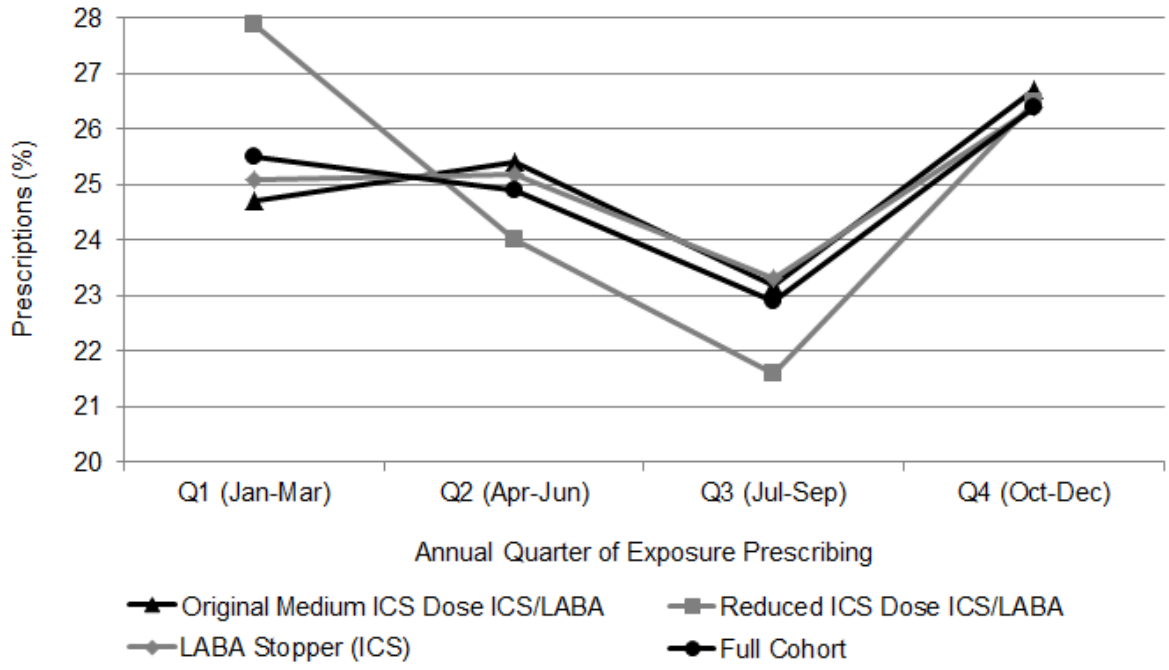


Figure 5-5. Distribution of prescriptions in the step-down therapy cohort with original medium ICS/LABA dose initiators. ICS, inhaled corticosteroids; LABA, long-acting beta-agonists

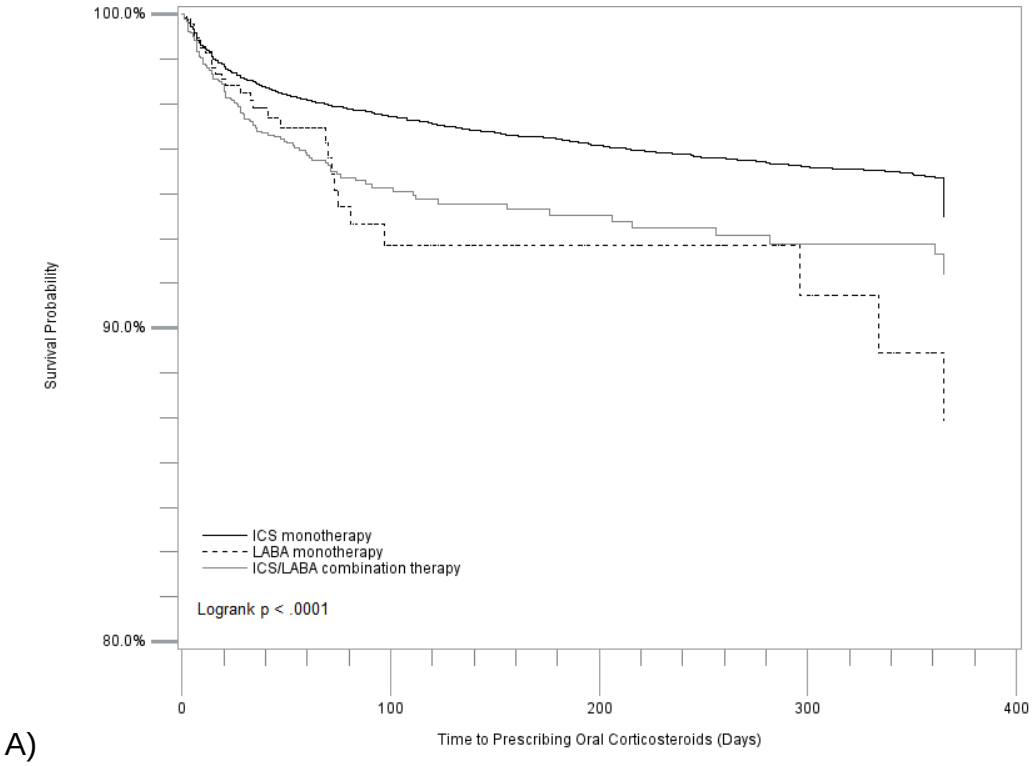


A)

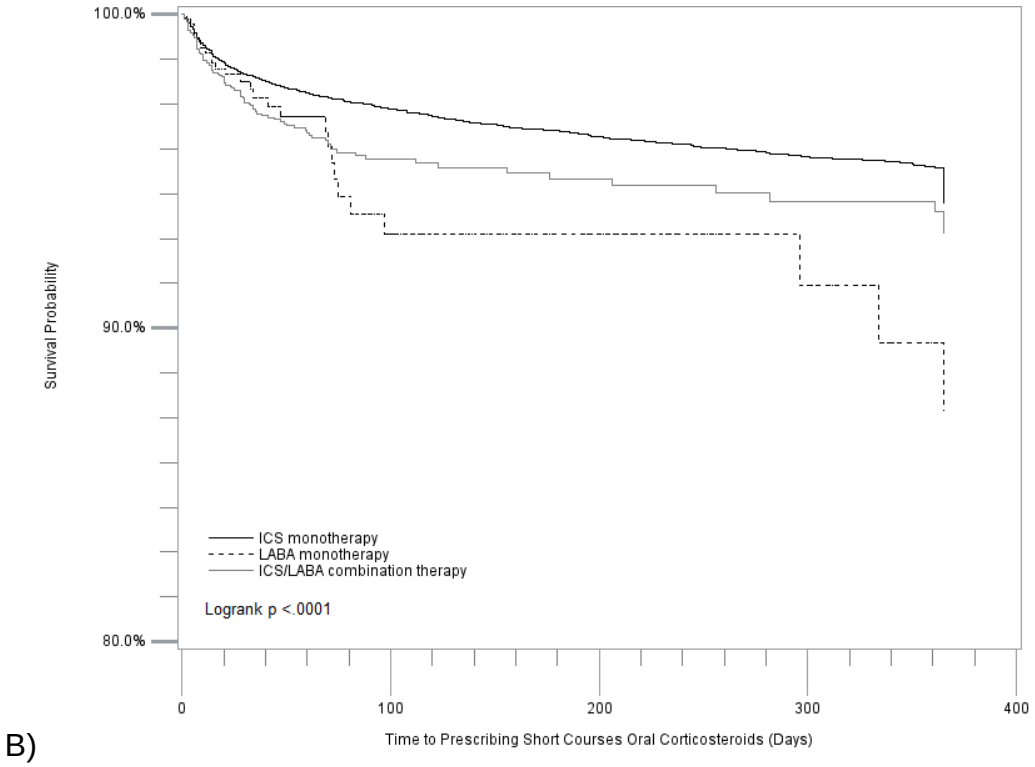


B)

Figure 5-6. Prescribing trend of study exposures in step-down therapy cohort with A) original high ICS/LABA dose initiators and B) original medium ICS/LABA dose initiators. ICS, inhaled corticosteroids; LABA, long-acting beta-agonists.



A)



B)

Figure 5-7. Product-limit survival estimates of prescribing A) long courses and B) short courses oral corticosteroids among original cohort of inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), and ICS/LABA initiators

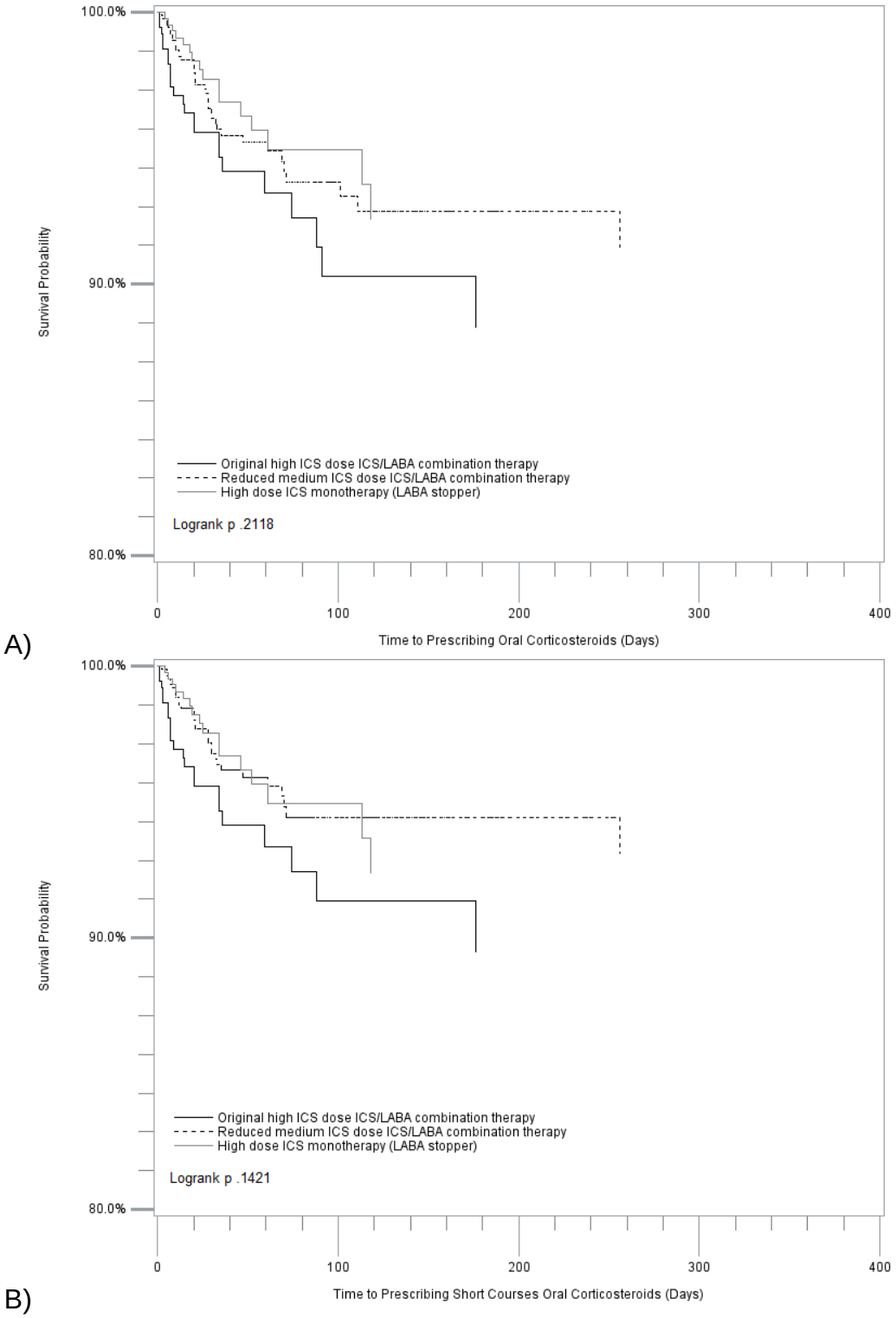


Figure 5-8. Product-limit survival estimates of prescribing A) long courses and B) short courses oral corticosteroids among high inhaled corticosteroids (ICS)/long-acting beta-agonists (LABA) dose initiators

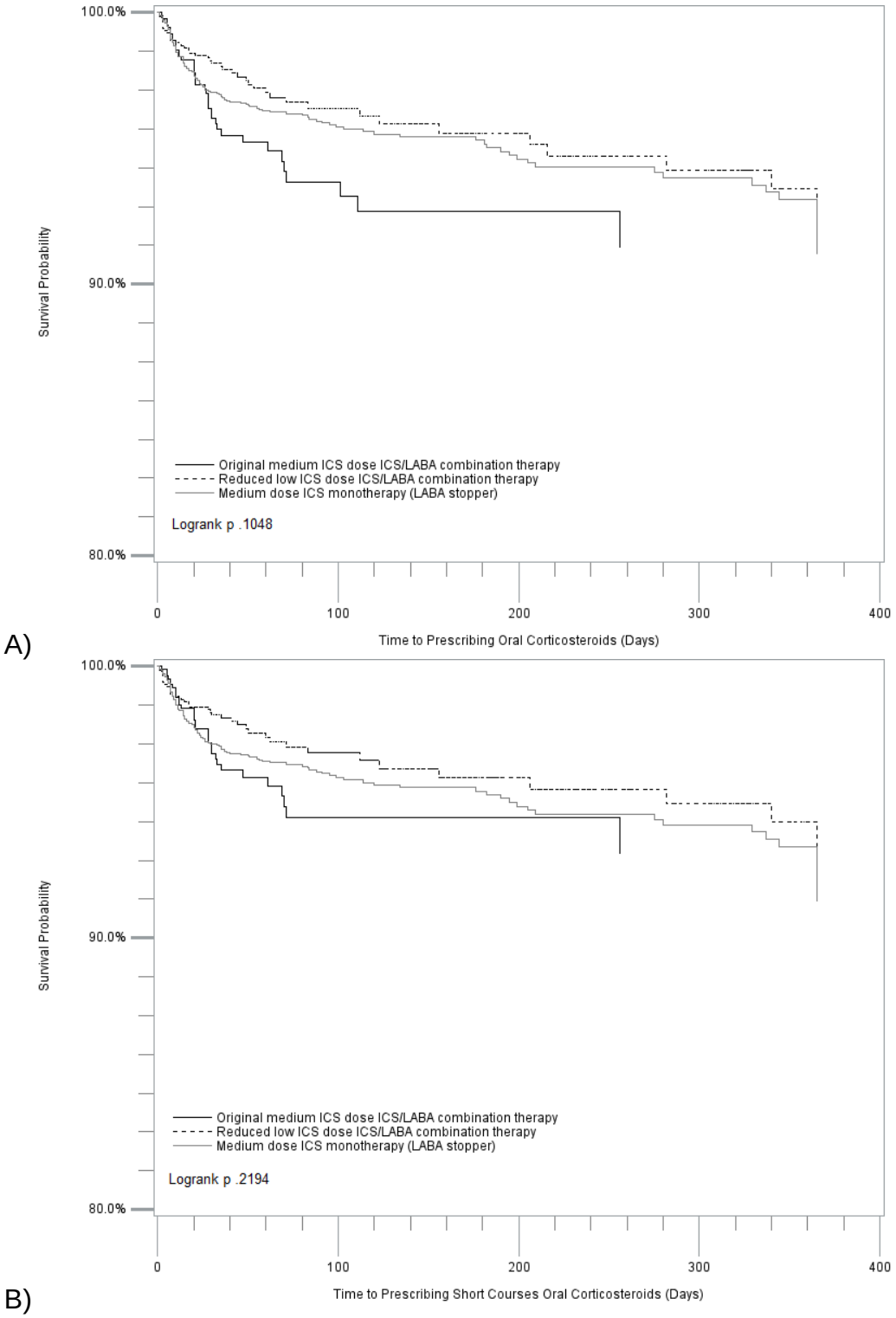


Figure 5-9. Product-limit survival estimates of prescribing A) long courses and B) short courses oral corticosteroids among medium inhaled corticosteroids (ICS)/long-acting beta-agonists (LABA) dose initiators

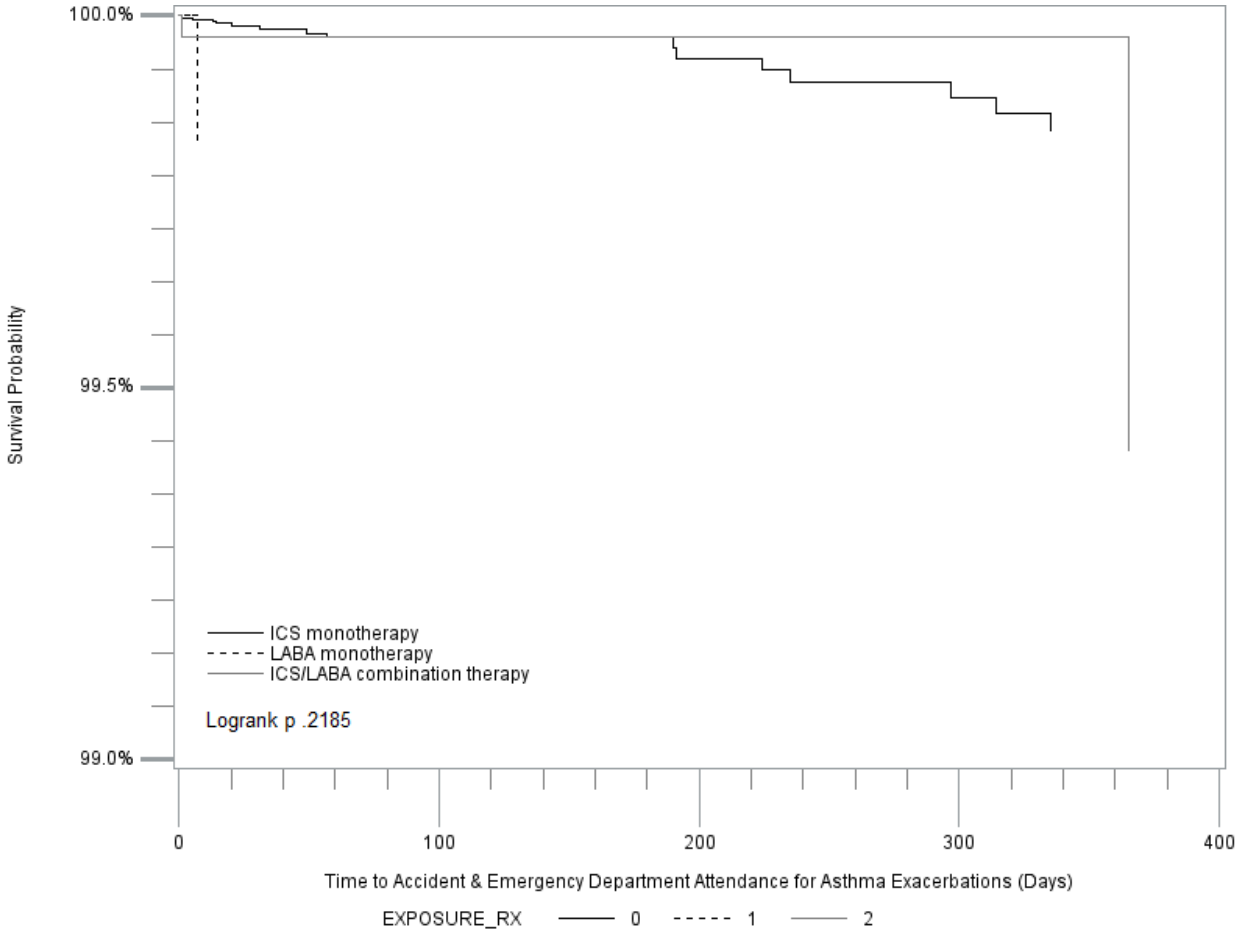


Figure 5-10. Product-limit survival estimates of attending accident and emergency departments for asthma exacerbations among original cohort of inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), and ICS/LABA initiators

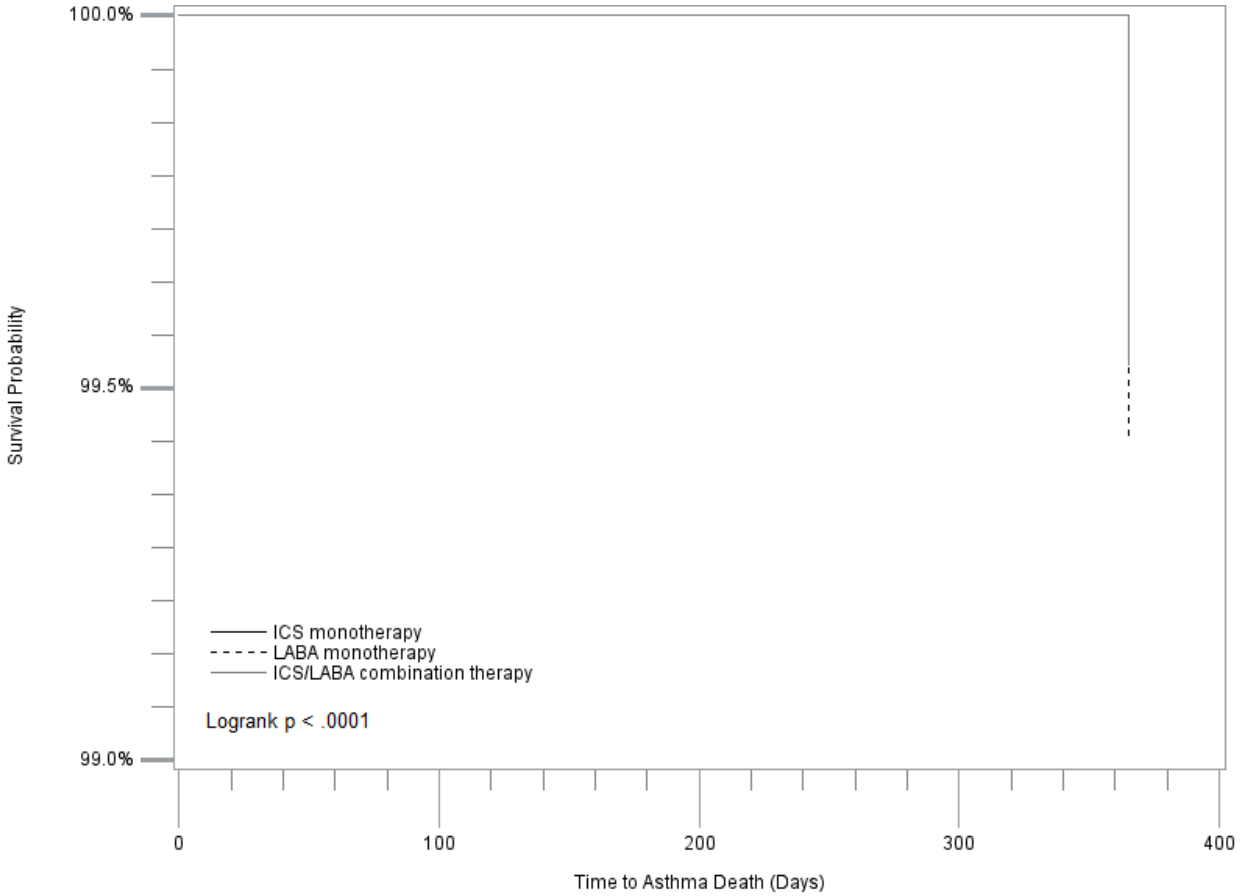


Figure 5-11. Product-limit survival estimates of asthma-related deaths among original cohort of inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), and ICS/LABA initiators in practices unlinked to the Office of National Statistics mortality database

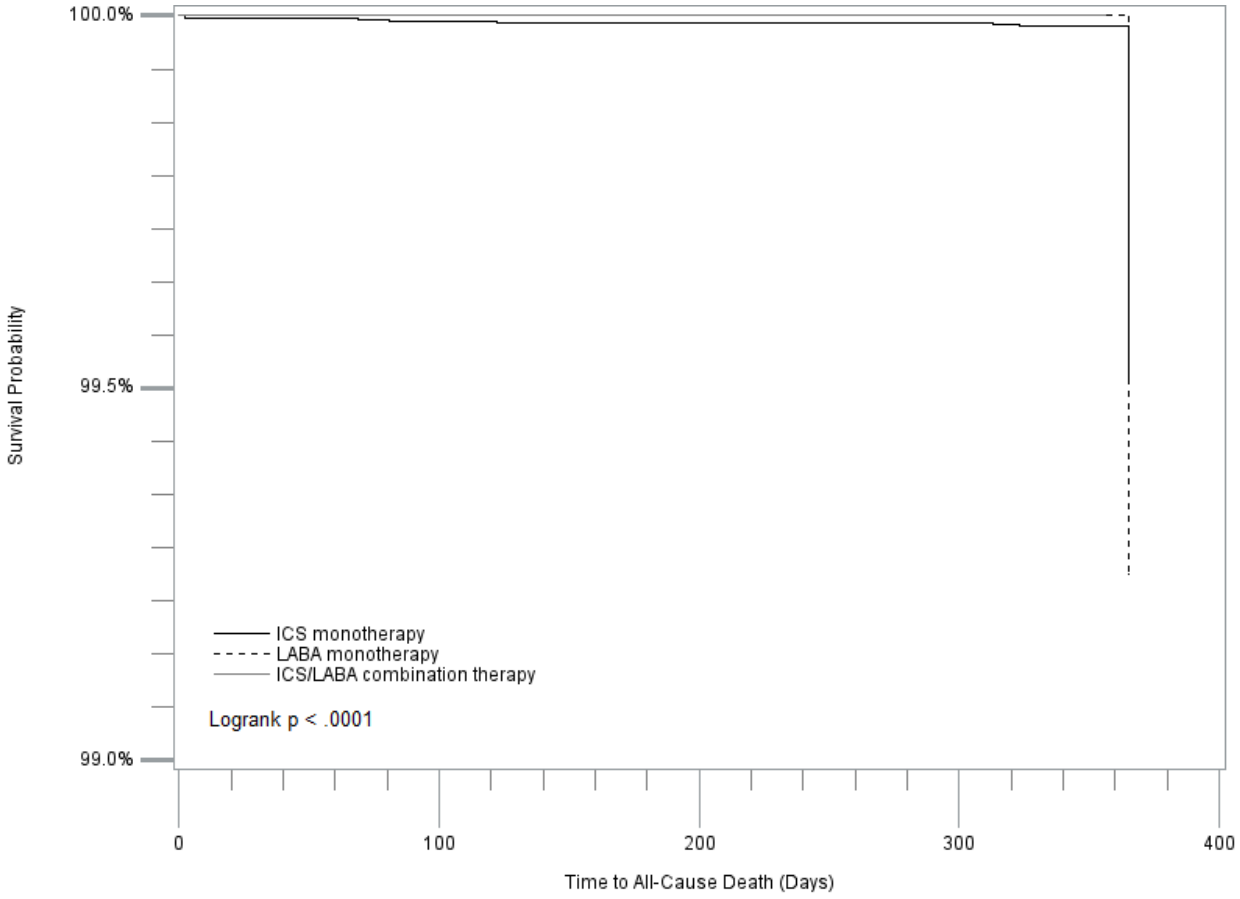


Figure 5-12. Product-limit survival estimates of all-cause deaths among original cohort of inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), and ICS/LABA initiators

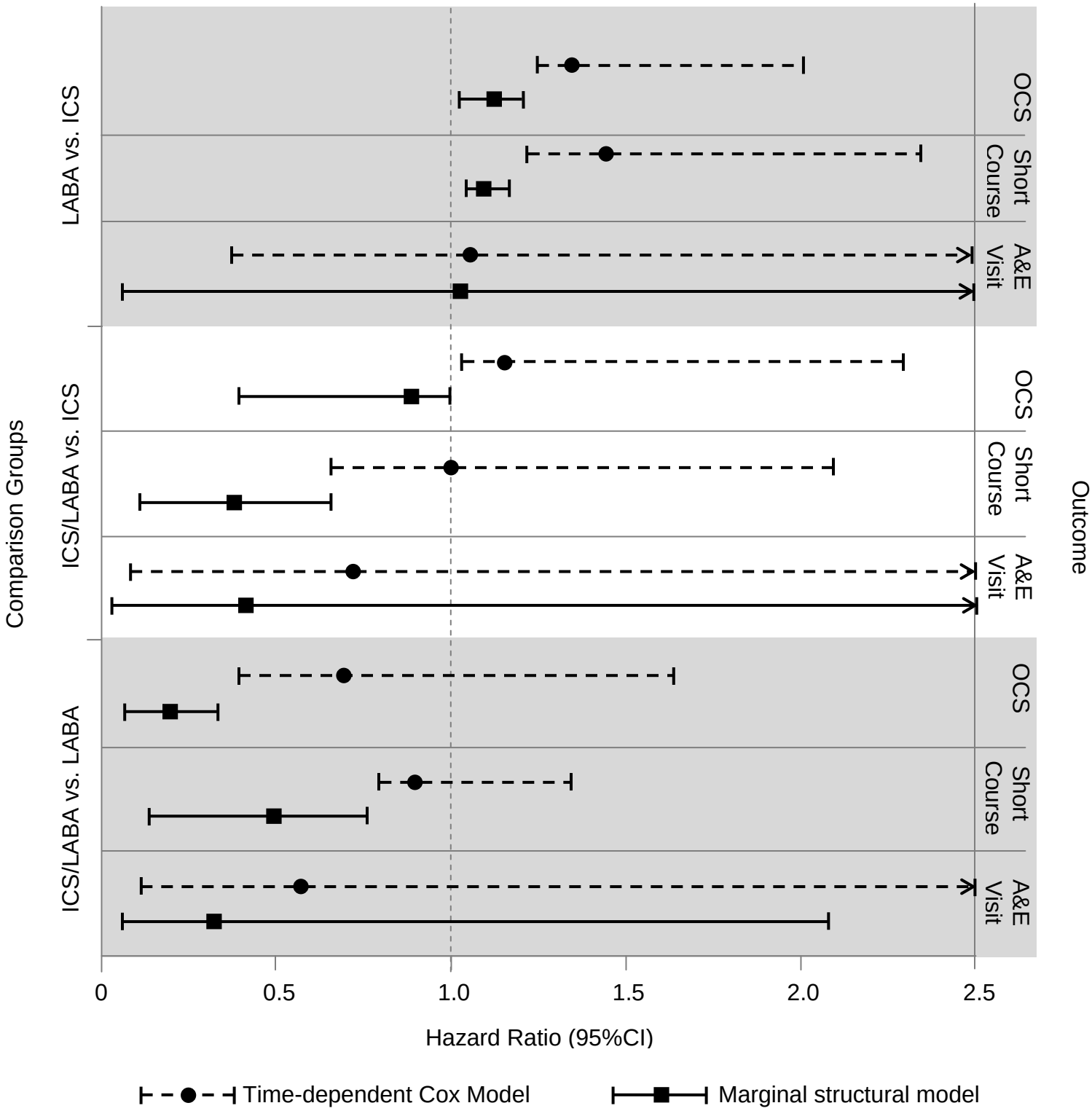


Figure 5-13. Hazard ratios of asthma-related morbidity outcomes stratified by comparison groups and regression models

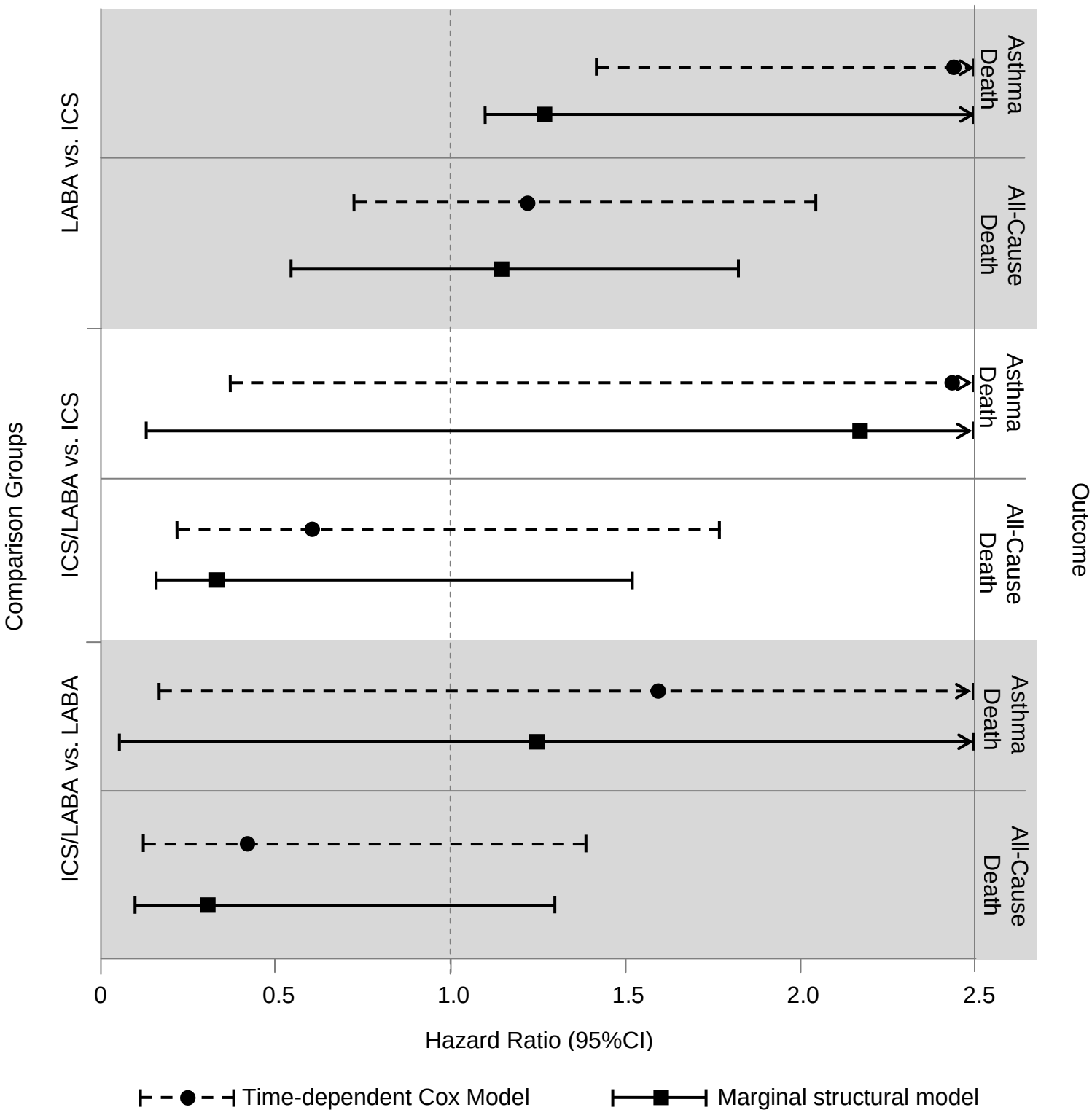


Figure 5-14. Hazard ratios of asthma-related and all-cause mortality outcomes stratified by comparison groups and regression models

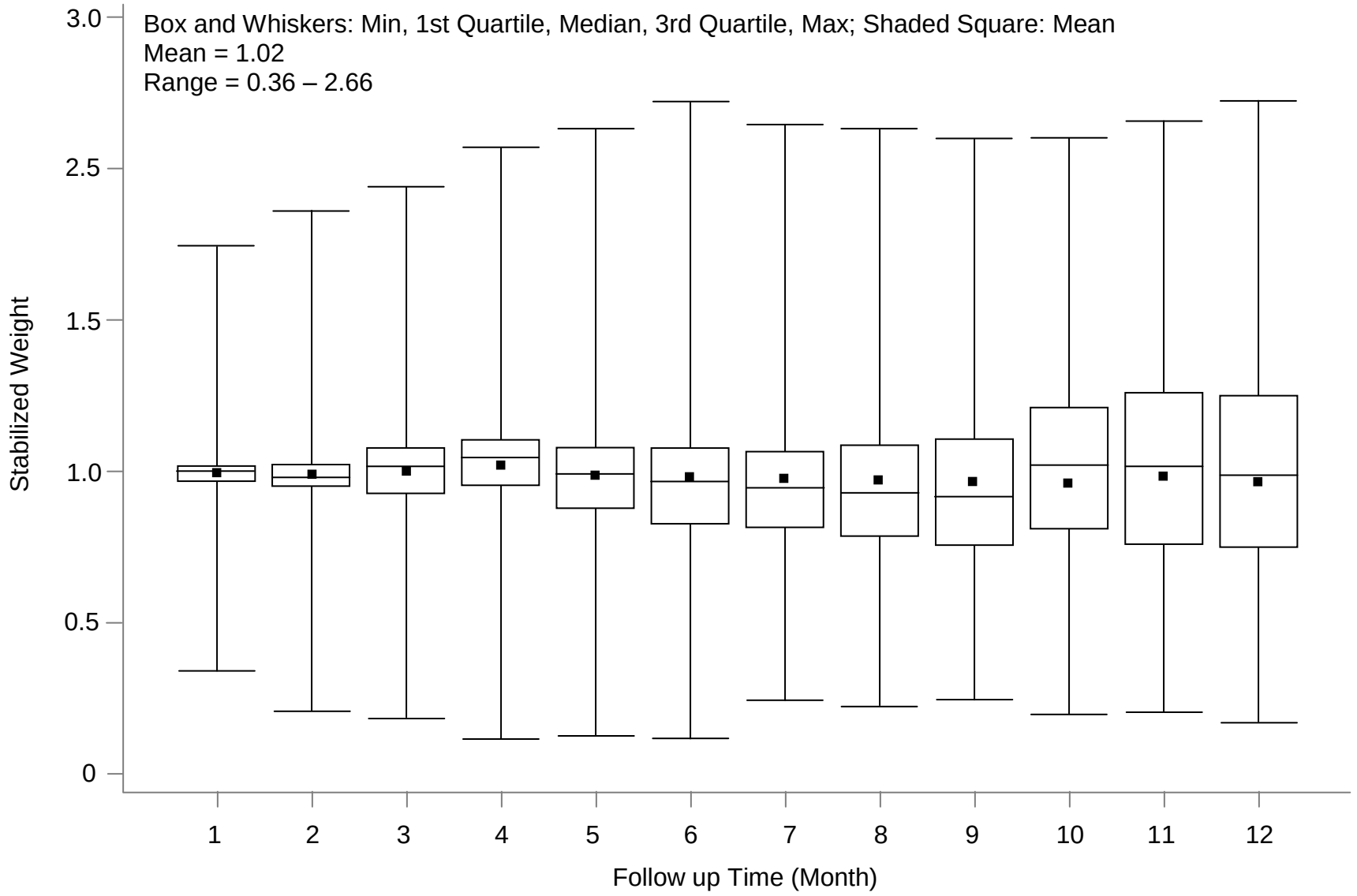


Figure 5-15. Distribution of stabilized weights estimated by marginal structural models across study follow-up year

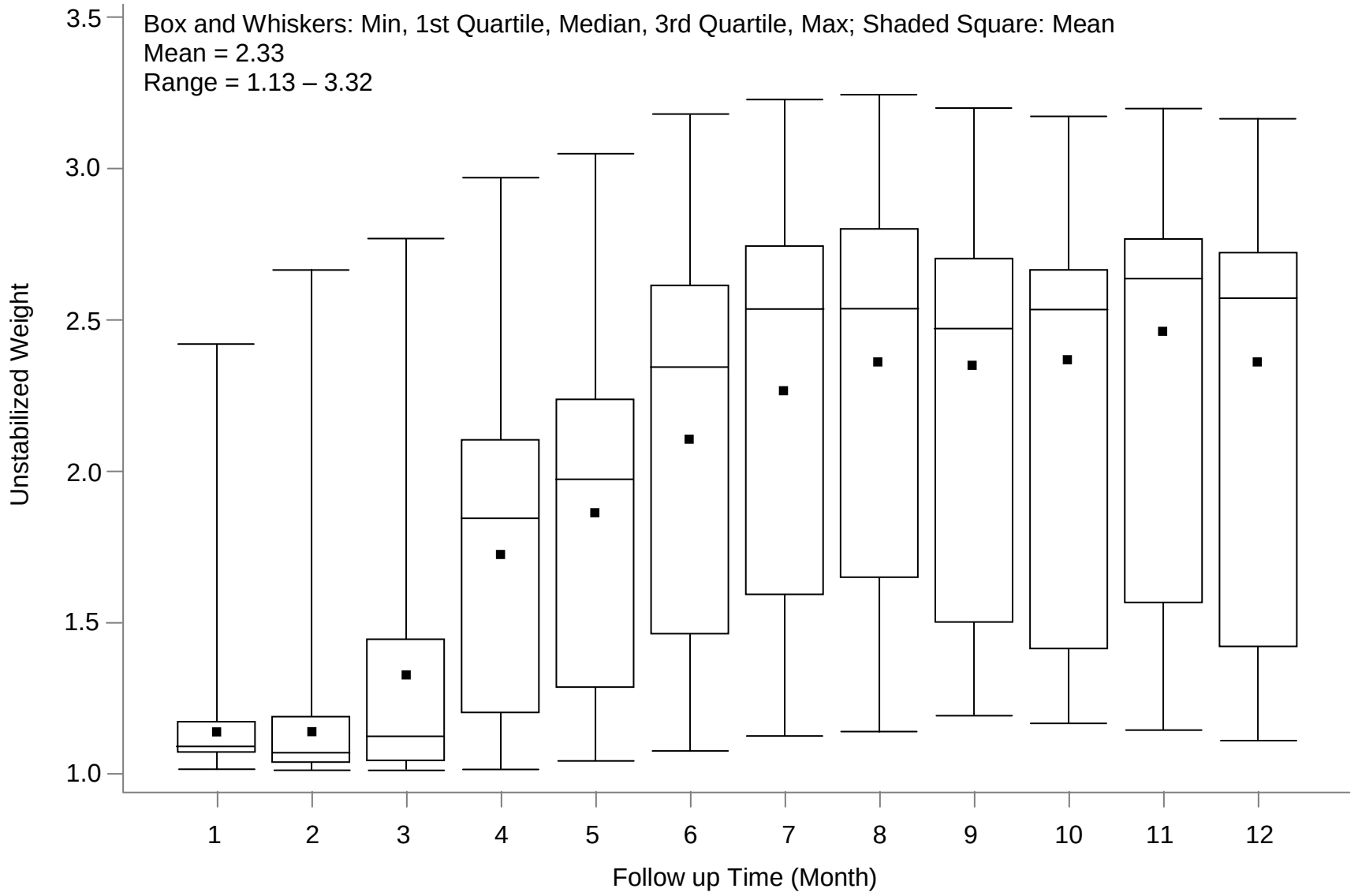


Figure 5-16. Distribution of unstabilized weights estimated by marginal structural models across study follow-up year

CHAPTER 6
DISCUSSION AND CONCLUSIONS

Discussion

Medical records of asthmatics in the GPRD were utilized to conduct a population-based cohort study to assess asthma-related morbidity and mortality after exposure to inhaled LABA bronchodilators as monotherapy and ICS-based regimens. From 1993 to 2010, a total of 51,103 asthmatics were followed for a maximum of 12 months after initiating ICS monotherapy, LABA monotherapy, or ICS/LABA combination therapy. Incidence rates of asthma deaths were separately calculated for England general practices that are linked to ONS-mortality database, and practices that are not part of the ONS-mortality linkage scheme. Asthma-related morbidity was measured by incidence rates of prescribing oral corticosteroids and asthma-related attendance to accident and emergency departments. Likewise, asthma morbidity outcomes were evaluated across step-down therapy approaches among a subgroup of asthmatics who initiated ICS/LABA combination therapy. Marginal structural models were applied to evaluate asthma outcomes in the cohort, and Cox proportional hazards regression with time-dependent covariates was applied to step-down therapy subgroup to evaluate asthma-related morbidity in terms of prescribing oral corticosteroids for asthma exacerbations.

Socioeconomic and behavioral information was not completely recorded for the majority of patients, except for smoking status, which was ascertained for most of the patients because the nature of the disease and smoking being a known risk factor for it. Unknown pertinent information was included as ‘unknown’ category for the relevant covariate. Most of asthmatics with uncontrolled asthma at baseline were prescribed ICS

monotherapy (two third of ICS initiators had uncontrolled asthma), which was consistent with step-therapy approach recommended by disease management guidelines (NHLBI, 2007; BTS, 2009; & GINA, 2009). Conversely, the majority of LABA initiators had controlled disease at baseline, and the ICS/LABA combination regime was rather equally prescribed to asthmatics with controlled (52%) and uncontrolled disease (48%), but mostly to patients with controlled disease. This might suggest inhaled LABA-based regimes, particularly monotherapy, were reserved for asthmatics with controlled disease (Table 5-1). However, anti-inflammatory LTRA were mostly prescribed to initiators of LABA-based therapies than ICS monotherapy, suggesting controller medications like LTRA are necessary as add-on therapies to bronchodilator formulations with LABA, particularly LABA monotherapy. In contrast, xanthine bronchodilators were mainly prescribed to ICS monotherapy initiators. Furthermore, most of LABA stoppers compared to other patients in step-down therapy cohort received inhaled SABA as rescue bronchodilators (Tables 5-2 and 5-3), which is consistent with recommendations from disease management guidelines of not using LABA inhalers as rescue bronchodilators. Similarly, LTRA anti-inflammatory medications were mostly co-prescribed to ICS/LABA combination therapy users than LABA stoppers (ICS monotherapy users), indicating more controlled disease on ICS monotherapy, and stepping-off LABA when disease is controlled, which is consistent with practice guidelines.

Prescribing study drugs was the lowest in asthmatics during the third quarter of the year, which is the summer season in UK climate. During summer there is a reduction in asthma exacerbations, and thus the need to prescribe bronchodilators and controller

medications. In contrast, prescribing trend was higher in other quarters of the year that are associated with higher triggers and allergens, e.g. pollens in spring and cold in winter. This trend was similar across ICS-based therapies (ICS monotherapy and ICS/LABA combination therapy); however, LABA monotherapy was least prescribed during first quarter, when winter is ending and spring is beginning. During these times, there might be a lower need for bronchodilator therapy compared to anti-inflammatory therapy; therefore, LABA bronchodilators were mostly prescribed during autumn and the beginning of winter (third and fourth quarters, respectively) when fluctuations in temperatures, cold weather and chances of contracting viral respiratory infections are high. These factors increases exacerbations and the need for bronchodilator maintenance could be necessary.

Among step-down therapy approaches, stopping LABA and continuing ICS monotherapy was mostly prescribing during the fourth quarter of the year, regardless of ICS dose. However, prescribing trends for the step-down therapy approach with ICS dose reduction while maintaining LABA as ICS/LABA combination therapy was different across ICS dosage. Combination therapies containing medium ICS dose were mainly prescribed during the fourth quarter, while combination therapies containing low ICS dose were mainly prescribed during the first quarter. These quarters encompass winter season in the UK, which is associated with increased triggers for asthma exacerbations. In particular, the fourth quarter covers the beginning of winter and higher doses of ICS might be necessary to control exacerbation risks than the end of winter and beginning of spring which spans the middle and late parts of first quarter. Although a randomized clinical trial showed that ICS do not have an effect on the intensity or duration of

wheezing episodes in asthmatics (Doull et al., 1997), prescribing higher doses of ICS during winter in the current study might reflect a prescribing behavior in general practice in the UK.

Additionally, the study showed that asthmatics who stopped LABA and continued ICS as high-dose monotherapy encountered asthma exacerbations faster than asthmatics who continued LABA as add-on to ICS (i.e., combination therapy). Particularly, patients who continued LABA with medium dose ICS had more months free of exacerbations (Table 5-8, Figures 5-8 and 5-9). However, the trend was not the same in patients with medium-dose ICS at baseline (medium-dose ICS step-down therapy cohort), suggesting patients with worse asthma might benefit more from adding LABA but contemporarily reducing ICS dose to medium from original high dose.

Asthma-related mortality

Among practices linked to the ONS-mortality database, the current study found an incidence rate of 5 per 100 person-yrs for asthma deaths among asthmatics initiated ICS monotherapy; the figure reduced to 0.1 per 100 person-yr for the same group of patients when asthma death was identified among practices unlinked to the mortality database. The incidence of asthma deaths among LABA initiators was 6 times the incidence among ICS initiators (0.6 per person-yrs). There was no power to detect differences between exposure groups in terms of asthma deaths among linked practices; yet, among unlinked practices, asthmatics who initiated LABA monotherapy and survived for one year had 25% increased risk of dying from asthma compared to counterparts who initiated ICS monotherapy and survived for one year after exposure (HR, 1.25; 95%CI, 1.11-3.01). There was no statistically different finding between

asthmatics received combination therapy and monotherapies. Equally, the study revealed no statistically significant results in terms of all-cause mortality between exposure groups. These findings should be interpreted with caution, since there was no asthma-deaths identified in the LABA group among practices linked to ONS-mortality database, and the outcome in unlinked practices was derived by an untested algorithm that might introduced outcome classification bias, where identified asthma deaths could be due to any other reason but was misclassified as such because of the presence of asthma-related Read clinical terms within 21 days of death date, e. g., severe asthma, asthma attack, or endotracheal intubation. Such clinical terms could be recorded routinely at every visit. In concordance with previous studies using the GPRD (de Vries, Setakis, Zhang, & van Staa, 2010), we conclude there was no statistical power to detect asthma deaths among linked practices, or all-cause deaths among all practices. However, among unlinked practices, we carefully conclude that inhaled LABA monotherapy is increases asthma deaths compared to ICS monotherapy.

There has been conflicting discussions about the role of inhaled LABA monotherapy in increasing asthma deaths. Post hoc analyses of the SMART clinical trial showed the increased asthma deaths in salmeterol users compared to placebo users was mainly attributed by lack of concomitant ICS use at baseline (RR=4.37; 95%CI=1.24-15.3); however, information about ICS use was measured by prescribing rate of ICS rather than actual ICS used by patients (Nelson et al., 2006). Likewise, one meta-analysis concluded that about 80% of asthma-related deaths in the US was attributed to LABA products, regardless of ICS use (Hagan, 2006; Salpeter, S, Buckley, Ormiston, & Salpeter, E., 2006). It is important to remember that SMART study

contributed to the majority of patients in this meta-analysis. Subsequent meta-analyses did not find enough power to detect any difference in asthma-mortality rates between LABA products and other asthma medications, including ICS (Jaeschke et al., 2008; Nelson et al., 2010). Contrarily, inhaled LABA monotherapy was found to increase asthma deaths compared to ICS/LABA monotherapy or placebo in one meta-analysis (RR, 3.83; 95%CI, 1.21-12.1) (Rodrigo, Moral, Marcos, & Castro-Rodriguez, 2009). Another systematic review of placebo-controlled trials (Weatherall et al., 2010)—which was 86% weighted by data from the SMART and SNS trials—found an increased risk of asthma deaths in patients who used salmeterol but were not prescribed ICS (OR, 7.3; 95%CI, 1.8-29.4), but a decreased risk of asthma deaths in counterparts who used salmeterol and were prescribed ICS (OR, 2.1; 95%CI, 0.6-7.9). Nevertheless, a systematic review suggested no difference in asthma deaths between LABA monotherapy or ICS/LABA combination therapy (OR, 1.05; 95%CI, 0.32-3.47) (Cates, Lasserson, & Jaeschke, 2009). In sum, it is recommended to retest the hypothesis among practices that are linked to ONS-mortality database but with broader coverage in the rest of UK's countries; as well as, including incident-users who are free from immortal-person time after exposure.

Asthma-related morbidity

The current study showed that inhaled LABA monotherapy is associated with 10-14% increase in prescribing short OCS for asthma exacerbations compared with ICS monotherapy, but did not produce significant difference in terms of asthma-related A&E department visits. However, prescribing ICS concomitantly with LABA as a single-device inhaler or separate-devices is associated with 9-62% decrease in prescribing

OCS for asthma exacerbations compared with ICS monotherapy, and 50-77% decrease in prescribing OCS compared with LABA monotherapy. Equally, there was no difference in asthma-related visits to A&E departments between exposure groups. The findings suggest prescribing inhaled LABA bronchodilators as an add-on therapy to ICS to reduce asthma exacerbations. These findings are consistent with the results of clinical trials and observational studies. A meta-analysis (Bateman et al., 2008) comparing ICS/salmeterol combination therapy with ICS monotherapy showed a significant reduction in asthma exacerbations requiring oral corticosteroids (Risk Difference, -0.02; 95%CI, -0.04 to -0.01). Another meta-analysis (Rodrigo, Moral, Marcos, & Castro-Rodriguez, 2009) showed ICS/LABA combination therapy is associated with less asthma exacerbations requiring systemic steroids (OR, 0.73; 95%CI, 0.67-0.79).

Among step-down therapy approaches, there was no difference in asthma-related visits to A&E departments between LABA stoppers (medium ICS monotherapy) and ICS dose reducers (low ICS/LABA combination therapy). The study showed that any step-down therapy approach is better than continuing original dose regimen, but within step-down therapy approaches there are differences: among high-dose ICS, stopping LABA while continuing high dose ICS is associated with lower exacerbation rates than reducing ICS dose to medium and continuing LABA (OCS: HR, 0.33; 95%CI, 0.07-0.52 and short courses OCS: HR, 0.35; 95%CI, 0.06-0.51). However, discontinuing LABA while maintaining medium dose ICS is associated with higher exacerbation rates than reducing ICS dose to low and continuing LABA (OCS: HR, 1.28; 95%CI, 1.09-5.08 and short courses OCS: HR, 1.24; 95%CI, 1.07-5.01). These findings are consistent with a similar study in the GPRD (Thomas, von Ziegenweidt, Lee, & Price, 2009) compared

stepping-up therapy approaches in initiators of ICS monotherapy showed that continuing ICS monotherapy while increasing the dose is associated with 25% less likelihood for prescriptions of OCS for asthma exacerbations compared with adding LABA as a combination therapy (OR, 0.75; 95%CI, 0.71-0.78), and the difference was more prominent for prescribing short courses of OCS (OR, 0.5; 95%CI, 0.46-0.55). The relationship between inadequate doses of ICS and increased asthma morbidity rates is well documented, even before the introduction of LABA products (Suissa, S. & Ernst, P, 2001), and the findings of the current study recommend continuing LABA as an add-on therapy to ICS while maintaining adequate controller strength to achieve better asthma outcomes.

Limitations

The present study has many limitations and the findings must be interpreted in light of them. Given the observational nature of the study design, lack of randomization precludes equal distribution of known and unknown risk factors among exposure groups. Although attempts are made to account for all potential and actual confounders, residual confounding due to unmeasured factors is highly likely in observational datasets. Therefore, the estimated average causal effects of LABA products on asthma morbidity and mortality outcomes should be interpreted with caution. Furthermore, external validity of the findings is limited to the UK population, which could affect extrapolations of findings to asthmatics in other countries, e.g. US. Similarly regarding age and race factors, where findings cannot be related to children younger than 13 or elderlies >65 years old, or African Americans. Another limitation in the design is including patients who survived for a minimum of 12 months after first receiving

prescriptions for study drugs. Although the potential bias attributed by this criterion was accounted for by the analysis stage, patients are no longer considered incident-users.

In addition, inconsistency and incompleteness of records pertinent to potential confounding variables are the main drawback of retrospective database analysis. Yet, in attempts to account for the scarcity of information within variables, categories with unknown information are included to satisfy model convergence in statistical analyses. It should be noted that the data in the GPRD are prescribing rather than dispensing information, which imparts difficulty in applying approaches to measure patient's adherence. Low adherence with inhaled pharmaceutical dosage forms, particularly ICS is a widely recognized problem. It is reported among new users of chronic medications, ICS users had the highest treatment discontinuation rate within one year of initiation (Beekveldt-Postma et al., 2004). Read clinical terms denoting patient's compliance level with asthma medications and any other medication were identified and included as covariates; yet, the distribution these terms were relatively scarce. Likewise, lack of information on over-the-counter (OTC) products casts more limitations, especially when the OTC products influence asthma medication choices or asthma outcomes, e.g. NSAIDs or aspirin. Information about socioeconomic characteristics is included as proxies from patient' marital status, prescription payment options and capitation supplement levels. Such information might not be adequate surrogates for socioeconomic characteristics of patients. In contrast, indices of multiple deprivations are increasingly used in the UK as measures that reflect patient's socioeconomic status at the general practice level. Practice-specific scores are requested from the GPRD but were not generated duly, and the scores can be included in future work.

Information about prescriptions issued to patients in venues other than general practices are not recorded, and therefore, time-dependent exposure might not be fully categorized and exposure misclassification might happen when patients received a prescription for their subsequent exposure from an outpatient clinic or a hospital. Also, confounding misclassification could happen because lung function tests were not used as a severity measure, although the alternative measures are deemed sufficient given the nature of the database. Similarly, outcome misclassification is highly anticipated with regard to asthma-related deaths among practices that are unlinked to the ONS-mortality database, where a patient who died due to an etiology other than asthma, might be erroneously classified as died due to asthma when a Read clinical term denoting to asthma was found within 21 days of death date. Therefore, relying on findings from the linked practices is more informative and valid; unfortunately there were no asthma deaths in LABA-based groups and too few cases in ICS monotherapy group to establish the effect of LABA products on asthma mortality.

Conclusions

In tandem with recommendations from regulatory stakeholders and asthma management guidelines, this study showed that inhaled long-acting beta-agonist bronchodilators should be used with inhaled corticosteroids as either single-device or separate devices combination therapy. Such approach is associated with lower rates of asthma exacerbations defined by receiving prescriptions for oral corticosteroids or attending accident and emergency departments. Inhaled LABA should not be used as monotherapy, and when used in combination with ICS, LABA should be added to low-dose ICS instead of medium or high doses. When an increase in ICS dose is

necessary, it is recommended to discontinue LABA and continue ICS monotherapy in medium or high doses.

In conclusion, combination therapy with ICS/LABA has better asthma control than either ICS or LABA alone, and LABA monotherapy is associated with increased risk of death from asthma attacks than ICS monotherapy. There was no sufficient statistical power to establish the effect of ICS/LABA combination therapy on asthma deaths. LABA stoppers are associated with worsened asthma than ICS/LABA dose reducers when ICS monotherapy is in medium strength; however, when ICS monotherapy is in high strength, withdrawing LABA is associated with better asthma control than continuing LABA as reduced ICS/LABA regimen.

Future Work

The current study utilized marginal structural models to account for time-dependent confounding in an attempt to quantify the average causal effect of LABA bronchodilators on asthma morbidity and mortality. The methodology was compared with Cox proportional hazards model with time-dependent covariates, which essentially yield similar estimates and overlapping confidence intervals when time-dependent confounding is not present (Figures 5-13 and 5-14). The technique however was not tested for adequate confounding control (i.e. lack of residual confounding), and this can be extended for future assumption testing. Furthermore, the technique is inefficient to test for exposure-effect modification, and it is recommended to compare the results with structural nested models to test for effect modification by including patients with coexisting COPD and asthma, or prescribing for inhaled muscarinic receptor antagonists as a proxy indicator for COPD. Also, the research can be repeated by

further accounting for socioeconomic characteristics by including indices of multiple deprivations after acquiring the scores from the GPRD. This can further adjust for unmeasured confounding by socioeconomic factors. In addition, the analyses for mortality outcomes can be repeated in a cohort without immortal-person time after initiating study drugs to test the proposed design-level approach to account for depletion of susceptibles by prevalent users (Figure 4-3). Given the low power to detect differences in mortality outcomes between exposure groups, testing related hypotheses can be strengthened by linking the cohort with a larger number of practices that are linked to the national mortality database across different countries within the UK.

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BIOGRAPHICAL SKETCH

Dr. Ayad Ali earned his bachelor of pharmaceutical sciences degree from University of Mosul, Iraq in 2002. He was awarded the prestigious Fulbright Scholarship from the United States Department of State, Bureau of Educational and Cultural Affairs to further his educational and professional prospects by receiving his master of science in pharmacy degree from the University of Florida in 2007. He was admitted to the doctoral program at the University of Florida in 2008 and earned his doctor of philosophy in pharmaceutical sciences in 2012 with concentration in pharmaceutical outcomes and policy and specialization in pharmacoepidemiology & pharmacovigilance.

Dr. Ali has been the recipient of numerous awards and honors from professional and educational organizations for his leadership, service, and productivity in research. Also, he has multiple publications and presented his research at local, national, and international venues. He received many research and travel grants and has professional experience in community, hospital, academic, and industry pharmacy sectors. Dr. Ali is passionate about pharmacy and public health, and longs to contribute to the global improvement in pharmaceutical systems and drug safety, especially in developing and transitional countries, including his home country, Iraq.