ADDITION OF LEUKOTRIENE RECEPTOR ANTAGONISTS VERSUS LONG ACTING BETA AGONISTS TO INHALED CORTICOSTEROID THERAPY FOR ASTHMA TREATMENT IN OLDER ADULTS: A RETROSPECTIVE DATA ANALYSIS OF EFFECTIVENESS, SAFETY AND COST

by

Shoroq Mahmoud Altawalbeh

Doctor of Pharmacy (PharmD), Jordan University of Science & Technology (JUST), 2010

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This dissertation was presented

by

Shoroq M. Altawalbeh

It was defended on

September 1, 2015

and approved by

Carolyn T. Thorpe, PhD, MPH, Department of Pharmacy and Therapeutics, University of Pittsburgh

Janice C. Zgibor, PhD, MPH, Department of Epidemiology, University of Pittsburgh

Sandra Kane-Gill, PharmD, MS, Department of Pharmacy and Therapeutics, University of Pittsburgh

Dissertation Advisor: Joshua M. Thorpe, PhD, MPH, Department of Pharmacy and Therapeutics, University of Pittsburgh

ADDITION OF LEUKOTRIENE RECEPTOR ANTAGONISTS VERSUS LONG ACTING BETA AGONISTS TO INHALED CORTICOSTEROID THERAPY FOR ASTHMA TREATMENT IN OLDER ADULTS: A RETROSPECTIVE DATA ANALYSIS OF EFFECTIVENESS, SAFETY AND COST

Shoroq M. Altawalbeh, PharmD, PhD

University of Pittsburgh, 2015

Asthma treatment is challenging in older adults. To date, there is no evidence from research with older adults to support choosing the most appropriate add-on treatment for inadequately controlled asthma, despite using inhaled corticosteroids (ICS). We retrospectively investigated the comparative effectiveness, cardiovascular (CV) safety and costs associated with ICS + leukotriene receptor antagonists (ICS+LTRA) versus ICS + long acting beta agonists (ICS+LABA) treatments. We included asthmatic Medicare beneficiaries aged 66 and older, who continuously enrolled in Fee for Service Medicare with Part D coverage, and treated with ICS+LABA or ICS+LTRA in an exclusive manner.

This dissertation work was organized into two major studies. Firstly, effectiveness and CV safety outcomes were compared between the two treatments. The augmented inverse propensity weighted estimator was used to determine the effect of LABA vs. LTRA add-on therapy on asthma exacerbations requiring inpatient, emergency, or outpatient care as well as CV events, adjusting for several co-variables. Our results showed that LTRA add-on treatment was associated with increased odds of asthma-related hospitalizations/emergency department visits (OR=1.4, $p<0.001$), and outpatient exacerbations requiring oral corticosteroids or antibiotics (OR=1.41, $p<0.001$) compared to LABA treatment. LTRA add-on therapy also showed lower effectiveness in controlling symptoms as indicated by greater utilization of short-acting beta

agonists (RR=1.58, p<0.001). On the other hand, LTRA add-on treatment was associated with lower odds of experiencing a CV event compared to LABA (OR=0.86, p=0.006).

Secondly, multivariable regression models with nonparametric bootstrapped standard errors were employed to compare all-cause and asthma-related costs between the two treatment groups. The results showed that ICS+LTRA treatment was associated with increased asthma-related costs compared to ICS+LABA. With a mean of 1.06 person-years follow up, adjusted asthma-related costs were $4,724 for ICS+LTRA group vs $2,939 for ICS+LABA group (p<0.001). Total all-cause costs were not significantly different between treatment groups ($74,369 for ICS+LABA compared with $68,944 for ICS+LTRA (p=0.219)). Together, these findings provide new evidence specific to older adults to help health care providers weigh the risks and benefits of these add-on treatments. The economic evaluation conducted in this dissertation can enhance clinical decision-making and efficient evidence-based health practice in older adults.

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PREFACE

In the Name of Allah, Most Gracious, Most Merciful. All praise and thanks are due to Allah, and peace and blessings be upon his Messenger.

The completion of my PhD training would not have been possible without the guidance and support of many individuals. In turn, my overwhelming gratitude and sincere thanks go to my thesis advisor Dr. Josh Thorpe. His help, support, guidance, and expertise were extremely valuable to make this thesis possible. Dr. Thorpe has encouraged me to work independently, to organize my research work and to be well motivated, without his assistance; this work would have never been completed in such a great way. I am certainly grateful for the opportunity to work under his supervision in the past few years.

I would like to extend my thanks to my thesis committee members: Dr. Carolyn Thorpe; Dr. Sandra Kane-Gill; and Dr. Janice Zgibor for their continues guidance, valuable inputs, insightful suggestions, and the fantastic cooperation during my dissertation work. I also thank Dr. Yihuang Kang for his unlimited assistance with data manipulation and analysis.

Sincere thanks must go to the Dean of School of Pharmacy (Dr. Patricia Kroboth), the Vice Dean (Dr. Randy Smith), faculty (especially Dr. Maggie Folan), staff (especially Lori Schmotzer), and graduate students, who have been helpful in the academic and administrative aspects of my graduate study. I also thank all my wonderful friends and colleagues at Pittsburgh, particularly those at the Graduate School of Public Health.

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I dedicate this work to my lovely parents, brother, and sisters for their continuous support and unlimited prayers. Without their help, I surely could not have made it into, and come this far in my life. Finally, the biggest “thank you” is to my ever-supportive husband, Osama, who has always been my home, and means the world to me, and to my little boys, Mohammad and Ahmad, the most beautiful gifts from Allah to me.

1.0 INTRODUCTION

Asthma is common among older adults and causes great morbidity and mortality [1-3]. Asthma in older adults is more severe, less controlled and more likely to have higher costs than asthma in adulthood [4, 5]. Despite that, few studies have focused exclusively on measuring the effectiveness and safety of treatments in older adults with asthma. The fact that older adults are under-represented in clinical trials has led to a paucity of knowledge regarding the relative effectiveness, safety and costs of asthma treatments in this population [1, 6]. The evidence for treatment of asthma in older patients is mostly based on research conducted in younger adults or age-pooled populations [1].

LABA is the first line add-on treatment to inhaled corticosteroids among all ages [7]. LTRA is recommended as a second line add-on treatment. To date, there is no evidence from research focused on older adults to support choosing the most appropriate add-on treatment in patients with inadequately controlled asthma symptoms who are already using inhaled corticosteroids.

The focus of this dissertation is on evaluating three important facets of health outcomes associated with the two most common add-on treatments (LTRA and LABA) in older adults with persistent asthma. Chapter 2 presents a review of the disease focusing on burden and treatment challenges in older adult patients. Further, Chapter 2 provides a review of the available literature and gaps that support the rationale for this dissertation. The specific research aims and hypotheses as well as the conceptual framework for the studies are presented in Chapter 3. The comparative effectiveness and CV safety of the two add-on treatments are investigated in Chapter 4 (study #1). Several indicators of asthma treatment effectiveness and CV safety were examined and compared between the two treatments, including: 1) asthma exacerbations requiring hospitalization or emergency department (ED) use; 2) asthma exacerbations treated in

an outpatient setting; 3) extent of use of short-acting beta agonists (SABA); 4) CV exacerbations requiring hospitalization or emergency department (ED) use; 5) changing the treatment which defined as adding or switching to the other add-on treatment; and 6) all-cause mortality. Chapter 5 (study #2) compares the economic outcomes associated with the two add-on treatments. Economic outcomes investigated in this study include all-cause costs (medical, pharmacy and total) and asthma related costs (medical, pharmacy and total). Finally, Chapter 6 summarizes the findings of the two studies, describes the implications and insights that the dissertation provides for informing health care-related decision-making, and summarizes the major limitations in this dissertation work with directions for future research to address these limitations.

2.0 BACKGROUND AND LITERATURE REVIEW

2.1 OVERVIEW OF ASTHMA

2.1.1 Definition and Clinical Presentation

Asthma is an inflammatory chronic lung disease that affects and narrows the airways, and causes recurrent episodes of breathlessness, wheezing, chest tightness, and coughing. These episodes are typically associated with airflow obstruction that is usually reversible spontaneously or with the treatment [7].

Clinical presentation:

Asthma presentation can vary from chronic daily symptoms to only intermittent symptoms with weeks, months, or years in between episodes. Chronic asthma is characterized by episodic dyspnea associated with wheezing, chest tightness, coughing (particularly at night), or a whistling sound when breathing. These symptoms often occur with exercise, stress or in response to allergens. Uncontrolled asthma can progress to an acute state featured by inflammation, airway edema, excessive accumulation of mucus, and severe bronchospasm. Severe asthma attack can result in intense airway narrowing that is poorly responsive to usual bronchodilator therapy and can become a life-threatening emergency [7-11].

2.1.2 Epidemiology

Asthma is a common respiratory chronic disease with more than 300 million people worldwide affected by the disease [12, 13]. The World Health Organization (WHO) has estimated that 15 million disability-adjusted life-years are lost and 250,000 asthma deaths per year are reported

worldwide [14]. Asthma is one of the most commonly diagnosed chronic diseases in the US. It is estimated that asthma affects 5-10% of the US population, or about 23.4 million persons [15].

2.1.3 Pathophysiology

Airflow limitation in asthma is recurrent and caused by a variety of changes in the airway as depicted in **Figure 2-1** [11, 16-20]. These changes include:

- Intermittent obstruction: The major characteristics of asthma include a variable degree of airflow obstruction that can be due to bronchospasm, edema, hyper-secretion and airway remodeling. Bronchoconstriction featured by airway smooth muscle contraction is mostly acute and allergen-induced as a consequence of immunoglobulin E-dependent mediator from mast cells that includes histamine, tryptase, leukotrienes, and prostaglandins. In addition, other stimuli for acute airflow obstruction including exercise, cold air, and irritants.
- Airway inflammation: Inflammation and associated edema and mucus hyper-secretion contribute to airflow obstruction and bronchial reactivity. Mast cells, eosinophils, epithelial cells, macrophages, and activated T lymphocytes are the principal cells identified in airway. Structural changes including hypertrophy and hyperplasia of the airway smooth muscle can result from chronic inflammation.
- Bronchial hyperresponsiveness, which is an exaggerated ability of the airways to narrow in response to a variety of stimuli. Inflammation acts as the major factor in determining the degree of airway hyperresponsiveness. Other contributing factors include dysfunctional neuroregulation and structural changes.

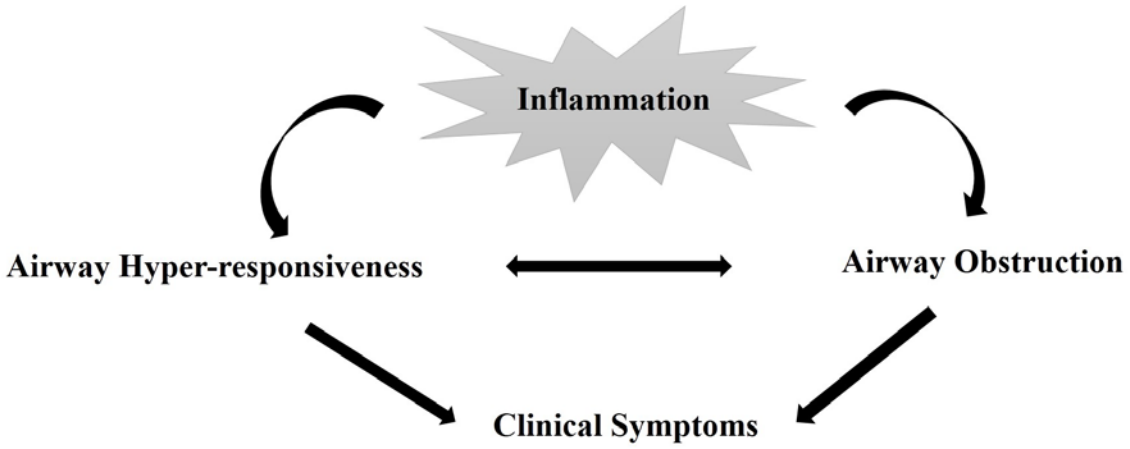

Figure 2-1 Pathophysiology of asthma.

Adapted from: National Institutes of Health (2007). National Asthma Education and Prevention Program [11]

2.1.4 Classification of Asthma

Based on the symptoms, asthma can be classified into the following [11]:

- Intermittent asthma: Symptoms occur on fewer than 2 days a week and do not interfere with normal activities.
- Mild persistent asthma: Symptoms occur on more than 2 days a week but not every day, interfere with daily activities (minor) or occur at night 3-4 times a month.
- Moderate persistent asthma: Symptoms occur daily, interfere with daily activities or occur at night more than 1 time a week, but do not happen every day.
- Sever persistent asthma: Symptoms occur throughout the day, severely limit daily activities, or occur at night often or every night.

2.1.5 Treatment of Chronic Asthma

Desired outcomes: The goals of treatment for chronic asthma are to 1) achieve good control of symptoms and maintain normal pulmonary function; 2) prevent troublesome symptoms; 3) maintain normal activity levels including exercise and other normal physical activities; 4) prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations; 5) provide optimal pharmacotherapy with minimal or no adverse effects; and 6) improve quality of life [7, 16].

General approach [7, 11, 21, 22]:

- Avoidance of triggers known to precipitate or worsen asthma
- Quick relief medications include short-acting beta2-agonists, anticholinergics, and systemic corticosteroids
- Long-term control medications include inhaled corticosteroids, inhaled long acting beta agonists, oral leukotriene receptor antagonists, oral theophylline, and systemic corticosteroids in patients with severe asthma

- Non-pharmacologic treatment:

This includes patient education of self-management skills, avoidance of known allergenic triggers, avoidance of dehydration and supplemental oxygen therapy in acute severe asthma. Patients should play an active role in their therapy. Patients must understand the role of long-term control versus quick relief medications in their asthma treatment. Moreover, proper use of medication delivery devices should be continually evaluated.

- Pharmacologic treatment:

Stepwize approach: in this approach, the dose and number of medications and frequency of administration are increased as necessary and decreased when possible (**Figure 2-2**).

- Step one: As needed reliever inhaler.

  Intermittent asthma: Long-term control medications are not necessary, and patients should use a short-acting inhaled beta2-agonist to prevent or treat symptoms.
- Step two: One low dose controller medication plus as needed reliever medication.

  Mild persistent asthma: Daily use of a low-dose inhaled corticosteroid is the preferred treatment in all age groups. Cromolyn, nedocromil, and leukotriene modifiers are alternatives for patients who cannot take inhaled corticosteroids.
- Step three and four: One or two controllers plus as needed reliever medication.

  Moderate persistent asthma: The addition of a long-acting inhaled beta 2 agonist to low dose inhaled corticosteroids is the preferred treatment (step 3). Alternative is using medium-dose inhaled corticosteroids. Those with risks for severe exacerbations, the combination of a medium-dose inhaled corticosteroid plus a long-acting inhaled β2-agonist may be preferred for asthma control (step four).
- Step five and six: Two or more controllers plus as needed reliever medication:

  Severe persistent asthma: The treatment choice depends on selection in the prior step. Patients with severe persistent asthma should receive high dose inhaled corticosteroids and a long-acting inhaled beta2-agonist. If not well controlled, adding another add-on controller like a leukotriene receptor antagonists or theophylline is suggested as better alternative to starting systemic corticosteroids because of the significant adverse effects

seen with long-term therapy. Adding leukotriene receptor antagonists may permit dose reduction of inhaled corticosteroids in moderate and severe asthmatics and improve outcomes.

All patients with chronic asthma should be prescribed a short-acting inhaled beta agonist to treat symptoms as needed. In addition, non-pharmacological strategies should be emphasized continuously.

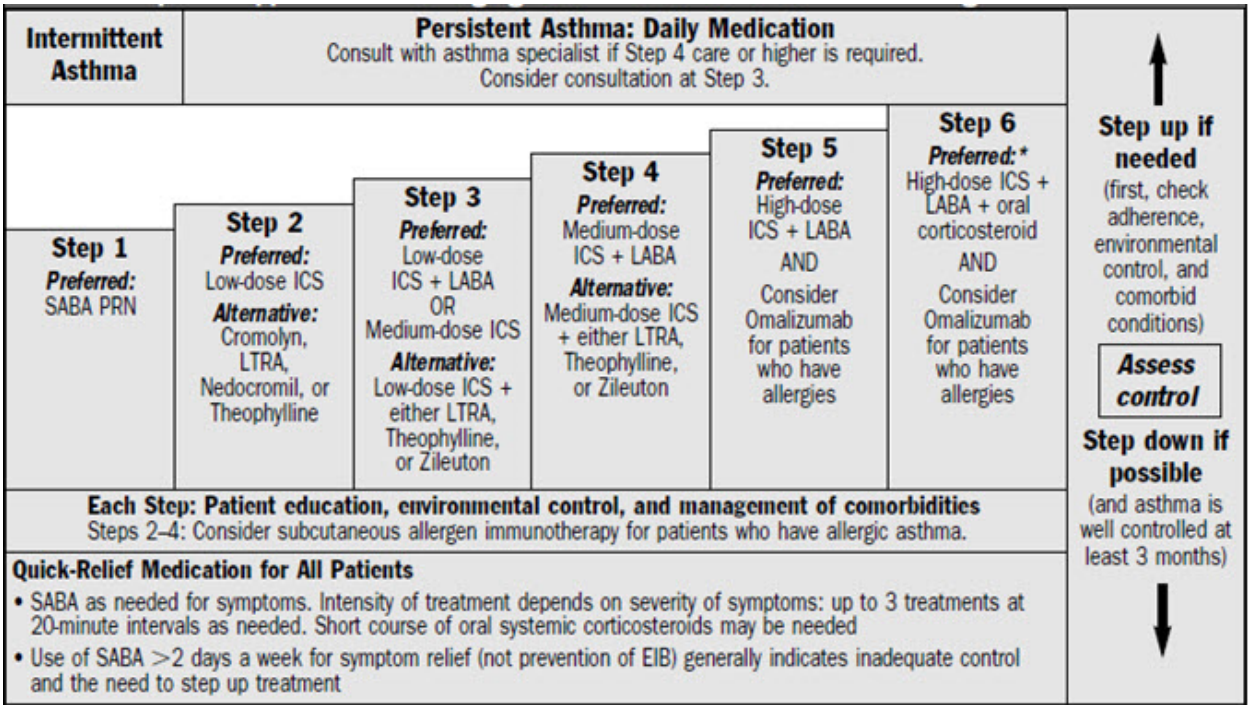

Figure 2-2 Stepwise approach for managing asthma in youths ≥ 12 years of age and adults.

EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, long-acting inhaled beta2-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta2-agonist. Adapted from National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma 2007 [11].

Main pharmacologic classes [11, 21, 22]

Beta agonists:

Mechanism of action: Beta 2-Adrenergic receptor stimulation activates adenyl cyclase, which produces an increase in intracellular cyclic AMP. This results in smooth muscle relaxation, mast cell membrane stabilization, and skeletal muscle stimulation.

- Short acting beta agonists are the first treatment of choice for acute severe asthma. Used for treatment of intermittent episodes of bronchospasm. Example: Albuterol.
- Long acting beta agonists: indicated as adjunctive long-term control for patients with symptoms who are already on low to medium doses of inhaled corticosteroids. Examples: Formoterol and Salmeterol.

Corticosteroids:

Mechanism of action: corticosteroids suppress airway inflammation primarily by decreasing inflammatory cytokines transcription and production e.g. interleukin (IL)-4 (IL-4), IL-13. ICS reverse the mucosal edema, decrease vascular permeability by vasoconstriction, and inhibit the release of pro-inflammatory leukotrienes. In addition, Corticosteroids increase the number of beta adrenergic receptors and improve receptor responsiveness to beta 2 adrenergic stimulation, reduce mucus production and hypersecretion, and prevent and reverse airway remodeling.

- Inhaled corticosteroids are the most effective long-term control therapy for persistent asthma and the only therapy shown to reduce the risk of death from asthma. Examples: Fluticasone, Budesonide and Beclomethasone.
- Systemic corticosteroids are indicated in acute severe asthma not responding completely to aggressive inhaled beta-2 agonists. Example: Prednisone.

Leukotriene Modifiers:

Mechanism of action: leukotriene modifiers act by preventing the action of leukotrienes in the body. Leukotrienes are released from mast cells, basophils and eosinophils and causes airway constriction, increased mucus production, swelling and inflammation in the airways. They are recommended as an alternative to ICS when ICS cannot be used or as add-on treatment in asthma that is not completely controlled by an ICS. Examples: Zafirlukast and Montelukast acting by blocking leukotriene receptors; Zileuton acts by inhibiting leukotriene synthesis.

2.2 ASTHMA IN OLDER ADULTS

2.2.1 Overview

Older adults with asthma are characterized by distinct health care needs as well as distinct pathophysiology of the disease [23-27]. Compared to younger patients, asthma in older adults is less reversible and associated with features of airway remodeling that are not observed in younger ages [28-30]. Still, there are multiple unanswered questions about the underlying pathophysiology in older adults [30]. The frequent coexistence of comorbid conditions, poor recall and perception of symptoms, physical disability, depressive symptoms, reduced psychological and physical quality of life, low adherence and treatment side effects are the major factors making older adults population different from younger patients [1, 31-35]. Older adults have a high prevalence of multi-morbidities. In a recent study, older adults with asthma had a mean of 8.4 chronic comorbid conditions compared to 3.4 in younger adults [36]. Comorbid conditions impose substantial burdens on the older adults [37]. In addition, comorbid conditions contribute to poor asthma outcomes including impaired quality of life, unscheduled asthma care, emergency department visits, hospitalizations and fatality after asthma hospitalizations [2, 38-41]. Comorbidities including chronic obstructive pulmonary disease (COPD), depression, obesity, gastroesophageal reflux disease, cardiac diseases and sleep apnea are frequently exist with asthma, and may potentially impact asthma outcomes in older adults [2]. Beside survival, quality of life (QoL) is of great concern and it is interactively related to treatment outcomes and adherence [26]. Treatment side effects can greatly affect QoL within this population. The incidence of drug-induced adverse effects in older adults is high, and adherence to therapeutic regimes is often poor [1, 42]. Thirty seven percent of respondents to qualitative survey of older

asthmatic adults in Australia were concerned about medication side effects. About 41% reported side effects from their medication including voice changes and a sore dry throat, and half of them reported tremor [24, 43]. Asthma management in older adults is challenging and patients' response to pharmacological treatments might be different from younger ages [42, 44]. Treatment effectiveness and safety determined among younger cohorts may not be appropriately applied for older adult patients with a special concern of underestimating the safety facet of some treatments. As previous clinical trials have rarely focused on older adult patients [1, 6], further research is needed on treatment effectiveness and safety in controlling asthma and in the presence of co-morbidities in the older adult population.

2.2.2 Epidemiology

Asthma is frequent in the older adult population, with the prevalence estimated to be greater than 10% [1]. It was estimated that around 15% of adults with asthma are 65 years of age or older [45]. However, the true prevalence of asthma in older adults is suggested to be much higher due to poor perception of symptoms and misdiagnosis with other conditions such as chronic obstructive pulmonary disease and gastroesophageal reflux disease [46-51]. Available data suggest that asthma burden in older adults is increasing both due to the high prevalence of asthma and the aging of the population [3, 52]. The population of older adults is expanding in USA; by 2030, an estimated 21% of the population will be 65 years of age or older [53]. In fact, the burden of asthma is more significant in the older adults than in younger patients. Asthma in older adults is associated with higher medical demands, worse outcomes and greater socioeconomic costs compared to younger adults [1, 2].

2.2.3 Asthma Mortality, Morbidity and Economic Burden in Older Adults

Older adults have greater asthma mortality compared to younger ages. More than 50% of asthma deaths occur among persons aged 65 years and older, and older asthmatics were shown to have a 5- fold increased risk of overall mortality compared with younger adults (adjusted odds ratio, 5.2; 95% CI, 4.0-6.9) [3, 54, 55]. Moreover, mortality rates in asthmatic older adults are increasing more rapidly than in younger ages (**Figure 2-3**) [54].

Asthma in older adults is more severe and uncontrolled than asthma in adulthood [4, 5, 56]. Higher rates of hospital admission, longer length of hospital stay, higher number of medication prescriptions and higher number of emergency department visits contribute to the poor economic outcomes in older adult patients [52, 57]. Specifically, 54%, 35% and 7% of direct asthma related costs in older adult asthmatic patients account for hospital inpatient care, medications and outpatient care, respectively [52]. Second only to 0-4 age group, asthmatic older adult patients contribute to highest number of hospital discharges [54]. Few reports have focused primarily on measuring asthma costs in older adults. A study conducted in 1994-1995 showed that asthma direct costs were double in older adults asthmatics (average per year $1,490 vs. $773) than in younger adult asthmatic [52]. Obviously, such poor outcomes mandate further attention to find the contributing factors and the possible interventions needed to attain better clinical and economic outcomes.

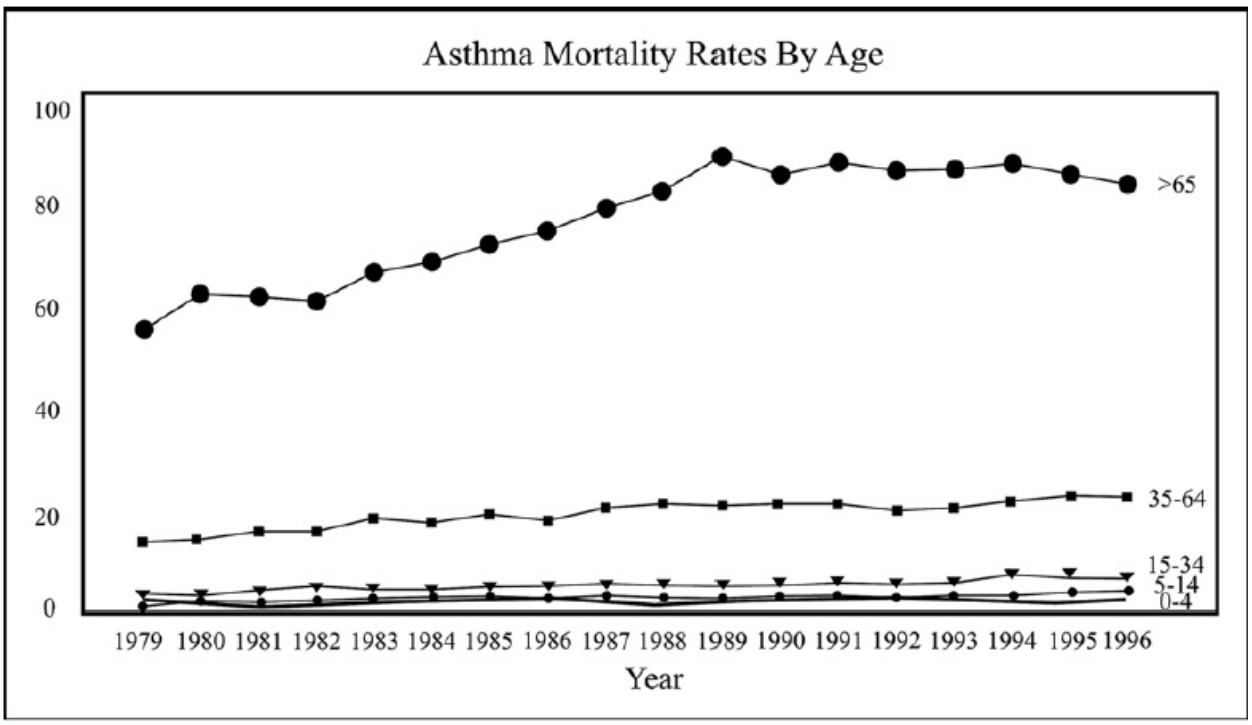

Figure 2-3 Asthma mortality rates by age per million, age-adjusted to the 1970 standard million (adapted from [54]).

2.2.4 Asthma Treatment in Older Adults; The Add-on Challenge

Treatment guidelines for asthma in older adults are primarily based on clinical trials conducted in adult populations [1], in which older ages were systematically excluded as ineligible [6]. ICS started at a low doses, are recommended as initial therapy for patients with persistent asthma [33]. When asthma symptoms are not well-controlled on low dose ICS, it is recommended to increase the dose of ICS or to add another agent, such as LABA or LTRA [33]. In patients with high risk for steroid side effects (e.g., osteoporosis or glaucoma), it is preferable to add either LABA or LTRA agents [33, 44].

The Global Initiative for Asthma (GINA) guidelines recommend LABA as the first line add-on treatment among all ages, and LTRA as the second-line add-on therapy [7]. These

guidelines acknowledge the fact that asthma treatments are still understudied in older adults. Combination of ICS and LABA treatments were shown to be an effective treatment [58, 59]. In a meta-analysis in which older adults were under-represented (patients aged 12 years or over), combination of ICS and LABA treatments improved lung function and symptoms, decreased rates of exacerbation and decreased the use of SABA compared to increased dose of inhaled steroid [59]. Similarly, ICS+LABA treatment has been shown to be more effective than ICS+LTRA in controlling asthma in populations mostly composed of non-older adult patients [60-63]. However, the overall pulmonary and CV safety of LABA for asthma is questioned in several studies [42, 64]. A growing concern is asthma-related morbidity and mortality associated with LABA when given with or without ICS [65-71]. In a meta-analysis of randomized, placebo-controlled trials of >3 months conducted in age pooled populations, LABA increased exacerbations requiring hospitalization (OR are 2.6) and life-threatening exacerbations (OR 1.8) compared to placebo [70]. These effects were present even when LABA treatment was combined with ICS [71]. However, other studies conducted in adults showed a non-significant increase in asthma related hospitalizations with uncertain effect regarding asthma deaths [72, 73]. It was proposed that the development of tolerance to LABA broncho-protective effects over time is the main mechanism behind these poor asthma related outcomes [71]. This phenomenon was shown to increase with age and also is suggested to involve other unknown mechanisms [74].

Another major concern regarding LABA agents in older adults is their CV safety [75, 76]. In a large meta-analysis of placebo controlled clinical trials that compared LABA treatment to placebo in age pooled populations, LABA were shown to increase the risk for adverse cardiovascular events including arrhythmias, ischemia, hypertension, congestive heart failure and death (**Figure 2-4**) [76]. The inotropic and chronotropic effects of LABA are the major

suggested pathways for increasing arrhythmias, cardiomyopathy and myocardial ischemia. LABA can also cause electrolyte disturbances that contribute to arrhythmias [74]. Other side effects of LABA that are significant to the older adults patients and shown to be quality of life detrimental include tremor, tachycardia, hypokalemia and blood pressure changes [42, 76] **Figure 2-5** summarize the suggested biological pathways behind LABA associated cardio and pulmonary adverse effects.

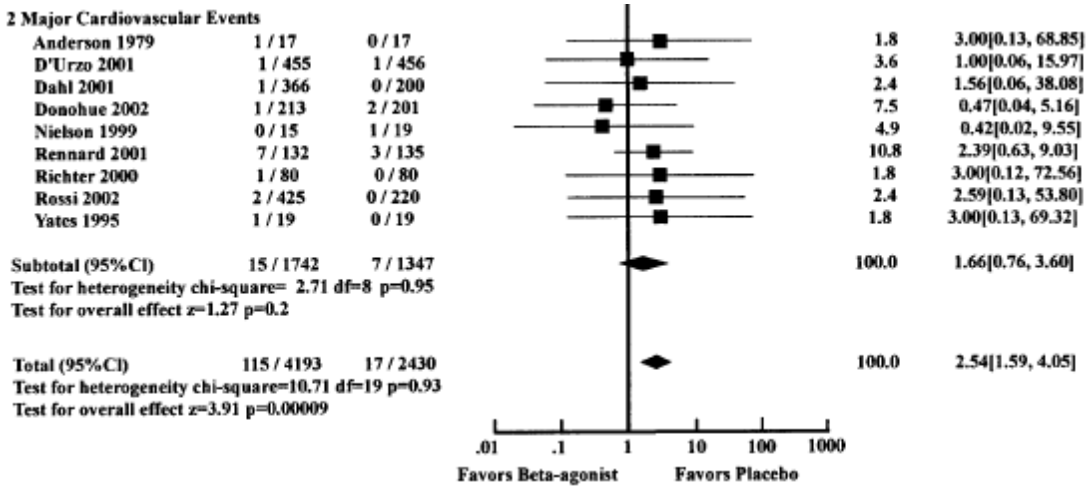

Figure 2-4 Cardiovascular effects of beta agonist use. Adapted from [76].

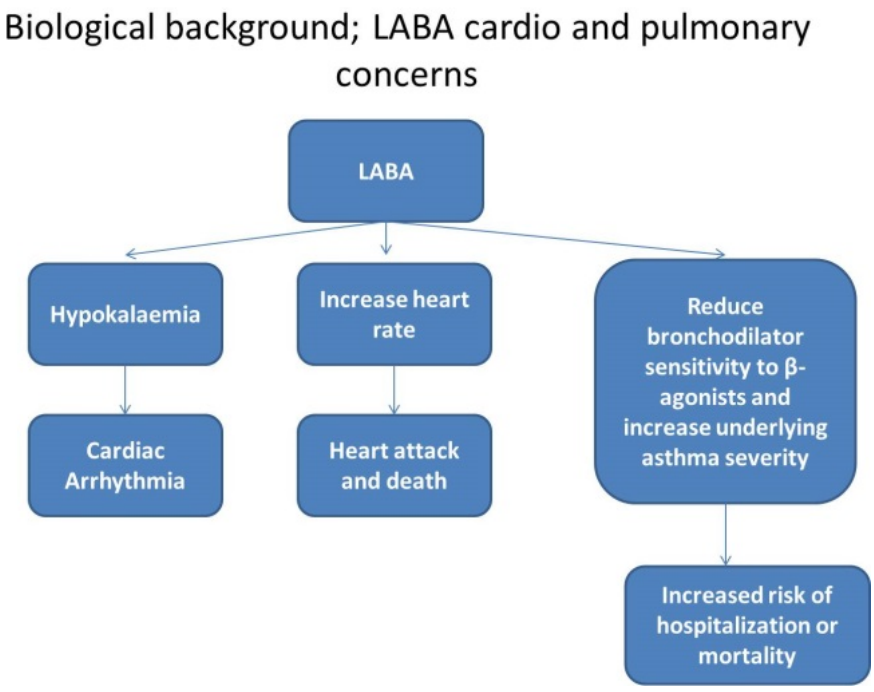

Figure 2-5 Suggested biological pathways behind LABA associated cardio and pulmonary adverse effects [77, 78].

As an alternative to LABA, LTRA treatment has been shown to be effective in controlling asthma symptoms when compared to placebo as monotherapy and when added as an adjunctive treatment among all ages [79-83]. Montelukast, as add-on therapy to ICS, was shown to improve clinical outcomes significantly as compared to ICS alone [79]. In a study of older adult population (more than 60-year old), montelukast, as add-on therapy to ICS, was shown to increase days without asthma symptoms, reduce days with beta-agonist use, and improve the mean asthma control test score significantly as compared to ICS alone [79]. In another study, after 4 weeks of using LTRA (zafirlukast), older adult patients demonstrated improvement in morning peak expiratory flow (PEF) and a decrease in symptoms compared to baseline [82]. Still, as the case with other asthma treatments, there are relatively few LTRA studies in older adults, and LTRA effectiveness needs to be further evaluated in a representative older adult

population and in comparison with other asthma treatments [44, 80]. In general, LTRA safety profiles are encouraging, particularly in older adults [44, 83, 84]. Interestingly, it was suggested that LTRA agents, beyond their actions in asthma, are promising in the secondary prevention of CV and cerebrovascular (CBV) diseases [85, 86]. The anti-inflammatory effect of LTRA treatment was suggested to inhibit the development of atherosclerosis, reduce intimal hyperplasia after vascular injury and exert a protective effect after cerebral ischemia and reperfusion [85]. In a nationwide population-based cohort of approximately 7 million persons, montelukast was associated with a lower risk (versus persons not taking montelukast) of recurrent stroke (HR, 0.62; 95% CI, 0.38-0.99) accounting for age, sex, education level, and yearly income in asthmatic patients. Also, montelukast use was significantly associated with lower risk of recurrent myocardial infarction in male subjects (HR, 0.65; 95% CI, 0.43-0.99) [86]. This is of special importance particularly in older adult populations in which the CV and CBV diseases have a higher prevalence and contribute to substantial clinical and economic burden [87, 88]. Suggested biological pathways behind LTRA cardio-protective effect are depicted in **Figure 2-6.** In addition, LTRA have characteristics that make them potentially favored in older adult population, such as having few and mild side effects and simplicity of use; orally once or twice daily [44]. Further, there is no concern in the literature regarding the CV safety of LTRA therapy in adults or older adult population. Rare cases of acute hepatitis and Churg-Strauss syndrome have been described in older adult patients; but with uncertain relationship with age [83].

The fact that older adult patients are under-represented in clinical trials generates a paucity of knowledge regarding the relative effectiveness, safety and costs of these add-on treatments in older adults. Both asthma and CV outcomes have not been compared directly between ICS+LABA and ICS+LTRA in representative older adult population.

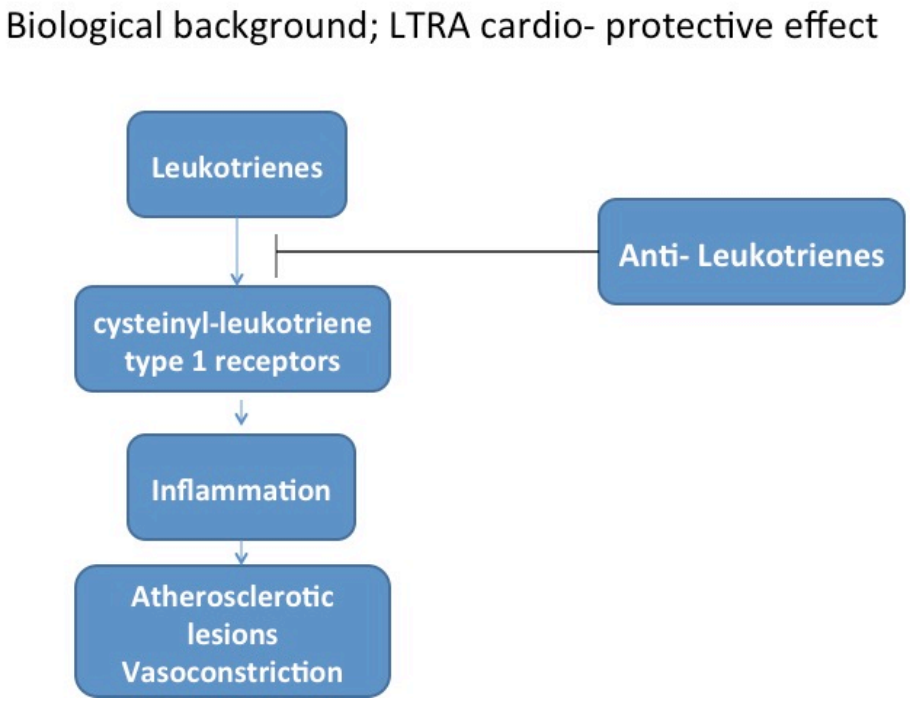

Figure 2-6 Suggested biological pathways behind LTRA cardio-protective effect [85, 86].

2.2.5 ICS+LTRA versus ICS+LABA Direct Comparison in Non-older Adult Population

Effectiveness:

A considerable body of observational retrospective research conducted in non-older adult populations had suggested that LABA treatment is more effective as add-on treatment than LTRA treatment [61-63]. Tan et al explored asthma outcomes in patients aged 18 through 64 years old, and they found that LTRA add-on treatment was associated with higher odds of inpatients or ED visits (OR = 1.40; CI=1.13-1.73), higher odds of OCS (OR=1.33; CI= 1.23-1.44) and higher SABA utilization [63]. Another retrospective study showed that asthma exacerbations were more likely with ICS+ montelukast compared with ICS+ LABA in adults (18–56 years) initiating asthma controller (OR = 1.4, 1.2–1.6) [61]. Similarly, some relatively short term clinical trials showed that ICS+LABA is superior in improving lung function and controlling daily symptoms [60, 89, 90]. However, longer-term clinical trials showed evidence of non-inferiority of LTRA versus LABA add-on treatment [84]. A 52 week, double blind, multicentre trial including patients 15-72 years old showed that adding montelukast to ICS is at least as effective as adding salmeterol in preventing asthma exacerbations [91]. This non-inferiority was also supported by a network meta-analysis shows that there is no significant difference in preventing severe asthma exacerbations between ICS+LABA and ICS+LTRA [92].

Several studies have consistently shown lower SABA use in patients treated with ICS+LABA compared to ICS+LTRA [61-63, 93]. This is logical and expected since both LABA and SABA belong to the same family of beta 2 agonists with similar mechanism of action.

Overall, data from mostly non-older adults based research still conflicting. However, the majority of evidence favored ICS+LABA as superior treatment in controlling asthma compared

to ICS+LTRA. **Table 2-1** summarizes the available literature that compared effectiveness in controlling asthma between the two add-on treatments in younger adults or age pooled research.

Table 2-1 Head to head asthma outcome comparisons between ICS+LABA and ICS+LTRA treated asthmatic adults.

Outcomes	Study	ICS+LABA Age±SD (N)	ICS+LTRA Age±SD (N)	Relative effect	Favor	Design
Asthma related inpatient visit or ED visit	Stempel 2002[62]	40.5±16.3 703	30.9±19.8 216	OR= 1.28	ICS+LABA	Retrospective cohort study; claims data
Asthma related inpatient visit or ED visit	Tan 2009 [63]	43±12 23,549	44±12 1,065	OR= 1.40	ICS+LABA*	Retrospective cohort study; claims data
Asthma related inpatient visit or ED visit	Lee 2010 [61]	39.30 ±10.65 13 608	38.76 ±10.69 590	RR= 1.39	ICS+LABA*	Retrospective cohort study; claims data
Asthma related inpatient visit or ED visit	Allen-Ramey, 2006 [93]	28.3±16.6 608	27.9±15.9 608	OR= 0.58	ICS+LTRA*	Retrospective cohort study; data claims
Asthma related inpatient visit	Stempel 2002 [62]	40.5±16.3 703	30.9±19.8 216	OR= 2.48	ICS+LABA	Retrospective cohort study; claims data
Asthma related ED visit	Stempel 2002 [62]	40.5±16.3 703	30.9±19.8 216	OR= 1.28	ICS+LABA	Retrospective cohort study; claims data
Use of OCSs	Tan 2009 [63]	43±12 23,549	44±12 1,065	RR= 1.33	ICS+LABA*	Retrospective cohort study; claims data
Use of OCSs	Allen-Ramey, 2006 [93]	28.3±16.6 608	27.9±15.9 608	OR=1.04	ICS+LABA	Retrospective cohort study; data claims
Asthma related inpatient visit	Bjermer 2003 [91]	41.0±13.7 743	41.2 ±13.6 747	RR = 0.71	ICS+LTRA	A 52 week, double blind, multicentre trial

Asthma related inpatient visit	Ilowite 2004 [94]	38.1 (15–70) 730	39.0 (14–73) 743	RR= 0.59	ICS+LTRA	A 48 weeks randomized, double-blind, double-dummy, multicenter study
Asthma related ED visit	Bjermer 2003 [91]	41.0±13.7 743	41.2±13.6 747	RR= 0.99	ICS+LTRA	A 52 week, double blind, multicentre trial
Asthma related ED visit	Ilowite 2004 [94]	38.1 (15–70) 730	39.0 (14–73) 743	RR=0.92	ICS+LTRA	A 48 weeks randomized, double-blind, double-dummy, multicenter study
Use of oral, intramuscular, intravenous, or rectal corticosteroid	Bjermer 2003 [91]	41.0±13.7 743	41.2±13.6 747	RR= 1.10	ICS+LTRA	A 52 week, double blind, multicentre trial
asthma exacerbations, which need OCS or Hospitalization for asthma.	Price 2011 [95]	49.7±16.1 182	51.0±16.0 170	OR= 1.02	ICS+LABA	Parallel, multicenter, pragmatic 2 years trial
Asthma exacerbation any severity	Ringdal 2003 [90]	43±15.8 356	43±14.8 369	9.6 % CS/LABA 14.6% ICS+LTRA	ICS+LABA*	Multinational, randomized, double-blind, double-dummy, parallel-group design, 12 weeks study

asthma exacerbation of either moderate or severe intensity	Ringdal 2003 [90]	43±15.8 356	43±14.8 369	4.8 % ICS+LABA 8.4% ICS+LTRA	ICS+LABA	Multinational, randomized, double-blind, double-dummy, parallel-group design, 12 weeks study
Asthma exacerbation any severity	Nelson 2000 [89]	40.2±14.4 222	43.0±13.7 225	2% ICS+LABA 6% ICS+LTRA	ICS+LABA*	Multicenter, double-blind, double dummy, parallel-group, 12-week study
≥6 SABA canisters	Tan 2009 [63]	43±12 23,549	44±12 1,065	OR=2.13	ICS+LABA*	Retrospective cohort study; claims data
≥6 SABA fills	Lee 2010 [61]	39.30 ±10.65 13,608	38.76 ±10.69 590	OR= 1.3	ICS+LABA	Retrospective cohort study ; claims data
SABA use	Allen-Ramey, 2006[93]	28.3±16.6 608	27.9±15.9 608	RR =1.33	ICS+LABA*	Retrospective cohort study; data claims
SABA use (Adjusted SABA canister refills)	Stempel 2002 [62]	40.5±16.3 703	30.9±19.8 216	3.29 ICS+LABA versus 4.45 ICS+LTRA	ICS+LABA*	Retrospective cohort study; data claims

* Statistically significant

Cardiovascular safety:

There is no published research designed specifically to measure cardiovascular events as a primary endpoint in asthma patients treated with ICS+LABA or ICS+LTRA. However, few studies have reported adverse CV outcomes. One meta-analysis of placebo controlled clinical trials found that LABA increased the risk for adverse cardiovascular events and death [76]. Another meta-analysis used mostly unpublished data from five studies with 5163 adults concluded that there is no statistically significant difference in the risk of cardiovascular events between ICS+LABA and ICS+LTRA (RR 1.09, 95% CI 0.77 to 1.53) [96]. Other studies showed that ICS+LTRA treatment was associated with less frequency of severe adverse events in general compared to ICS+LABA. A 52 week, double blind, multicentre trial including 15-72 year old patients showed that patients receiving salmeterol add-on treatment had a significantly higher incidence of drug related adverse events (10.0% v 6.3%, p = 0.01) and serious adverse experiences (7.4% v 4.6%, p = 0.022) compared with patients receiving montelukast add-on therapy [91]. The general safety of LTRA treatment was largely demonstrated in previous literature [83, 84]. **Table 2-2** summarizes the comparative general safety and treatment satisfaction reported from adult cohorts.

Table 2-2 Head to head general safety and treatment satisfaction comparisons between ICS+LABA and ICS+LTRA treated asthmatic adults.

Outcomes	Study	ICS+LABA Age±SD (N)	ICS+LTRA Age±SD (N)	Relative effect	Favor	Design
Serious adverse events; No of patients (%) with >1 serious adverse	Bjermer 2003 [91]	41.0±13.7 743	41.2±13.6 747	5% ICS+LTRA 7%ICS+LABA	ICS+LTRA*	A 52 week, double blind, multicentre trial
Satisfaction with treatment	Ringdal 2003 [97]	43±15.8 356	43±14.8 369	84% ICS+LTRA 93% ICS+LABA	ICS+LABA*	Multinational, randomized, double-blind, double-dummy, parallel-group design, 12 weeks study
Satisfaction with treatment	Fish 2001 [60]	39.9±0.6 476	39.5±0.6 472	84% ICS+LABA 79% ICS+LTRA	ICS+LABA*	Randomized, double-blind, double-dummy, parallel-group, multicenter trials of 12-week duration.

* Statistically significant

Economic outcomes

As for effectiveness and safety outcomes, economic burdens associated with these add-on treatments were not compared particularly in older adult populations. A large body of research in the non-older adult population consistently showed that patients receiving ICS+ LTRA incur higher asthma related costs as compared with patients receiving ICS+LABA [61-63].

Tan et al showed, in their retrospective study, that the total asthma related annual costs in ICS+LTRA treated group was 38% higher ($p<0.001$) than those for ICS+LABA group [63]. Similarly, Lee et al reported higher adjusted mean total asthma-related costs in patients treated with ICS+LTRA compared to ICS/LABA patients ($1223 vs. $873 per year) [61]. Pharmacy costs were a major driver of asthma expenditures and were significantly higher in patients treated with ICS+LTRA compared to ICS+LABA ($987 vs $606, respectively) [62]. Very few studies have evaluated all-cause costs in asthmatic adults. Stempel and coworkers showed that non-older adult patients treated with ICS+LABA incurred significantly lower total all-cause cost compared with ICS+LTRA ($3466 ICS+LABA versus $4346 ICS+LTRA). Another study evaluated total all-cause costs incurred by asthmatic patients treated with different asthma controllers found that compared to ICS only group as a reference, ICS+LTRA treated patients incurred $618 higher all-cause costs whereas ICS+LABA treated patients incurred $1811 higher all-cause costs (compared to ICS alone) [98]. The difference in annual costs between the two add-on treatments was mainly due to lower non-asthma costs associated with ICS+LTRA. One potential explanation for such observation may be that LTRA are safer and more compatible with other heath conditions. However, total health care costs were not compared directly between the two add-on treatments. **Table 2-3** summarizes available studies that compared economic outcomes between ICS+LABA and ICS+LTRA treated asthmatic adults.

Table 2-3 Head to head economic outcome comparisons between ICS+LABA and ICS+LTRA in adults.

Outcomes	Study	ICS+LABA Age±SD (N)	ICS+LTRA Age±SD (N)	Relative effect	Favor	Design
Annual total asthma-related cost	Stempel 2002 [62]	40.5±16.3 703	30.9±19.8 216	$952 ICS+LABA versus $1552 ICS+LTRA	ICS+LABA*	Retrospective cohort study; claims data
Annual total asthma-related cost	Tan 2009 [63]	43±12 23,549	44±12 1,065	1226 ICS+LABA 1687 ICS+LTRA	ICS+LABA*	Retrospective cohort study; claims data
Annual total asthma-related cost	Lee 2010 [61]	39.30 ±10.65 13,608	38.76 ±10.69 590	873 ICS+LABA versus $1223 ICS+LTRA	ICS+LABA*	Retrospective cohort study; claims data
Annual total asthma-related cost (1st year initiation)	Balkrishnan 2005 [99]	24.0±18.2 97	22.0±19.5 101	2224.60 (4326.01) ICS+LABA 1695.44 (3538.50) ICS+LTRA	ICS+LTRA	Retrospective cohort study; claims data
Annual total asthma-related cost (2nd year after initiation)	Balkrishnan 2005 [99]	24.0±18.2 97	22.0±19.5 101	2205.43 (4155.40) ICS+LABA 1911.29 (4289.93) ICS+LTRA	ICS+LTRA	Retrospective cohort study; claims data
Annual asthma-related pharmacy	Stempel 2002 [62]	40.5±16.3 703	30.9±19.8 216	$606 ICS+LABA versus $987 ICS+LTRA	ICS+LABA*	Retrospective cohort study; claims ata
Annual total health care costs	Stempel 2002 [62]	40.5±16.3 703	30.9±19.8 216	$3466 ICS+LABA versus $4346 ICS+LTRA	ICS+LABA*	Retrospective cohort study; claims data
Annual total health care costs (unadjusted mean)	Zeiger 2008 [98]	47.1±19.9 8,125	33.8±23.5 1,235	$5414 ICS+LABA $4478 ICS+LTRA	ICS+LTRA	Retrospective cohort study, claims data

* Statistically significant

3.0 RESEARCH SUMMARY, HYPOTHESIS, OBJECTIVES AND CONCEPTUAL MODEL

3.1 HYPOTHESIS AND SPESIFIC AIMS

Older adult patients with asthma experience poor health outcomes and contribute a great economic and health burden to society. Guidelines recommend LABA as the first line add-on treatment in asthmatic patients. Serious pulmonary and CV concerns were raised in the literature regarding the use of LABA agents in asthmatic patients. These concerns emerged from general population research with evidence of a potentially more serious problem among older adults as previously described. Very limited research focuses exclusively on measuring the effectiveness and safety of LABA treatment for older adults with asthma. An alternative to LABA add-on therapy is LTRA which is potentially a much safer treatment with promising benefits in older adults. Yet, as the case with LABA, LTRA agents are understudied in older adults.

The main objective of this dissertation work was to compare the effectiveness in controlling asthma, cardiovascular safety and costs associated with ICS+LTRA versus ICS+LABA treatments in older patients with asthma. We used Medicare fee for service data for two consecutive years (2009-2010) to test the following specific aims and hypotheses guiding the work:

Aim 1: To compare asthma related outcomes associated with LTRA versus LABA add-on treatments in older adults with asthma.

Hypothesis 1: Older adult patients treated with LABA add-on therapy have lower likelihood of asthma related exacerbations compared with those treated with LTRA add-on treatment.

Aim 2: To compare the CV related exacerbations associated with LTRA versus LABA add-on treatments in older adults with asthma.

Hypothesis 2: Older adult patients treated with LTRA add-on treatment have lower likelihood of CV related exacerbations compared with those treated with LABA add-on treatment.

Aim 3: To compare expenditures incurred by patients treated with LTRA versus LABA add-on treatments.

Hypothesis 3: Using LTRA add-on treatment is associated with higher asthma related costs but with lower all-cause costs compared with LABA.

3.2 CONCEPTUAL MODEL

This dissertation was guided by the conceptual model depicted in **Figure 3-1**. The conceptual model is derived from the Andersen behavioral model of health services utilization as a theoretical framework to assess predisposing, enabling, and need based factors that will likely affect health care utilization and outcomes [100]. The Andersen behavioral model of health services utilization suggests that health service use is a function of 3 main elements: predisposing, enabling, and need factors. Predisposing factors are those factors enhance the likelihood of using health services, and include demographic variables, socioeconomic status, attitudes, and beliefs. Enabling factors include factors such as the individual's income, health insurance, and access to different health care resources. Finally, medical need factors include individual's perceived health care need and illness experience as well as professional assessments of their health status and need for medical care [101, 102].

In Chapter 4 (study #1), treatment effects on asthma exacerbations, SABA use, CV exacerbations, all-cause mortality and treatment change were examined using the augmented inverse propensity weighted (AIPW) estimator accounting for predisposing, enabling, and need based factors as shown in **Figure 3-1**. In Chapter 5 (study #2), treatment effects on all-cause health care expenditures and asthma related expenditures were examined using nonparametric bootstrapping models accounting for predisposing, enabling, and need based factors as shown in **Figure 3-1.**

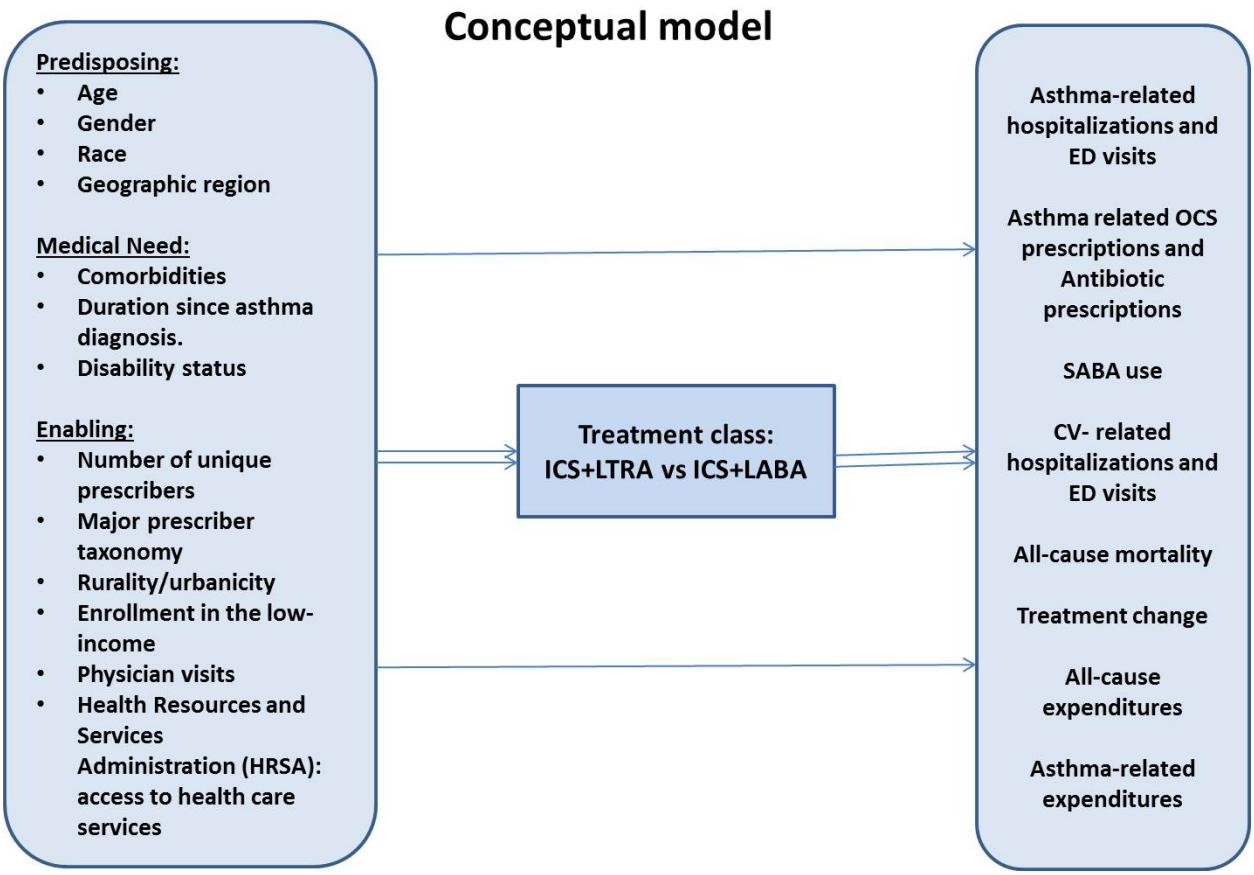

Figure 3-1 Dissertation conceptual model

4.0 ANTI-LEUKOTRIENE AGENTS VERSUS LONG ACTING BETA AGONIST IN OLDER ADULTS WITH PERSISTENT ASTHMA: A COMPARISON OF ADD-ON THERAPIES

4.1 ABSTRACT

Asthma treatment guidelines recommend LABA over LTRA as the first-line add-on therapy when inhaled corticosteroids fail to achieve adequate asthma control. However, older adults were excluded from asthma trials and there is no conclusive evidence regarding the comparative effectiveness and safety of these agents in older adults. The safety profile of LABA in older adults may differ from that in younger adults due to a higher baseline risk of CV events. Thus, this study sought to compare the effectiveness and cardiovascular safety of LABA versus LTRA add-on treatments in older patients with asthma.

This retrospective cohort study was conducted using Medicare claims and enrollment data for 2009-2010. We included asthmatic patients aged 66 years or older who were continuously enrolled in Fee for Service (FFS) Medicare with Part D coverage. We followed patients who were exclusively treated with each add-on treatment; in the primary analyses, patients were censored if they switched to or added the other treatment. The augmented inverse propensity weighted (AIPW) estimator was used to determine the effect of LABA vs. LTRA add-on therapy on asthma exacerbations requiring inpatient, emergency, or outpatient care as well as CV events, adjusting for demographics, comorbidities, and county level health care access variables.

The primary analysis included 14,702 patients, of whom 12,940 were treated with ICS+LABA and 1,762 were treated with ICS+LTRA. Our results showed that LTRA add-on treatment was associated with increased odds of asthma-related hospitalizations/ED visits (OR=1.4, $p<0.001$), as well as outpatient exacerbations requiring oral corticosteroids or antibiotics (OR=1.41, $p<0.001$) compared to LABA treatment. LTRA add-on therapy also showed lower effectiveness in preventing acute symptoms as indicated by greater utilization of

SABA (RR=1.58, $p<0.001$). On the other hand, LTRA add-on treatment was associated with lower odds of experiencing a CV event compared to LABA (OR=0.86, $p=0.006$).

Collectively, this study provides new evidence specific to older patients to help health care providers weigh the risks and benefits of these add-on treatments in older adults. Further subgroup analysis is needed to personalize asthma treatments in this higher-risk population.

4.2 INTRODUCTION

Asthma is a common respiratory chronic disease that affects all ages worldwide [12]. It was estimated that around 15% of adults with asthma are 65 years of age or older [45]. In fact, asthma is frequent in the older adult population, with prevalence estimated to be greater than 10% [1]. Because the older adult population in the U.S. continues to expand [53], optimizing asthma care for this population is critical. The burden of asthma is more significant in older adults than in the younger patients, with higher mortality, risk of hospitalization, and medical costs. Approximately, 50% of asthma deaths occur among persons aged 65 years and older [54]. Indeed, asthma in older adults tends to be more sever and uncontrolled than in adulthood [56]. Higher rates of hospital admission, longer length of hospital stay, greater medication use, and higher number of emergency department visits also contribute to higher economic burden of asthma in older adult patients [4, 5, 52]. Second only to the 0-4 year age group, asthmatic older adults contribute to highest number of hospital discharges [54]. Despite this, most studies of asthma therapies are focused on young adults. Very limited information exists on the use and outcomes of asthma therapies in older adults. In part, this is attributable to the systematic exclusion of older age groups from clinical trials [1, 6].

When asthma symptoms are not well-controlled on low dose ICS, it is recommended to add another agent, such as a LABA or LTRA. The Global Initiative for Asthma (GINA) guidelines recommend LABA as a first line add-on treatment among all ages, and LTRA as a second-line add-on therapy [7]. These guidelines acknowledge the fact that asthma treatments are still understudied in older adults. ICS+LABA treatment has been shown to be more effective than ICS+LTRA in controlling asthma in populations mostly composed of non-older adult patients [60-63]. However, the overall safety of LABA for asthma is questioned in several

studies [42, 64, 75, 76]. A growing concern is asthma-related morbidity and mortality associated with LABA when given with or without ICS [65-71]. Another major concern regarding LABA agents is their CV safety with an evidence of increased risks of major CV events including arrhythmias, ischemia, hypertension, congestive heart failure and death [75, 76]. Both asthma and CV concerns associated with LABA were raised from research in non-older adults or age pooled populations.

As an alternative to LABA, LTRA treatment has been shown to be effective in controlling asthma symptoms when compared to placebo as monotherapy and when added as an adjunctive treatment among all ages [79-83]. Still, as the case with other asthma treatments, LTRA still understudied in older adults [44, 80]. In general, LTRA safety profiles are encouraging, particularly in older adults [44, 83, 84]. Interestingly, it was suggested that LTRA agents, beyond their actions in asthma, are promising in the secondary prevention of CV and cerebrovascular (CBV) diseases [85, 86]. This is of special importance particularly in older adult populations in which the CV and CBV diseases have a high prevalence and contribute to substantial clinical and economic burden [87, 88].

Both asthma and CV outcomes have not been compared directly between ICS+LABA and ICS+LTRA in representative older adult population. The objective of this chapter was to compare the effectiveness in controlling asthma and cardiovascular safety of LABA versus LTRA add-on treatments in older patients with asthma.

4.3 METHODS

4.3.1 Data Source

The data source for this study consisted of 2009-2010 Medicare fee-for-service (FFS) medical claims (Parts A and B), Part D prescription drug event (PDE) data, and Beneficiary Summary Files (BSF) obtained from the Centers for Medicare and Medicaid Services (CMS) for a 10% random sample of beneficiaries continuously enrolled in Parts A, B, and D in 2009. The Part D prescription drug event data, MedPAR file, outpatient file, and carrier/professional services file provided information on asthma treatment exposures, outcomes, and covariates. Further, the beneficiary summary files were used to extract information on demographics, beneficiary entitlement and enrollment status, date of death, and comorbidities.

4.3.2 Primary Study Design

This study used a retrospective cohort design in which two treatment groups were identified: 1) exclusive users of ICS + LABA, and 2) exclusive users of ICS + LTRA. To be included, each patient was required to have at least 4 months of "wash-in" to eliminate any residual effect from prior use of the other add-on therapies that could potentially confound results. Patients were followed starting on the date of the first prescription for the add-on treatment after the 4 months wash in period. Patients were censored if they died or switched to or added the other add-on treatment (**Figure 4-1**).

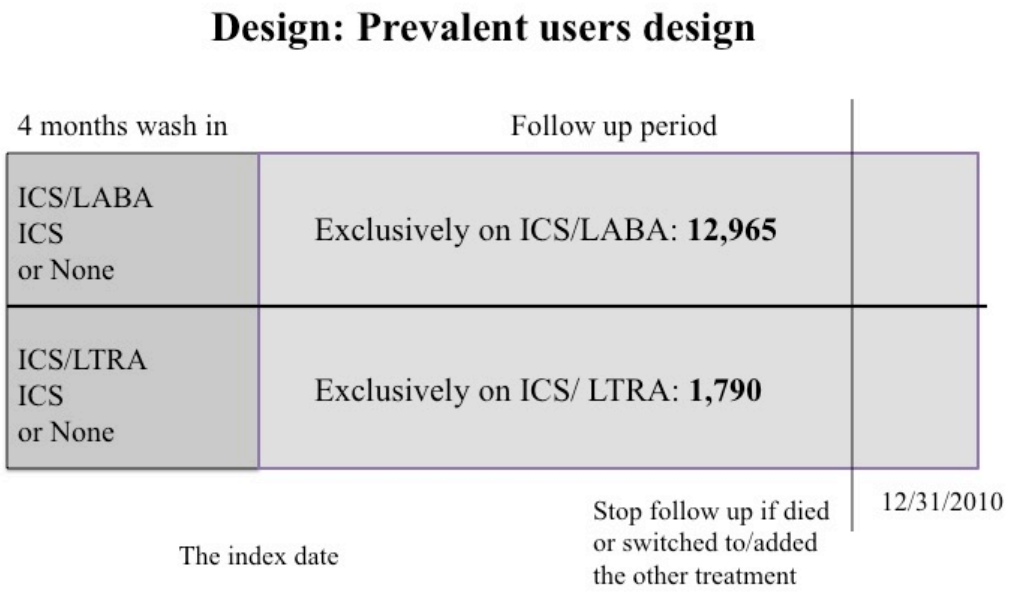

Figure 4-1 Primary analyses design

Follow up periods start on the date of the first prescription for the add-on treatment after the 4 months wash in period. Follow up periods end if died or switched to or added the other add-on treatment.

4.3.3 Sample

Sample population consists of beneficiaries 65 years old or more as of Jan 1 2009 and continuously enrolled in FFS Medicare Parts A and B with Part D coverage from Jan-1 2009 to Dec-31-2010 (n= 1,160,380). The sample was then limited to those who met criteria of having an asthma diagnosis as of Jan 1 2009, as per the CMS Chronic Conditions Data Warehouse's algorithm for detecting asthma in FFS Medicare beneficiaries (n= 128,928) [103, 104]. According to this validated algorithm, asthma diagnosis was identified by at least 1 inpatient, skilled nursing facility (SNF), home health agency (HHA) claim, or 2 hospital outpatient (HOP) or carrier claims defined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for asthma (493.XX). The sample was further limited to beneficiaries who were treated with at least one asthma controller medication, including ICS, LTRA, and/or LABA over 2009-2010 (n=56,300). Among these patients, only those who met the above wash-in criteria for being treated with ICS+LABA or ICS+LTRA in an exclusive manner over 2009-2010 years were included. Patients whose ages were less than 66 years as of Jan 2009 were excluded to make sure that all patients had enough periods (at least one year) of medical claims to capture an accurate asthma diagnosis. Finally, individuals living in Europe and Philippines were excluded, due to lack of availability of important geographic covariates in the Area Resource File (described below).

4.3.4 Outcomes

Several indicators of asthma treatment effectiveness were examined, including: 1) asthma exacerbations requiring hospitalization or ED use; 2) asthma exacerbations treated in an

outpatient setting; and 3) extent of use of short-acting beta agonists (SABA). Hospitalizations were identified from the MedPAR file and were considered asthma-related if the primary or secondary diagnosis ICD-9-CM code of these events was 493.XX [61, 98]. ED visits were identified in MedPAR and outpatient facility files using an established method [105] and were considered asthma-related if the primary or secondary diagnosis code was (493.XX). Asthma exacerbations treated in an outpatient setting were defined as face-to-face outpatient physician visits in the carrier file (identified through Current Procedural Terminology (CPT) codes) associated with a primary or secondary asthma diagnosis code and a PDE record for an antibiotic or oral corticosteroid (OCS) on the same day or within the next 7 days [106]. Finally, the extent of use of SABA (an indicator of effectiveness in preventing daily symptoms of asthma) was operationalized as the count of SABA prescriptions during the follow up period [107]. Part D event files were searched for SABA, OCS and antibiotics using national drug codes NDC (provided by the Healthcare Effectiveness Data and Information Set (HEDIS)).

The measure of CV safety consisted of any CV-related hospitalization or ED visit during the follow up period. Hospitalizations and ED visits were identified as CV related events if the primary or secondary diagnosis ICD-9-CM codes were (410.XX–414.XX) for ischemic heart disease, (427.XX) for cardiac dysrhythmias, (428.XX) for heart failure, (401.XX–405.XX) for hypertensive disease and (430.XX–438.XX) for cerebrovascular diseases.

All-cause death was identified using date of death in The Master Beneficiary Summary File Base segment.

Finally, switching to or adding the other add-on treatment after at least 6 months on the original treatment was considered and measured as treatment change. Such treatment change

might indicate poor effectiveness in controlling asthma and/or poor tolerance for side effects or other safety issues with the treatment.

4.3.5 Covariates

Several control variables were constructed to account for differences in baseline patient demographics, comorbidities, county level health access variables and other variables that might affect both treatment choice and outcomes. We obtained the following data from the Beneficiary Summary Files: patient ages were calculated as of Jan-1-2009, patient race/ethnicity (non-Hispanic White, Black, Hispanic or others), state of residence, gender, enrollment in the low-income subsidy, disability indicator, asthma duration since the first diagnosis in Medicare data and comorbid conditions. Many pre-existing comorbid conditions were adjusted for in our models including chronic obstructive pulmonary disease (COPD), cardiovascular disease, kidney diseases, depression, cancers and others. The first diagnosis for these conditions was required to occur before the date of starting patient follows up. Prescriber characteristics including number of unique prescribers of asthma medications as well as the specialty of the prescriber who accounted for the majority of asthma prescriptions were formulated using part D prescriber characteristics file. Part D data were also utilized to capture ICS strength at the date of starting follow up for each patient as a proxy for ICS dose and asthma severity. Also, beta blockers were accounted for in the analysis because these medications may affect both asthma and CV outcomes [108]. Outpatient doctor visits in the "wash-in" period were also measured since higher outpatient visits might lead to higher admissions. Medicare data were linked to Health Resource and Services Administration's (HRSA) Area Resource File (ARF) using zip codes to characterize some county level health care access variables including numbers for primary care

physicians, medical specialty physicians, allergy immunology specialty, CV specialty, pulmonary specialty, emergency medicine specialty, preventive medicine specialty, hospitals number and hospitals with emergency department. These variables were calculated as the number per 10,000 older adult residents for each county. County level rurality/urbanicity, average household size and percent below poverty variables were also extracted.

4.3.6 Statistical Analysis

Primary analysis: Treatment effects (Augmented inverse propensity weighting models):

All analyses were conducted in Stata v13 ((StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). As differences in patient and clinical characteristics at baseline would have the potential to bias results, propensity scores (PS) methodology was applied to balance treatment groups on potential confounders [109]. Augmented inverse propensity weighting with binary outcomes was utilized to obtain the adjusted probabilities for asthma and CV exacerbations, all-cause death and treatment change [110]. This method was used with count outcomes to obtain adjusted predicted rates for SABA fills. Odd ratios and rate ratios were calculated based on the adjusted predicted probabilities and rates produced by the augmented inverse propensity weighting estimator. The differing lengths of follow-up time across patients were addressed by adjusting for the natural log of person-years. These models included all covariates as defined above.

Augmented inverse propensity weighting estimator models both the outcome and the treatment probability and is considered “doubly robust” since only one of the two models must be correctly specified to consistently estimate the treatment effects [110].

Main analyses were repeated after excluding patients who died assuming these patients are sicker than the other population.

Imputation for missing values was implemented using the hotdeck procedure, where missing values were replaced by random values from the same variable, using the Schonlau implementation for the Stata software [111]. Hotdeck imputation has the advantage of being simple to use and preserves the distributional characteristics of the variable [112].

Treatment effect modification by major comorbidities:

Interactions between the treatment and the presence of preexisting CVD, as well as between treatment and the presence of COPD, were analyzed for each outcome model using the likelihood ratio test after estimating regression models with and without the interaction. Stratified analyses were performed for the outcome models in which interactions contributed significantly to treatment effect. Two analyses were conducted to test treatment interaction with preexisting CVD. In the first analysis, preexisting CVDs were defined as having a prior diagnosis of ischemic heart disease, acute myocardial infarction, congestive heart failure (CHF), atrial fibrillation (AF) and/or stroke/transient ischemic attack, as per established CMS Chronic Conditions Data Warehouse's algorithms [103]. In the second analysis, preexisting CVD status were further categorized into three levels: having no preexisting CVD; having preexisting ischemic heart disease, acute myocardial infarction, or stroke/transient ischemic attack (ischemic diseases); and having congestive heart failure or atrial fibrillation (CHF/AF diseases) since both conditions share common risk factors, frequently coexist and each predisposes to the other [113]. In both analyses, patients with hypertension alone, without any other CVD, were assumed to be relatively stable and were included in the non CVD strata.

The effect of LABA add-on strengths (as a proxy for LABA dose):

This analysis sought to investigate the effect of LABA add-on strength on all outcomes investigated in the primary analysis. LTRA treatment strengths were not different across the patients and so were not categorized. The main explanatory variable in this analysis was a three level treatment variable; 0= LTRA add-on, 1= LABA low strength add-on, and 2= LABA medium-high strength add-on. LABA strengths were measured at the first LABA prescription after the 4 months wash-in period. Multivariable logistic regression models were constructed and adjusted for all covariates as measured above.

Sensitivity analysis 1: incident user design:

In this design, only those new initiators of either LTRA or LABA add-on treatments (incident users) were included. Incident users were defined as those who used only ICS in the 3 months preceding the initiation of add-on therapy (LTRA or LABA). Patients were followed for the same outcomes in the primary analysis after the index date, which was defined as the date of the first pharmacy claim for either treatments (LTRA or LABA add-on) (**Figure 4-2**). Multivariable logistic regression/ Poisson regression were used and were adjusted for all covariates as mentioned above (baseline outpatient doctor visits were measured in the 3 months pre-index period). Patient characteristic and baseline variables were compared between treatment groups using unadjusted bi-variable tests (chi-square for categorical variables and t-test for continuous variables).

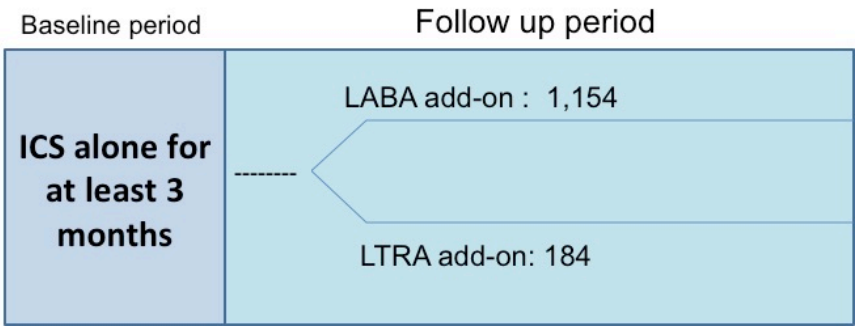

Figure 4-2 Incident users design

Patients were required to have at least 3 months of ICS only prescriptions (without LABA or LTRA)

Sensitivity analysis 2: discontinuation design:

In this analysis, patients' fills were followed to exclude periods of no treatment supply based on 'days supply' field in Medicare part D event file. Outcomes were followed only during the periods in which treatments were continuously available for patients as indicated by their fills. Accordingly, patients were censored once they had more than 30 days without treatment supply for either the ICS or the add-on treatment (treatment discontinuation) (**Figure 4-3**). All primary and sensitivity analyses mentioned above were repeated after applying the discontinuation design.

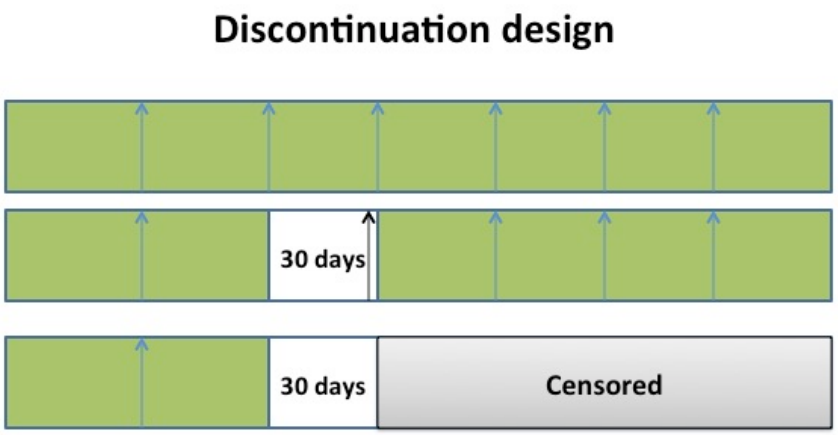

Figure 4-3 Discontinuation design

Patient prescriptions were followed and patients were censored once they were running out of either ICS or the add-on treatment for more than 30 days. Each arrow represents a prescription.

4.4 RESULTS

4.4.1 Patient Characteristics/Baseline Comparisons

A total of 14,702 patients met the inclusion criteria, of whom 1,762 were receiving ICS+LTRA and 12,940 were receiving ICS+LABA in an exclusive manner. **Table 4-1** compares all patient characteristic and baseline variables between treatment groups using unadjusted bi-variable tests (chi-square for categorical variables and t-test for continuous variables). Overall, patients averaged 76.5 years of age; 72% were female and 78% were non-hispanic whites. The ICS+LABA group generally had greater co-morbidities, with a higher prevalence of ischemic heart disease, congestive heart failure, atrial fibrillation, cerebrovascular disease, COPD, diabetes and other comorbidities. The most common co-morbid conditions (among the whole sample) were hypertension (91%), hyperlipidemia (83%), cataract (77.8) and COPD (77.7%). The average number of comorbid chronic diseases per patient was 9 across the whole sample; 9 for ICS+LABA group and 8 for ICS+LTRA group.

Table 4-1 Study population characteristics by total and asthma add-on medication group

	Total sample n= 14,702 (%)		LABA add-on n= 12,940 (%)		LTRA add-on n= 1,762 (%)		p value*
Age							
65-70	2,883	(29.6)	2,495	(19.3)	388	(22.0)	0.008
70-75	3,967	(27.0)	3,472	(26.8)	495	(28.1)	
75-80	3,478	(23.6)	3,097	(23.9)	381	(21.6)	
80+	4,374	(29.8)	3,876	(30.0)	498	(28.3)	
Female gender	10,614	(72.2)	9,225	(71.3)	1,389	(78.8)	<0.001
Race							
Non-Hispanic white	11,423	(77.8)	10,086	(78.0)	1,337	(75.9)	<0.001
Black	1,293	(8.8)	1,148	(8.9)	145	(8.2)	
Hispanic	1,234	(8.4)	1,083	(8.4)	151	(8.6)	
Others	738	(5.0)	610	(4.7)	128	(7.3)	
Geographic region							
Northeast	3,192	(21.7)	2,748	(21.2)	444	(25.2)	0.001
Midwest	3,317	(22.6)	2,910	(22.5)	407	(23.1)	
South	5,323	(36.2)	4,728	(36.5)	595	(33.8)	
West	2,868	(19.5)	2,553	(19.7)	315	(19.1)	
Asthma duration							
<6 months	781	(5.3)	726	(5.6)	55	(3.1)	<0.001
6-12 months	944	(6.4)	854	(6.6)	90	(5.1)	
1-2 years	1,682	(11.4)	1,496	(11.6)	186	(10.6)	
>2 years	11,295	(76.8)	9,864	(76.2)	1,431	(81.2)	
Disability	2,495	(17.0)	2,212	(17.1)	283	(16.1)	0.278
Major prescriber specialty asthma drugs							
Asthma	2,893	(19.7)	2,521	(19.5)	372	(21.1)	0.081
General	9,360	(63.7)	8,230	(63.6)	1,130	(64.1)	
Non-physician	1,019	(6.9)	907	(7.0)	112	(6.4)	
Others	1,430	(9.7)	1,282	(9.9)	148	(8.4)	
Rural Urban							
Metro	11,471	(78.6)	10,108	(78.7)	1,363	(78.2)	0.909
Urban	2,715	(18.6)	2,386	(18.6)	329	(18.9)	
Rural	404	(2.8)	354	(2.8)	50	(2.9)	
Low income enrollment	6,718	(45.7)	5,833	(45.1)	885	(50.1)	<0.001
Using beta blockers	5,863	(49.9)	5,265	(40.7)	598	(33.9)	<0.001
Medium to high ICS strength at index prescription	11,223	(76.3)	10,114	(78.2)	1,109	(62.9)	<0.001

Outpatients physician visits in the 4 months wash in period Means (SE)	4.7	(0.033)	4.72	(0.035)	4.42	(0.097)	<0.001
Number of unique asthma prescribers Mean (SE)	1.5	(0.006)	1.4	(0.007)	1.7	(0.020)	<0.001
Study population Comorbidities							
Alzheimer	2,638	(17.9)	2,321	(17.9)	317	(18.0)	0.956
Acute myocardial infarction	1,068	(7.3)	1,001	(7.7)	67	(3.8)	<0.001
Anemia	9,974	(67.8)	8,848	(68.4)	1,126	(63.9)	<0.001
Atrial fibrillation	2,990	(20.3)	2,688	(20.8)	302	(17.1)	<0.001
Cancers (other than lung cancer)	2,260	(15.4)	2,023	(15.6)	237	(13.5)	0.017
Cataract	11,440	(77.8)	10,052	(77.7)	1,388	(78.8)	0.3
Chronic kidney disease (CKD)							
No CKD	10,468	(71.2)	9,087	(70.2)	1,381	(78.4)	<0.001
CKD, no ESRD	4,109	(28.0)	3,737	(28.9)	372	(21.1)	<0.001
ESRD	125	(0.85)	116	(0.9)	9	(0.5)	<0.001
Chronic obstructive pulmonary disease	11,422	(77.7)	10,210	(78.9)	1,212	(68.8)	<0.001
Congestive heart failure	7,556	(51.4)	6,783	(52.4)	773	(43.9)	<0.001
Depression	6,316	(43.0)	5,638	(43.6)	678	(38.5)	<0.001
Diabetes	6,683	(45.5)	5,949	(46)	734	(41.7)	0.001
Glaucoma	3,907	(26.6)	3,434	(26.5)	473	(26.8)	0.785
Hip fracture	732	(5.0)	661	(5.1)	71	(4.0)	0.051
Hyperlipidemia	12,265	(83.4)	10,813	(83.6)	1,452	(82.4)	0.221
Benign Prostatic Hyperplasia	2,313	(15.7)	2,104	(16.3)	209	(11.9)	<0.001
Hypertension	13,378	(91.0)	11,815	(91.3)	1,563	(88.7)	<0.001
Hypothyroidism	3,978	(27.1)	3,523	(27.2)	455	(25.8)	0.214
Ischemic heart	10,069	(68.5)	8,999	(69.5)	1,070	(60.7)	<0.001
Lung cancer	510	(3.5)	480	(3.7)	30	(1.7)	<0.001
Osteoporosis	5,002	(34.0)	4,375	(33.8)	627	(35.6)	0.14
Rheumatoid arthritis, Osteoarthritis	10,293	(70.0)	9,101	(70.3)	1,192	(67.7)	0.021
Stroke, transient ischemic attack	2,991	(20.3)	2,685	(20.8)	306	(17.4)	0.001
Counties level health care access variables calculated as mean per 10,000 older adults (SE)							
Primary care physicians	55.7	(0.21)	55.6	(0.23)	56.4	(0.62)	0.216

Medical specialty physicians	72.3	(0.54)	71.8	(0.57)	75.7	(1.52)	0.019
Allergy immunology specialty	1.02	(0.01)	1	(0.01)	1.1	(0.03)	0.042
Cardiovascular specialty	5.5	(0.04)	5.5	(0.05)	5.8	(0.123)	0.029
Pulmonary specialty	2.6	(0.02)	2.6	(0.02)	2.7	(0.06)	0.183
Emergency medicine specialty	7.8	(0.05)	7.8	(0.06)	7.9	(0.14)	0.301
Preventive medicine specialty	0.43	(0.01)	0.4	(0.01)	0.4	(0.02)	0.572
Hospitals number	1.6	(0.01)	1.7	(0.01)	1.6	(0.04)	0.026
Hospitals with emergency department	1.01	(0.01)	1	(0.01)	1	(0.03)	0.427
Average household size	2.57	(0.002)	2.58	(0.002)	2.56	(0.01)	0.004
Percent below poverty	11.35	(0.04)	11.4	(0.04)	11.2	(0.11)	0.066

*Variables were compared between the two treatment groups using bivariate analysis (un-adjusted).
ESRD: End stage renal disease; LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist; ICS: inhaled corticosteroids; SE: standard error.

4.4.2 Primary Analysis: Treatment Effects (Augmented Inverse Propensity Weighting Models)

Results of the augmented inverse propensity weighting models (**Table 4-2**) revealed significantly increased probabilities of asthma related hospitalizations and/or ED visits with ICS+LTRA compared with ICS+LABA (calculated OR: 1.40, $p<0.001$). Similarly, results showed that treatment with ICS+LTRA was associated with a higher probability for exacerbations needing OCS or antibiotics (calculated OR: 1.41, $p<0.001$). SABA fills were significantly greater among patients who received ICS+LTRA versus ICS+LABA (RR: 1.58, $p<0.001$). Treatment change and all-cause death were not different between the two treatment groups. On the other hand, our results showed that ICS+LTRA is associated with a significantly lower probability for CV related hospitalizations/ED visits (calculated OR: 0.86, $p=0.006$) versus ICS+LABA. After excluding patients who died during the study period, the interpretation of our results did not change (**Table 4-3**). The overlap plots showed no evidence that the overlap assumption is violated and are displayed in Appendix A: Figure 1. Further, all covariates were well balanced after applying propensity score weighting (Appendix A: Table 6).

Table 4-2 Primary analysis results: ORs and RRs for asthma, cardiovascular and other outcomes by treatment group: ICS + LTRA vs ICS + LABA

	OR	Adjusted probability LABA add-on	Adjusted probability LTRA add-on	p value	Favor
Effectiveness outcomes					
Asthma Hospitalizations or ED visits	1.4	0.18	0.24	<0.001	LABA
Asthma related oral corticosteroids or antibiotics prescriptions	1.41	0.17	0.22	<0.001	LABA
Any asthma exacerbation	1.53	0.3	0.4	<0.001	LABA
SABA use	1.58 (RR)	1.98 (rate)	3.11 (rate)	<0.001	LABA
Cardiovascular safety					
CV hospitalization/ED	0.86	0.44	0.4	0.006	LTRA
Other outcomes					
Change treatment *	1.1	0.088	0.096	0.279	Neither
All-cause death *	0.85	0.054	0.046	0.14	Neither

ORs and RRs were calculated based on adjusted probabilities and rates estimated by the augmented inverse propensity weighting estimator.
Total sample size= 14,702 (1,762 on ICS+LTRA and 12,940 on ICS+LABA). Average follow up periods= 1.06+ 0.47 person years.
Change treatment: switching to/or adding the other add-on treatment after at least 6 months on the original treatment.
* Multivariable logistic regression was used due to propensity scores modelling issues.
Abbreviations: ED: emergency department; SABA: short acting beta agonists; CV: cardiovascular, LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist; ICS: inhaled corticosteroids; OR: odds ratio; RR: rate ratio.

Table 4-3 Results after excluding patients who died during the study period. ORs and RRs for asthma, cardiovascular and other outcomes by treatment group: ICS + LTRA vs ICS + LABA.

	OR	Adjusted probability LABA add-on	Adjusted probability LTRA add-on	p value	Favor
Effectiveness outcomes					
Asthma Hospitalizations or ED visits	1.36	0.18	0.23	<0.001	LABA
Asthma related oral corticosteroids or antibiotics prescriptions	1.44	0.18	0.24	<0.001	LABA
Any asthma exacerbation	1.51	0.3	0.4	<0.001	LABA
SABA use	1.55 (RR)	1.98 (rate)	3.07 (rate)	<0.001	LABA
Cardiovascular safety					
CV hospitalization/ED	0.85	0.41	0.37	0.005	LTRA
Other outcomes					
Change treatment*	1.096	0.09	0.098	0.313	Neither

ORs and RRs were calculated based on adjusted probabilities and rates estimated by the augmented inverse propensity weighting estimator. Total sample size= 13,528 (1,642 on ICS+LTRA and 11,886 on ICS+LABA). Average follow up periods= 1.08 $\pm$ 0.47 person years.
Change treatment: switching to/or adding the other add-on treatment after at least 6 months on the original treatment.
* Multivariable logistic regression was used due to propensity scores modeling issues.
Abbreviations: ED: emergency department; SABA: short acting beta agonists; CV: cardiovascular, LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist; ICS: inhaled corticosteroids; OR: odds ratio; RR: rate ratio.

4.4.3 Treatment Effect Modification by Major Comorbidities

Treatment effects on asthma hospitalization/ED visits and on any asthma exacerbations were significantly different by the presence of any of the major CVDs. Likelihood-ratio test results are provided in Appendix A: Table 1. In the CVD stratified analysis, the odds ratio of asthma hospitalization/ED visits associated with ICS+LTRA versus ICS+LABA was 1.5; $p < 0.001$ for patients with CVD and 1.15; $p = 0.329$ for patients without CVDs. Similarly, odds ratio of any asthma exacerbation was attenuated in the absence of CVD (**Table 4-4**).

Table 4-4 Stratified analysis by the presence of cardiovascular disease (CVD). Results are shown for outcome models in which treatment effect is different by the presence of CVDs.

	With CVD (ischemic heart disease, congestive heart failure, myocardial infarction, atrial fibrillation or stroke/transient ischemic attack)					Without CVD				
Sample size	11,544 (ICS+LTRA: 1,265, ICS+LABA: 10,279)					3,158 (ICS+LTRA: 497, ICS+LABA: 2,661)				
	OR	**Adjusted probability LABA add-on**	**Adjusted probability LTRA add-on**	**P value**	**Favor**	**OR**	**Adjusted probability LABA add-on**	**Adjusted probability LTRA add-on**	**p value**	**Favor**
Asthma Hospitalizations or ED visits	1.5	0.19	0.26	<0.001	LABA	1.15	0.16	0.18	0.329	Neither
Any asthma exacerbation	1.59	0.29	0.4	<0.001	LABA	1.24	0.33	0.39	0.043	LABA

ORs were calculated based on adjusted probabilities estimated by the augmented inverse propensity weighting estimator; ICS + LTRA vs ICS + LABA.

Abbreviations: ED: emergency department; CVD: cardiovascular disease, LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist; ICS: inhaled corticosteroids; OR: odds ratio.

In the second analysis of CVDs interaction, the odds of asthma hospitalization/ED visits associated with ICS+LTRA were significantly higher compared to ICS+LABA in the CHF/AF group, however, no significant difference was noticed in the ischemic diseases or in the non-CVD group. Considering any asthma exacerbation, the odds ratios were significant and favoring LABA add-on treatment in both CVD groups (the ischemic diseases and the CHF/AF diseases) but not in the non-CVD group (**Table 4-5**). Likelihood-ratio test results are provided in Appendix A: Table 2.

Table 4-5 Stratified analysis by the presence of cardiovascular diseases (CVDs). Results are shown for outcome models in which treatment effect is different by the presence of CVDs. CVDs were categorized into three levels: no CVD; having preexisting ischemic diseases; or having CHF/AF diseases.

	Without CVD				Ischemia diseases; ischemic heart disease, acute myocardial infarction, or stroke/transient ischemic attack				Congestive heart failure or atrial fibrillation diseases (CHF/AF diseases)			
Sample size	3,158 (ICS+LTRA: 497, ICS+LABA: 2,661)				3,404 (ICS+LTRA: 416, ICS+LABA: 2,988)				8140 (ICS+LTRA: 849, ICS+LABA: 7,291)			
	OR	**Adjusted probability LABA add-on**	**Adjusted probability LTRA add-on**	**P value (Favor)**	**OR**	**Adjusted probability LABA add-on**	**Adjusted probability LTRA add-on**	**P value (Favor)**	**OR**	**Adjusted probability LABA add-on**	**Adjusted probability LTRA add-on**	**P value (Favor)**
Asthma Hospitalizations or ED visits	1.15	0.16	0.18	0.329 (Neither)	1.29	0.17	0.2	0.096 (Neither)	11.55	0.2	0.27	<0.001 (LABA)
Any asthma exacerbation	1.24	0.33	0.39	0.043 (LABA)	1.57	0.3	0.4	<0.001 (LABA)	11.56	0.29	0.39	<0.001 (LABA)

ORs were calculated based on adjusted probabilities estimated by the augmented inverse propensity weighting estimator; ICS + LTRA vs ICS + LABA.

Abbreviations: ED: emergency department; CVD: cardiovascular disease, LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist; ICS: inhaled corticosteroids; OR: odds ratio.

Treatment interaction with the presence of COPD was also significant in determining asthma outcomes associated with each treatment. Likelihood-ratio test results are provided in Appendix A: Table 3. Testing for treatment effect by the presence of comorbid COPD revealed that ICS+LTRA associated asthma hospitalizations/ED visits as well as asthma related oral corticosteroids or antibiotics prescriptions were not significantly different from ICS+LABA in the absence of COPD. Similarly treatment changes were not significantly different between the two groups in the absence of COPD. On the other hand, SABA use was even higher in patients receiving ICS+LTRA compared to ICS+LABA in the absence of COPD (**Table 4-6**).

Table 4-6 Stratified analysis by the presence of COPD comorbidity. Results are shown for outcome models in which treatment effect is different by the presence of COPD.

	With COPD					Without COPD				
Sample size	11,422 (ICS+LTRA: 1,212, ICS+LABA: 10,210)					3,280 (ICS+LTRA: 550, ICS+LABA: 2,730)				
	OR	**Adjusted probability LABA add-on**	**Adjusted probability LTRA add-on**	**p value**	**Favor**	**OR**	**Adjusted probability LABA add-on**	**Adjusted probability LTRA add-on**	**p value**	**Favor**
Asthma Hospitalizations or ED visits	1.5	0.18	0.25	<0.001	LABA	1.15	0.18	0.2	0.305	Neither
Asthma related oral corticosteroids or antibiotics prescriptions	1.5	0.15	0.22	<0.001	LABA	1.13	0.23	0.25	0.29	Neither
Any asthma exacerbation	1.59	0.29	0.4	<0.001	LABA	1.28	0.34	0.4	0.02	LABA
SABA use (RR)	1.55	2.14	3.32	<0.001	LABA	1.65	1.44	2.37	<0.001	LABA
Change treatment*	1.23	0.06	0.07	0.048	LABA	0.82	0.07	0.06	0.267	Neither

ORs were calculated based on adjusted probabilities estimated by the augmented inverse propensity weighting estimator; ICS + LTRA vs ICS + LABA.

*Multivariable logistic regression was used due to propensity scores modeling issue (not concave).
ORs and RRs : ICS + LTRA vs ICS + LABA.
Abbreviations: ED: emergency department, COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids; LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist; OR: odds ratio; RR: rate ratio.

Further interactions between treatment and age (80 or older versus 66-79 years old) as well as between treatment and ICS strengths (as a proxy for asthma severity) were tested. Patients treated with lower ICS strengths (assumed to have milder asthma) were less likely to switch away from LTRA compared to patients treated with medium-high ICS strengths (assumed to have more severe asthma) who were more likely to switch to or add LABA add-on treatment ($p = 0.030$). No significant interaction was found between treatment and age for all outcomes.

Secondary analysis: The effect of LABA Add-on strength (as a proxy for LABA dose).

Results are provided in Appendix A: Table 4.

4.4.4 Sensitivity Analysis (Incident Users Design)

In comparison to the prevalent users design we used in the primary analysis, in which most patients were prevalent users, this analysis included incident users only and showed no significant difference between the two treatment groups on any of the outcomes investigated in the primary analysis (**Table 4-7**).

Patient characteristic and baseline variables comparisons are provided in Appendix A: Table 5.

Table 4-7 Incident users' design. ORs and RRs for asthma, cardiovascular and other outcomes by treatment group: ICS + LTRA vs ICS + LABA.

	OR	CI	Adjusted probability LABA add-on	Adjusted probability LTRA add-on	P value	Favor
Effectiveness outcomes						
Asthma Hospitalizations or ED visits	0.88	0.59 - 1.30	0.2	0.18	0.521	Neither
Asthma related oral corticosteroids or	1.13	0.76 - 1.67	0.16	0.17	0.548	Neither
Any asthma exacerbation	0.93	0.66 - 1.31	0.34	0.33	0.665	Neither
SABA use (RR)	0.93	0.84 - 1.02	2.23	2.06	0.105	Neither
Cardiovascular safety						
CV hospitalization/ED	1.08	0.75 - 1.56	0.44	0.46	0.661	Neither
Other outcomes						
All-cause death	0.63	0.31 - 1.27	0.05	0.03	0.198	Neither

Multivariable logistic regression/ Poisson regression were used and were adjusted for all covariates mentioned above.
Total sample size= 1,338 (184 on ICS+LTRA and 1,154 on ICS+LABA).
Average follow up periods = 0.98 $\pm$ 0.51 person years.
Abbreviations: ED: emergency department; SABA: short acting beta agonists; CV: cardiovascular, LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist; ICS: inhaled corticosteroids; OR: odds ratio; RR: rate ratio.

4.4.5 Sensitivity Analysis (Discontinuation Design)

In agreement with primary analysis, results for the discontinuation design showed that patients receiving LTRA add-on treatment were more likely to have asthma related hospitalizations/ED and asthma related OCS/antibiotic (calculated ORs were 1.29 and 1.3 respectively with $p<0.05$). However, treatment change was significantly lower in patient treated with ICS+LTRA compared to ICS+LABA (OR= 0.61, p= 0.047). Adjusted SABA prescription rates were significantly higher with ICS+LTRA (calculated RR =1.85, $p<0.001$). Similar to results from the main analysis, LTRA add-on treatment was associated with lower odds of CV related hospitalizations/ED visits (calculated OR: 0.8, p = 0.004) (**Table 4-8**).

The follow up periods after applying the discontinuation design were on average 39.8% and 33.3% of the original follow up periods (primary analysis) for ICS+LABA and ICS+LTRA, respectively.

After excluding patients who died during the study period, the interpretation of the results did not change compared to using the full sample in the discontinuation design analysis (**Table 4-9**).

Table 4-8 Discontinuation design results. ORs and RRs for asthma, cardiovascular and other outcomes by treatment group: ICS + LTRA vs ICS + LABA.

	OR	Adjusted probability LABA add-on	Adjusted probability LTRA add-on	p value	Favor
Effectiveness outcomes					
Asthma Hospitalizations or ED visits	1.29	0.07	0.09	0.036	LABA
Asthma related oral corticosteroids or antibiotics prescriptions	1.3	0.067	0.085	0.03	LABA
Any asthma exacerbation	1.34	0.13	0.16	0.001	LABA
SABA use	1.85 (RR)	0.77 (rate)	1.43 (rate)	<0.001	LABA
Cardiovascular safety					
CV Hospitalizations or ED visits	0.8	0.22	0.18	0.004	LTRA
Other outcomes					
Change treatment*	0.61	0.013	0.008	0.047	LTRA
All-cause death*	0.88	0.01	0.009	0.612	Neither

ORs and RRs were calculated based on adjusted probabilities and rates estimated by the augmented inverse propensity weighting estimator.

*Multivariable logistic regression was used due to propensity scores modeling issue (not concave).

Abbreviations: ED: emergency department, SABA: short acting beta agonists; LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist; CV: cardiovascular; OR: odds ratio; RR: rate ratio.

Change treatment: switching to/or adding the other add-on treatment after at least 6 months on the original treatment.

Total sample size= 14,366 (1,498 on ICS+LTRA and 12,868 on ICS+LABA).

Average follow up periods = 0.33 $\pm$ 0.32 person years.

Table 4-9 Discontinuation design results after excluding patients who died in 2010

	OR	Adjusted probability LABA add-on	Adjusted probability LTRA add-on	p value	Favor
Effectiveness outcomes					
Asthma Hospitalizations or ED visits	1.29	0.067	0.085	0.041	LABA
Asthma related oral corticosteroids or antibiotics prescriptions	1.32	0.07	0.09	0.021	LABA
Any asthma exacerbation	1.35	0.12	0.16	0.001	LABA
SABA use	1.81 (RR)	0.76 (rate)	1.37 (rate)	<0.000	LABA
Cardiovascular safety					
CV hospitalization/ED	0.82	0.19	0.16	0.014	LTRA
Other outcomes					
Change treatment*	0.62	0.013	0.008	0.049	LTRA

ORs and RRs were calculated based on adjusted probabilities and rates estimated by the augmented inverse propensity weighting estimator.

*Multivariable logistic regression was used due to propensity scores modeling issue (not concave).

Abbreviations: ED: emergency department, SABA: short acting beta agonists; LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist; CV: cardiovascular; OR: odds ratio; RR: rate ratio. Total Change treatment: switching to/or adding the other add-on treatment after at least 6 months on the original treatment.

Total sample size= 13,220 (1,396 on ICS+LTRA and 11,824 on ICS+LABA).

Average follow up periods = 0.33 $\pm$ 0.3 person years.

All other results from the discontinuation design are provided in Appendix B: Tables 1-7.

Table 1: Discontinuation design: Likelihood-ratio test for adding the interaction between treatment group and the presence of preexisting CVD. CVD: ischemic heart disease, congestive heart failure, myocardial infarction, atrial fibrillation or transient ischemic attack.

Table 2: Discontinuation design: Stratified analysis by the presence of major cardiovascular diseases (CVD). Results are shown for outcome models in which treatment effect is different by the presence of CVDs.

Table 3: Discontinuation design: Likelihood-ratio test for adding the interaction between treatment group and the presence of preexisting CVD. CVDs were categorized into three levels: no CVD; having preexisting ischemic diseases; or having CHF/AF diseases.

Table 4: Discontinuation design: Likelihood-ratio test for adding the interaction between treatment group and the presence of preexisting COPD.

Table 5: Discontinuation design: Stratified analysis by the presence of COPD. Results are shown for outcome models in which treatment effect is different by the presence of COPD.

Table 6: Discontinuation design: Effect of different LABA add-on strengths versus LTRA add-on treatment.

Table 7: Discontinuation design: Incident users' design. ORs and RRs for asthma, cardiovascular and other outcomes by treatment group: ICS + LTRA vs ICS + LABA.

4.5 DISCUSSION

To our knowledge, this analysis of older adults with asthma is the first in evaluating effectiveness and CV safety outcomes associated with these most commonly used add-on treatments in a representative older adult population. Results showed that although LABA is more effective than LTRA in controlling asthma in older adults when added to ICS, patients treated with LABA add-on treatment were more likely to have major CV events.

Regarding effectiveness, results showed that LABA add-on treatment was associated with lower likelihood of exacerbations that need hospitalizations or ED visits as well as exacerbations treated in an outpatient setting by OCS or antibiotic. Further, LABA was associated with lower SABA use, a marker of better asthma symptom control. These results are consistent with evidence from previous studies of younger cohorts [60-63]. Tan et al studied asthma outcomes in patients aged 18 through 64 years old, and they found that LTRA add-on treatment was associated with higher odds of inpatient or ED visits (OR = 1.40; CI=1.13-1.73), higher odds of OCS (OR=1.33; CI= 1.23-1.44) and higher SABA utilization [63]. Another retrospective study showed that asthma exacerbations were more likely with ICS + montelukast compared with ICS+LABA in adults (18–56 years) initiating asthma controller (OR = 1.4, 1.2–1.6) [61].

Our results were robust even after applying the sensitivity discontinuation design. Following patients only for periods of continuous supply of treatments as measured by days' supply for their prescriptions, LTRA add-on was associated with a higher probability of asthma exacerbation and higher SABA utilizations. However, the odd ratios for asthma exacerbations

were attenuated in the discontinuation design but still favoring LABA. This indicates that improving adherence to ICS+LTRA (both ICS and LTRA) may improve the associated asthma outcomes. Even though treatment change was not different in the primary analysis, it was significantly lower with LTRA add-on treatment after applying the discontinuation design. This finding is in contrast to previous research that showed a significantly higher treatment satisfaction with ICS+LABA than with ICS+LTRA in adults [95, 96]. Our results suggest that older adults who adhere to their prescriptions of both ICS and LTRA are actually more satisfied than those who adhere to ICS +LABA treatment. This may be explained in part by the milder side effects and simplicity of use (as oral treatment) associated with LTRA in older adults [44].

One suggested explanation for the lower effectiveness for ICS+LTRA in controlling asthma in older adults is the high prevalence of COPD in older adults with asthma [80]. The prevalence of COPD diagnosis among our sample of asthmatic older adults was indeed high, at 78%. Compared to LABA, LTRA is known to be less effective in treating COPD [114]. The effects of LTRA versus LABA add-on treatments on asthma exacerbations were significantly different by the presence of COPD comorbidity. The probabilities of asthma exacerbations were not significantly different between the two add-on treatments in the absence of COPD. This might suggest that LTRA is more effective in controlling asthma in the absence of COPD comorbidity than in the presence of COPD. However, since we have only around 3000 patients without COPD, further research with a larger COPD free older adult sample size is required to confirm such effect.

Previous research has suggested that LABA might be associated with severe asthma-related hospitalizations and deaths when given with or without ICS [65-71]. In comparison, our results did not show any significant increase in asthma related hospitalizations associated with

ICS+LABA compared with ICS+LTRA. However, we were limited in this study by lack of availability of cause of death, and whether LABA is associated with higher asthma related deaths in older adults remains an important question for future research.

The other major finding in this study is that ICS+LTRA treatment was associated with lower odds of CV hospitalizations/ED visits compared to ICS+LABA. There are no published clinical trials designed specifically to measure cardiovascular events as a primary endpoint in asthma patients treated with ICS+LABA vs. ICS+LTRA. However, a few studies have reported adverse CV outcomes. One meta-analysis of placebo controlled clinical trials found that LABAs increased the risk for adverse CV events and death compared to placebo [76]. Although CV outcomes were never compared directly between the two add-on treatments, one meta-analysis used mostly unpublished data from five studies with 5163 adults concluded that there was no statistically significant difference in the risk of CV events between ICS+LABA and ICS+LTRA (RR 1.09, 95% CI 0.77 to 1.53) [96]. In comparison to this review, our results suggest that older adults may be more susceptible to CV events with ICS+LABA compared to younger ages. This is of concern since HCUPnet 2010 national statistics for older adults (65 to 84 old) showed that in-hospital mortality rates associated with CV hospitalizations are much higher than with asthma hospitalizations [115]. The lower tendency for CV events associated with LTRA was even lower when patients were consistently filling their prescriptions in our discontinuation design. This might indicate that the better the adherence for LTRA, the lower the CV risk (cardio-protective effect), or might imply that the more exposure for LABA in older adults, the more CV risk patients will have.

Interestingly, stratifying by the presence of major CVDs, ICS+LTRA was associated with lower odds for CV exacerbations in the presence and absence of major CVDs. However,

ICS+LTRA treatment was less effective in controlling asthma in patients with CVDs. This might indicate that CVDs may partially contribute to the worse asthma outcomes associated with LTRA.

In the incident users design, differences in treatment effects were not statistically different for all asthma, CV, treatment change and all-cause death outcomes. This may indicate that the both LTRA and LABA add-on treatments are equivalent in effectiveness and safety in the short term period after the initiation and so the differences between them are relatively long term effects that are not prominent early in the treatment. Whether this is a true conclusion or whether these non-significant results are simply due to the small sample size in this incident users design, need to be investigated using larger sample of incident users. The incident users design with enough sample size has some advantages over the primary design in this study that includes both incident and prevalent users regardless of the initiation time. Incident users design improves internal validity by improving confounder control, and captures earlier events that occurred after the start of therapy; only the less susceptible patients remain on each treatment [116, 117]. On the other hand, using prevalent user design increases the study size and increases the precision in estimates. This is especially important in instances where the number of incident users available is limited as in our case. Further, prevalent users design, as opposed to incident users design, can increase the ability to study long-term effects associated with cumulative years of exposure. One more advantage of prevalent users design is the generalizability; the estimates of incident users design may be more valid (internally), but apply to fewer patients. Requiring all patients to be incident users without prior use of maintenance medication may focus consideration on patients in the earlier or less severe stages in their natural history [116].

In summary, ICS+LABA treatment was associated with lower risk of asthma exacerbations but higher risk of CV events compared to ICS+LTRA in older adults. In addition to asthma outcomes, CV outcomes are especially important in evaluating asthma treatments in older adults compared to younger cohorts. Further subgroup analysis is needed to find out which patients may be at highest risk for CV adverse events when treated with LABA add-on treatment. In addition, further analyses in incident older adult users would be valuable in capturing early treatment effects associated with these add-on treatments.

5.0 HEALTH CARE EXPENDITURES IN PATIENTS WHO RECEIVED INHALED CORTICOSTEROIDS WITH EITHER LEUKOTRIENE RECEPTOR ANTAGONISTS OR LONG ACTING BETA AGONISTS AS A COMBINATION THERAPY IN OLDER ADULTS

5.1 ABSTRACT

There is a paucity of literature on the costs of pharmacologic treatments in asthmatic older adults who are not well controlled on inhaled corticosteroids. Also, the few studies that are available consider only asthma related costs and not the all-cause expenditures. All-cause costs are important since the adverse effects from pharmacological treatments can affect other comorbid conditions in this susceptible population. Understanding the resource utilization of older adults is important to better predict future healthcare expenditures in an aging population. This study was designed to compare asthma related and all-cause health care expenditures associated with ICS+LTRA and ICS+LABA in asthmatic older adults. This was a retrospective cohort study conducted using 2009-2010 Medicare fee-for-service (FFS) medical and pharmacy claims from 10% random sample of beneficiaries continuously enrolled in Parts A, B, and D in 2009. The sample comprised patients aged 66 years and older who were treated exclusively with ICS+LABA or ICS+LTRA. Outcomes assessed were asthma related costs (medical, pharmacy and total), and all-cause health care costs (medical, pharmacy and total). Multivariable regression models with nonparametric bootstrapped standard errors were used to compare all-cause and asthma related costs. All models were adjusted for demographics, comorbidities, and county level health care access variables in addition to follow up periods in person years. The primary analysis included 14,702 patients, of whom 12,940 were treated with ICS+LABA and 1,762 were treated with ICS+LTRA. The results showed that ICS+LTRA treatment was associated with increased asthma related costs compared to ICS+LABA. With a mean of 1.06 person years follow up period, adjusted asthma related costs were $4,724 for ICS+LTRA group vs $2,939 for ICS+LABA group ($p<0.001$). Total all-cause costs were not significantly different between treatment groups ($68,944 for ICS+LTRA compared with $74,369 for ICS+LABA ($p=0.219$)).

The findings reveal that ICS+LABA treatment was associated with lower asthma related expenditures compared to ICS+LTRA. However, the total all-cause costs did not differ between the two groups, suggesting that lower asthma related costs might be offset by higher non-asthma expenditures for older adults treated with ICS+LABA.

5.2 INTRODUCTION

The financial costs of asthma put a considerable burden on US health care resources. In 2007, it was estimated that 1.75 million emergency department (ED) visits and 456,000 hospitalizations were asthma-related [118]. Asthma is associated with enormous healthcare expenditures. The total annual medical cost for asthma in adults was estimated to be around $18 billion [119].

Asthma in older adults is more expensive than asthma in adulthood with higher medical use and worse outcomes [4, 5, 52, 54, 55, 120-125]. In comparison to younger ages, older adults experience higher rates of hospital admission, longer length of hospital stay, higher hospital charges, higher number of prescribed medications and a higher number of ED visits [52, 55, 57]. Few studies have estimated the direct cost of asthma in older adults with age's ≥65 year old [52]. A study conducted in 1994-1995 showed that asthma total direct costs were double in older adults compared to younger patients (average per year $1,490 vs. $773, respectively) [52]. In this study, hospital inpatient care, medications and outpatient care were found to account for 54%, 35% and 7% of direct costs, respectively [52]. This study does not evaluate all-cause costs for asthmatic older patients, which is a notable limitation since the adverse effects from pharmacological treatment can affect other comorbid conditions in this susceptible population.

As we previously mentioned, LABA and LTRA are the common add-on treatments recommended when asthma symptoms are not well-controlled with low dose ICS. Evidence from younger populations showed that asthma-related costs for those treated with ICS+LABA compared to ICS+LTRA were significantly lower; however, total all-cause costs were less studied [61, 63]. Both asthma-related and all-cause costs associated with recommended pharmacologic asthma treatments have not been studied in an older adult population. The current study was designed to address these gaps in the literature by evaluating asthma-related and all-

cause costs associated with the most common add-on treatments in older adult patients with persistent asthma.

5.3 METHODS

5.3.1 Data Source

The data source of this study consisted of health care claims and enrollment data of 2009-2010 Medicare fee-for-service (FFS) (Parts A and B), Part D prescription drug event (PDE) data, and Beneficiary Summary Files (BSF) obtained from the Centers for Medicare and Medicaid Services (CMS) for a 10% random sample of beneficiaries continuously enrolled in Parts A, B, and D in 2009.

5.3.2 Study Design

In this retrospective observational cohort investigation, medical and drug claims data were used to compare all-cause and asthma related costs among older adults using ICS + LABA versus ICS + LTRA in an exclusive manner. To be eligible to this study, each patient was required to have at least 4 months of "wash-in" to eliminate any residual effect from the use of other add-on therapies prior to 2009 that could potentially confound results. Follow up periods were started on the date of the first prescription for the add-on treatment after the 4 months wash-in period and ended by death, switching to/adding the other add-on treatment or the end of the study (Dec 31 2010).

5.3.3 Sample

The study population consists of eligible Medicare beneficiaries continuously enrolled in FFS Medicare Parts A and B with Part D coverage from Jan-1 2009 to Dec-31-2010. Among these beneficiaries, the final sample comprised those who: 1) were 66 years old or more as of Jan 1 2009, 2) met criteria for having an asthma diagnosis as of Jan 1 2009, as per the CMS Chronic Conditions Data Warehouse's algorithm for detecting asthma in FFS Medicare beneficiaries [103, 104], 3) met the above wash-in criteria for being treated exclusively with ICS+LABA or ICS+LTRA between 2009-2010, and 4) USA resident. According to CMS Chronic Conditions Data Warehouse's algorithm for detecting asthma, asthma diagnoses were identified by at least 1 inpatient, skilled nursing facility (SNF), home health agency (HHA) claim, or 2 hospital outpatient (HOP) or carrier claims defined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for asthma (493.XX).

5.3.4 Outcomes

Total all-cause costs were calculated as the sum of total all-cause medical and total all-cause pharmacy costs. All-cause medical costs were defined as the total of Medicare payments associated with inpatient, outpatient (institutional and non-institutional), skilled nursing facility, hospice care, home health agency (HHA) and durable medical equipment for any reason. All-cause pharmacy costs were defined as the sum of all costs associated with prescription medications in part D events file.

Total asthma related costs were calculated as the sum of asthma related medical and pharmacy costs. Asthma-related medical costs included Medicare payments associated with

inpatient admissions and ED visits assigned a primary or secondary ICD- 9 code for asthma (493.XX). Other costs such as physician visits, laboratory tests medical equipment, hospice, HHA and nursing home care were not included due to inadequate specificity in the data to be differentiated as asthma-related costs [98].

Asthma related pharmacy costs were defined as the costs associated with asthma prescription medications including LABAs, ICS, ICS+LABA, LTRA, oral corticosteroids (OCS) or antibiotics used to treat asthma exacerbations, SABA and other less commonly used asthma medications like methylxanthin. Asthma medications were identified using National Drug Codes (provided by the Healthcare Effectiveness Data and Information Set (HEDIS)).

Medical (all-cause and asthma related) health-care spending was defined as the amount paid by Medicare; costs paid by other sources were not included. Pharmacy costs were defined as the sum of the gross cost of pharmacy prescriptions (all-cause and asthma related).

5.3.5 Covariates

In addition to the main explanatory variable (treatment group with either ICS+LABA or ICS+LTRA), baseline patient characteristics were adjusted for in the multivariate models, including demographics, comorbidities, county level health access variables and other variables that might confound the association with outcomes. The Beneficiary Summary File was used to extract information about: patient age (as of Jan-1-2009), patient race/ethnicity (Non-Hispanic White, black, Hispanic or others), state of residence, sex, enrollment in the low-income subsidy, disability indicator, asthma duration since the first diagnosis in Medicare data and several comorbidities. The BSF includes diagnosis indicators for 21 chronic conditions along with the dates for their first diagnosis in the Medicare data. In order to be considered as preexisting

conditions, the first diagnoses in Medicare data were required to be before the date of starting patient follow up. Other covariates included in the model were use of beta blockers as these medications may affect asthma outcomes [108], ICS strength at the date of starting follow up as a proxy for ICS dose and asthma severity, outpatient doctor visits during the "wash-in" period, and prescriber characteristics including number of unique prescribers of asthma medications as well as the specialty of the prescriber who accounted for the majority of asthma prescriptions. Finally, Medicare data were linked to Health Resource and Services Administration's (HRSA) Area Resource File (ARF) to extract county level health care access variables including number of primary care physicians, medical specialty physicians, allergy immunology specialty, CV specialty, pulmonary specialty, emergency medicine specialty, preventive medicine specialty, hospitals number and hospitals with emergency department. These variables were calculated as the number per 10,000 older adult residents for each county. County level rurality/urbanicity, average household size and percent below poverty were also included. These covariates were selected based on the conceptual model presented in Chapter 3 in which they were organized into predisposing, medical need and enabling variables.

5.3.6 Statistical Analysis

Primary analysis:

All analyses were conducted in Stata v13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Bivariate analyses (two-sample t-tests and Wald chi-square tests) were used to compare the difference in population characteristics between the two treatment groups. Unadjusted costs per person year were summarized using descriptive statistics for the total sample and by treatment group (ICS+LABA vs. ICS+LTRA users). The group

comparisons on costs were tested by Wilcoxon test. Further, unadjusted total drug costs and number of prescriptions per person year were calculated for asthma treatment classes (ICS, ICS+LABA, LABA, LTRA, OCS, SABA, Antibiotics and others) by treatment groups.

Nonparametric bootstrap procedures with 1,000 replications were used to compare health care costs and asthma related costs between the two groups. Bootstrapping is frequently used when evaluating differences in costs. [126-128]. Bootstrapping compares arithmetic means without making assumptions about the cost distribution [129, 130]. Further, the nonparametric bootstrapping method was shown to be robust for data with large zero mass [131]. Treatment group indicator was the main explanatory variable in all models. All other covariates were adjusted for as described above. Adjusted predicted costs (or marginal costs) were predicted after regression models using the mean values for the other independent variables.

Sensitivity analysis; Discontinuation design:

In this analysis, patients' prescription fills were followed to exclude periods of no treatment supply based on the 'days supply' field in the Medicare part D event file. Patients were censored once they had more than 30 days without a treatment supply for either the ICS or the add-on treatment.

5.4 RESULTS

5.4.1 Patient Characteristics/Baseline Comparisons

The characteristics of the study cohort are summarized in Chapter 4 (**Table 4-1)**. A total of 14,702 patients met the inclusion criteria, of whom 1,762 were receiving ICS+LTRA and 12,940 were receiving ICS+LABA in an exclusive manner. The average follow up period across the whole sample was 1.06 $\pm$ 0.47 person years. The mean age of the study cohort was 76.5 years; 72% were female and 78% were Non-Hispanic Whites. The most common co-morbid conditions (among the whole sample) were hypertension (91%), hyperlipidemia (83%), cataracts (77.8) and COPD (77.7%). The ICS+LABA group had higher prevalence of comorbid chronic diseases. The average number of comorbid chronic diseases per patient was 9 across the entire sample; 9 for ICS+LABA group and 8 for ICS+LTRA group.

5.4.2 Cost of Care

Unadjusted costs:

Average unadjusted all-cause and asthma related costs/person year are summarized in **Table 5-1**. The average total all-cause costs per person year were lower for patients treated with ICS+LTRA compared with ICS+LABA group ($60,103 vs. $85,459 respectively), however, asthma related costs were higher for patients treated with ICS+LTRA compared with ICS+LABA group ($4,521 vs $3,324). Similarly, ICS+LTRA treatment was associated with lower all-cause medical costs but with higher asthma related medical costs compared with ICS+LABA group. On the other hand, both all-cause and asthma related pharmacy costs were higher for patients treated with ICS+LTRA. All comparisons were statistically significant ($p<0.05$). Unadjusted total drug costs and number of prescriptions per person year are depicted in **Figure 5-1** and **Figure 5-2**, respectively. LTRA treatment was contributed to the highest cost per person year as well as for the highest number of prescriptions per person year.

Table 5-1 Primary analysis: all-cause and asthma related expenditures by asthma treatment group (Unadjusted costs ($) / person year)

	Total sample Cost (95% CI)	**LABA add-on Cost (95% CI)**	**LTRA add-on Cost (95% CI)**	**p value**	**Favor**
Total all-cause costs Pharmacy and medical	82420 (76707 - 88134)	85459 (79058 – 91861)	60103 (52269 – 67937)	0.0352	LTRA
All-cause medical costs	76523 (70831 - 82214)	79692 (73315 – 86070)	53244 (45446 – 61042)	<0.001	LTRA
All-cause pharmacy costs	5898 (5755 – 6040)	5767 (5613 – 5921)	6859 (6488 – 7230)	<0.001	LABA
Total asthma related costs Pharmacy and medical	3467 (3282 – 3653)	3324 (3120 – 3528)	4521 (4131 – 4912)	<0.001	LABA
Medical (asthma inpatients/ED)	1753 (1581 – 1925)	1706 (1517 – 1896)	2097 (1753 – 2442)	<0.001	LABA
Asthma related pharmacy costs	1714 (1645 - 1783)	1618 (1544 – 1691)	2424 (2236 – 2612)	<0.001	LABA

ED: emergency department; LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist.

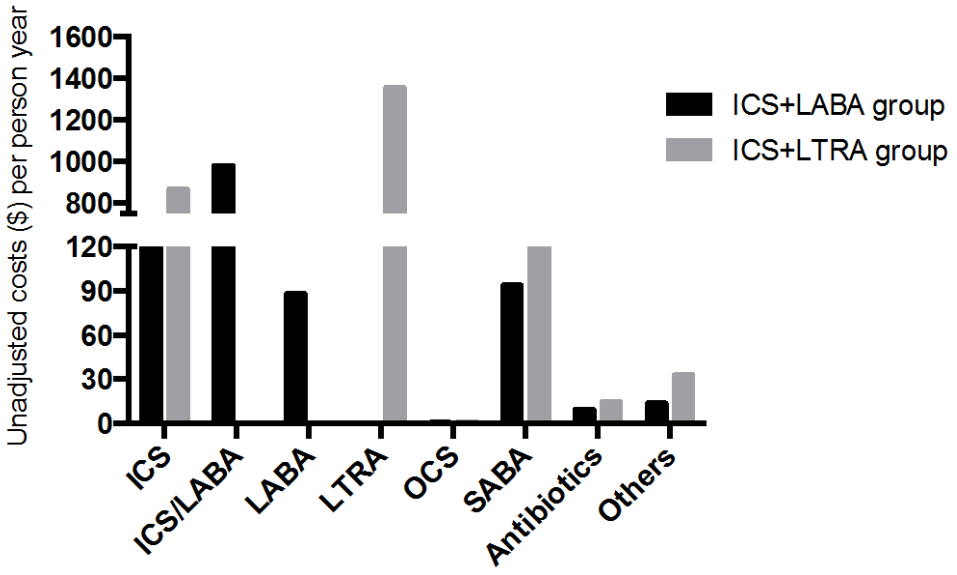

Figure 5-1 Unadjusted asthma drug expenditures per person years

ICS: inhaled corticosteroids; LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist; SABA: short acting beta agonists; OCS: oral corticosteroids; ICS+LABA: the inhaled corticosteroids/long acting beta agonists combination products (single inhaler)

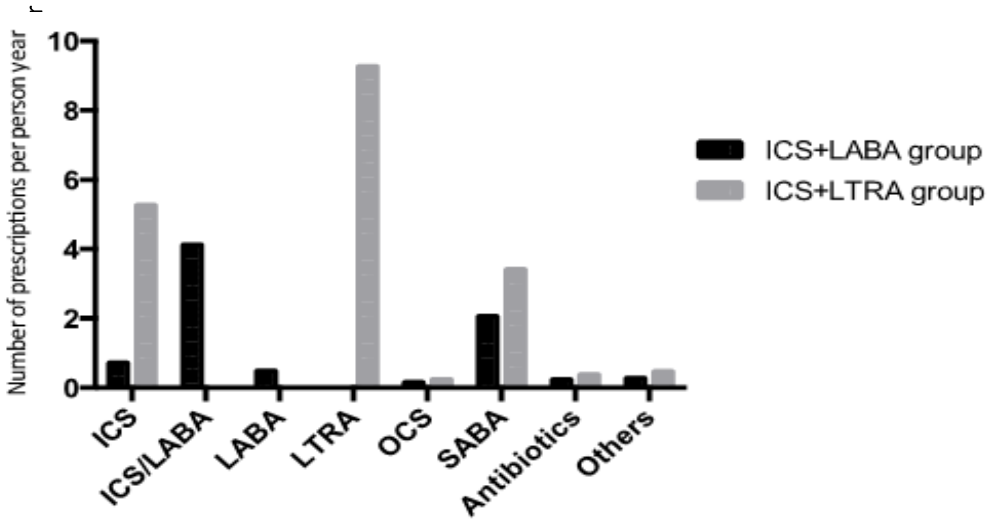

Figure 5-2 Total number of prescriptions filled per person years

ICS: inhaled corticosteroids; LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist; SABA: short acting beta agonists; OCS: oral corticosteroids; ICS+LABA: the inhaled corticosteroids/long acting beta agonists combination products (single inhaler)

Adjusted regression models:

All-cause costs

All-cause total and medical costs were not significantly different between the two treatment groups. Total all-cause costs were $74,369 for ICS+LABA and $68,944 for ICS+LTRA group. The corresponding values for total medical costs were $68,871for ICS+LBA compared with $61,724 for ICS+LTRA. All cause pharmacy costs were significantly higher for patients treated with ICS+LTRA ($7,219) compared with ICS+LABA group ($5,497) ($p<0.001$). All predicted costs were calculated over a mean of 1.06 person years follow up (**Table 5-2**).

Asthma-related costs

Compared with ICS+LTRA, treatment with ICS+LABA was associated with significantly lower asthma-related total, medical and pharmacy costs. Compared to ICS+LTRA, ICS+LABA treatment was associated with total asthma-related cost savings (medical + pharmacy) of $1,785, asthma related medical saving of $650 and asthma-related pharmacy cost savings of $1134 ($p<0.01$for all comparisons). All predicted costs were calculated over a mean of 1.06 person years follow up (**Table 5-2**).

Table 5-2 Primary analysis: all-cause and asthma related expenditures by asthma treatment groups (adjusted costs ($))

	LABA add-on Cost (95% CI)	**LTRA add-on Cost (95% CI)**	**Saving**	**p value**	**Favor**
Total all-cause costs Pharmacy and medical	74369 (70574 - 78164)	68944 (60944 - 76943)		0.219	Neither
All-cause medical costs	68871 (65118 - 72624)	61724 (53962 - 69487)		0.1	Neither
All-cause pharmacy costs	5497 (5393 - 5602)	7219 (6928 - 7510)	1722	<0.001	LABA
Total asthma related costs Pharmacy and medical	2939 (2832 - 3045)	4724 (4342 - 5105)	1785	<0.001	LABA
Medical (asthma inpatients/ED)	1590 (1491 - 1688)	2240 (1827 - 2654)	650	0.003	LABA
Asthma related pharmacy costs	1349 (1325 - 1373)	2483 (2402 - 2564)	1134	<0.001	LABA

All predicted costs were calculated over a mean of 1.06 person years follow up.

ED: emergency department; LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist.

Sensitivity analysis; Discontinuation design

Results were robust after applying the discontinuation design. Following patients for periods of continuous medication supply showed similar findings as in the primary analyses design. Compared to ICS+LTRA, ICS+ LABA was associated with similar all-cause total and medical costs but with significantly lower all-cause pharmacy costs. Also, ICS+LABA treatment was associated with significantly lower asthma total and pharmacy costs, however, asthma related medical costs (inpatient/ED visits) were not different between the two groups. All predicted costs were calculated using a mean of 0.33 person years follow up (**Table 5-3**).

Table 5-3 Discontinuation design: all-cause and asthma related expenditures by asthma treatment group (adjusted costs ($))

	LABA add-on Cost (95% CI)	**LTRA add-on Cost (95% CI)**	**Saving**	**p value**	**Favor**
Total all-cause costs Pharmacy and medical	24880 (23052 - 26709)	22017 (18145 - 25888)		0.195	Neither
All-cause medical costs	22585 (20620 - 24550)	19114 (15503 - 22725)		0.087	Neither
All-cause pharmacy costs	2295 (2237 - 2354)	2902 (2711 - 3094)	607	<0.001	LABA
Total asthma related costs Pharmacy and medical	1220 (1171 - 1269)	1657 (1496 - 1817)	437	<0.001	LABA
Medical (asthma inpatients/ED)	483 (439 - 528)	587 (428 - 746)		0.217	Neither
Asthma related pharmacy costs	737 (727 - 747)	1070 (1027 - 1112)	333	<0.001	LABA

All predicted costs were calculated using a mean of 0.33 person years follow up.

ED: emergency department; LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist.

5.5 DISCUSSION

Consistent with the findings from Chapter 4 (study #1), which showed that ICS+LABA treatment is associated with lower risks of asthma exacerbations, this economic evaluation showed that patients treated with ICS+LABA incurred significantly lower asthma related cost compared with ICS+LTRA. However, the total all-cause costs were similar between the two treatment groups.

Evaluations of younger populations consistently demonstrate that patients receiving ICS+ LTRA incur higher asthma related costs compared with patients receiving ICS+LABA [61-63]. Tan et al showed, in a retrospective observational study, that the total asthma related annual costs in the ICS+LTRA group was 38% higher than those in the ICS+LABA group ($p<0.001$) [63]. Similarly, Lee et al reported higher adjusted mean total asthma-related costs in patients treated with ICS+LTRA compared to ICS+LABA patients ($1223 vs. $873 per year) [61]. In agreement with these findings, this study showed that ICS+LTRA cohorts incurred higher asthma related medical and prescription expenditures in older adult population. Pharmacy costs were a major driver of asthma expenditures and were significantly higher in patients treated with ICS+LTRA ($2483) compared to ICS+LABA ($1349). Among the various asthma drugs, LTRA (mainly montelukast) treatment was the most expensive drug per person year mainly due to the highest number of prescriptions (9 per person year). These results agreed with previous evidence from younger ages in which asthma drugs cost higher in patients treated with ICS+LTRA than in patients treated with ICS+LABA ($987 vs $606, respectively) [62]. Even though the conclusion was similar to those reported from younger ages, asthma costs estimates in older adults were

much higher compared to those estimated in younger adults [61-63]. Although the outpatient care costs were not included in asthma related outcomes, this study showed that total asthma cost is at least 3-fold and 2-fold higher than previous estimates [61, 63]. Such large inflation in asthma costs clearly support the previous evidence that older asthmatic adults experiencing larger economic burden compared with younger ages and accordingly need further attention.

Very few studies have evaluated all-cause costs in asthmatic adults. Stempel and coworkers found that non-elderly patients treated with ICS+LABA incurred significantly lower total all-cause cost compared with ICS+LTRA ($3466 ICS+LABA versus $4346 ICS+LTRA per year). In comparison, our investigation showed that total all-cause costs were not different between the two treatment groups ($74,369 in ICS+LABA group and $68,944 in ICS+LTRA group). This suggests that the higher asthma costs associated with ICS+LTRA were compensated by lower incurring from other conditions in older adults (adjusted for all preexisting comorbid condition and other covariates). This may be explained, at least in part, by the suggested negative impact of ICS+LABA on the CV conditions in older adults, as revealed in chapter 4 in which results showed that older asthmatic patients treated with ICS+LABA were more likely to have CV hospitalization or ED visits compared to patients treated with ICS+LTRA.

Unsurprisingly, total all-cause estimates were much higher than their corresponding values estimated from younger ages [62, 98]. Such high numbers are likely due to the high prevalence of multi-morbidity among older adults noted in this study. The average number of comorbid conditions across the whole sample was nine chronic diseases per patient. An investigation of the Centers for Medicare & Medicaid Services that analyzed differences in Medicare Fee-for-Service utilization (Medicare perspective) by beneficiary characteristics including chronic conditions found an influential effect of chronic conditions on Medicare

payments [132]. The average annual payments for beneficiaries with nine comorbid conditions were $57,806 for Part A and $22,404 for Part B in 2010 compared with $10,989 and $9,189, respectively, for beneficiaries with four comorbid conditions.

Finally, this study showed that all-cause prescription drug costs were significantly higher in patients treated with ICS+LTRA compared to ICS+LABA. This in part was driven by asthma treatments that used approximately 25% of all-cause drug costs in ICS+LABA group and around 34% of all-cause drug costs in ICS+LTRA group.

Overall, all-cause and asthma related per-patient direct costs for asthmatic FFS Medicare beneficiaries were substantial. ICS+LTRA treatment was associated with higher asthma related costs (mainly driven by asthma drugs costs) compared to ICS+LABA, however, the total all-cause costs were not different between the two groups. Higher expenditures on non-asthma health conditions were able to offset saving on asthma condition in older adults treated with ICS+LABA.

6.0 CONCLUSIONS AND FUTURE DIRECTIONS

6.1 OVERVIEW

The objective of this dissertation research was to examine the comparative effectiveness, CV safety and costs associated with ICS+LTRA versus ICS+LABA in older adults. The efforts in this dissertation were directed to evaluate the relative benefits and risks associated with each add-on treatment. Asthma and CV outcomes were the major outcomes investigated in this research to reveal the relative effectiveness in controlling asthma as well as the relative CV safety associated with both treatments in older adults.

The results of this research were presented in two studies in Chapters 4 and 5. The first study examined the relative effectiveness, CV safety, changing treatment and all-cause mortality between ICS+LABA and ICS+LTRA. The second study examined all-cause and asthma related expenditures associated with the two treatments.

This final chapter summarizes the findings of this research, implications to policy-makers, study strengths and limitations, and directions for future research.

6.2 SUMMARY OF FINDINGS

In this sample of older Medicare beneficiaries with asthma, results from this dissertation showed that ICS+LABA was associated with lower risk of asthma exacerbations but with higher risk of CV events compared to ICS+LTRA. This picture was reinforced in the economic evaluation conducted in which results showed that the ICS+LABA treated patients incur less asthma related expenditures but similar all-cause total expenditures.

Our findings support the CV concerns that have been associated with LABA in previous literature and highlight the verdict that LABA-add on treatment may not be safe in older adults due to their susceptibility to CV adverse events. These extra CV risks were shown to be more prominent when patients adhere to their prescription fills. This may be explained in part by the suggested CV protective effect that had been attributed to LTRA in previous literature. However, this research was not designed to test such protective effect; rather, it was designed to test the relative CV safety between the two add-on treatments. An alternative explanation may be that the higher exposure to LABA, the worse the CV outcomes. Further research with longer follow up periods in which patients adhere to their medication or fills is warranted to confirm or assess such effects. While differences in CV safety profiles were more prominent in patients who adhered to their prescriptions, the relative differences between the two treatments for asthma related exacerbations were attenuated but still significant. This may be partially explained by the better asthma outcomes in ICS+LTRA treated patients during the periods in which they were consistently filling their ICS and LTRA prescriptions compared to periods of less adherence. Indeed, ICS+LTRA treated patients were filling their LTRA prescriptions more consistently than their ICS prescriptions. This is consistent with previous research suggested that older adults are more compliant with oral medication rather than with inhaled medications [133].

Treatment effects on asthma exacerbations were largely modified by the presence of preexisting comorbid conditions. LTRA add-on was associated with higher odds of asthma exacerbation in the presence of CVDs than in their absence, suggesting that the CVDs contribute partially to the worse asthma outcomes associated with LTRA. Similarly, asthma exacerbations were more equivalent between the two treatments in the absence of COPD. However, odds of CV exacerbations were higher with LABA add-on versus LTRA add-on regardless of CVD or COPD comorbid conditions in the primary analysis.

All-cause and asthma related per-patient direct costs for asthmatic FFS Medicare beneficiaries were substantial. ICS+LTRA treatment was associated with higher asthma related costs (mainly driven by asthma drugs costs) compared to ICS+LABA, however, the total all-cause costs were not different between the two groups. Higher expenditures on non-asthma health conditions were able to offset saving on asthma condition in older adults treated with ICS+LABA.

6.3 IMPLICATIONS

Through our investigation of health outcomes associated with these treatments, we have enhanced our knowledge regarding the benefits and risk of asthma treatments in older adults. We provided information to clinical decision makers that should help in choosing the treatment strategy that can maximize benefits at minimal risks. The results of the current research underscore the CV concerns associated with LABA treatment particularly in older adults. CV concerns associated with LABA should be carefully considered, especially in the older adult population. In-hospital mortality rates associated with CV hospitalizations are much higher than with asthma hospitalizations in older adults (**Figure 6-1**) [115].

The economic evaluation conducted in this dissertation can also enhance clinical decision-making in older adults. Efficient and evidence-based resource allocation in health practices is an urgent need in this era of inflated health care prices. Overall, this work along with those of future studies expanding upon our findings may lead to more personalized treatment and improve health outcomes in older adults with asthma by maximizing the benefits and minimizing the risks from asthma treatments.

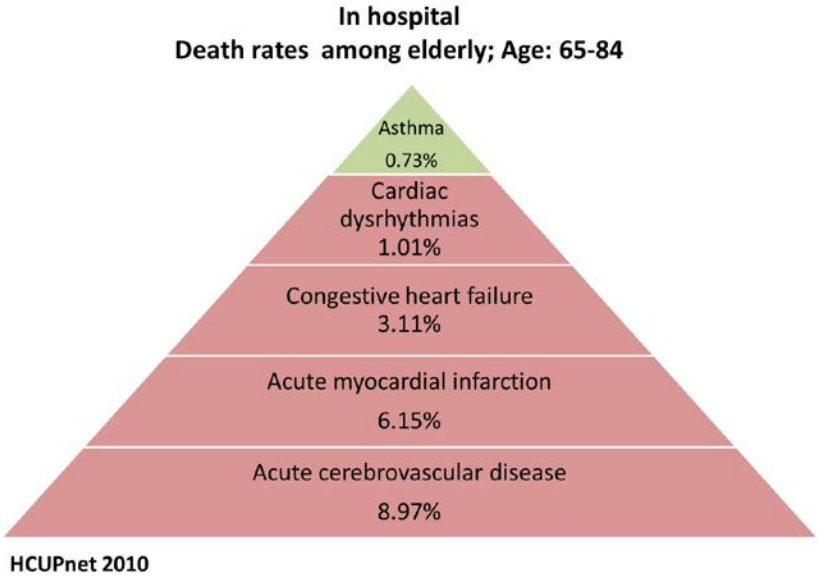

Figure 6-1 In-hospital mortality rates associated with asthma and CV hospitalizations in older adults (65 to 84 old). Adapted from [115].

Recommendations

- Our results support the reported concerns about the safety of LABA+ICS treatment in older adults with asthma. Accordingly, it should be prescribed with caution and only when benefits in controlling asthma outweigh the CV risks.
- Improving adherence to both ICS and LTRA can maximize the benefit from LTRA add-on treatment; however, it is still less effective than ICS+LABA. Better CV safety profile with acceptable, not necessarily better, effectiveness in controlling asthma might be a wise decision in some situations.
- According to our findings, benefit/risk ratio favors LTRA add-on treatment in the absence of COPD. This is mainly because of the equivalent effectiveness in preventing major asthma exacerbations between the two add-on treatments and the better CV safety associated with ICS+LABA in these patients. However, this conclusion needs to be confirmed in larger sample of COPD free patients.
- Similarly, our results indicate that the benefit/risk ratio favors LTRA add-on in the absence of major CVDs since both treatments were equivalent in preventing major asthma exacerbations, and ICS+LTRA were associated with better CV safety profiles in these patients. As the case with COPD comorbidity, this conclusion needs to be assessed in future research with larger sample of CVD free patients.
- Finally, disease specific exacerbation mortality, patients reported outcomes and subgroup analyses should be considered in patients with ambiguous benefit/risk ratio like those in whom ICS+LABA is clearly associated with better asthma outcomes but with worse CV outcomes.

6.4 STUDY STRENGTHS AND LIMITATIONS

This research has several limitations. We were limited by only having claims to measure health and economic outcomes and medication exposures. Inherently this conveys several drawbacks including: 1) lack of clinical effectiveness measures, such as respiratory function tests and patients perceived or reported outcome measures, however, exacerbations resulting in hospitalizations or ED visits have the greatest impact on quality of life and impose severe emotional and financial stress [134], 2) determining exposures based on prescription drug claims cannot guarantee actual usage of the medication, 3) inability to adjust for some important factors that might confound the results such as smoking history, obesity and education levels, and 4) inability to measure some kinds of costs such as over the counter treatments, indirect and intangible costs. Smoking history would only bias the results if there were differences in smoking rates between the two treatment groups. Even though this might be possible, we accounted for some co-morbidities that are often associated with smoking history such as COPD and CVDs. Our primary design in this research includes both incident and prevalent users regardless of the initiation time. The main concern in mixing incident and prevalent users is obscuring excess harm and those events may occur earlier in the course of therapy; only the less susceptible patients remain on each treatment [117]. Similarly, the economic burden at the beginning of the treatment may be different years after the initiation. However, using prevalent user design increases the sample size, enhances generalizability, increases the precision in estimates and enables studying long-term effects associated with cumulative years of exposure. Even though we applied incident users design to test the robustness of the result and to evaluate early outcomes, we were severely limited in sample size.

In the discontinuation design we applied in this research, the average follow up period was around 0.33 years. This may be not enough to measure the actual benefits and risks associated with the two treatments. Further, the discontinuation design was based on information captured from the 'days supply' field, which may be inaccurate for inhaled treatments.

Costs were measured from Medicare perspective and patient out-of-pocket and third party expenditures were not included. Hence, this study might underestimate the societal cost of asthma. However, Medicare expenditures contribute to more than 20% of all US healthcare expenditures [135]. In asthma related expenses, only inpatient, ED visits and drugs were included, however, outside of medication expenditures, exacerbations resulting in hospitalizations or ED visits were shown to have the greatest economic impact among all sources of direct costs [61, 63, 134].

Finally, the potential confounding by asthma severity is an important limitation in this study. In an attempt to partially amend this problem, we adjusted to ICS strength as a proxy for asthma severity. Higher ICS strengths are recommended for patients with greater severity. In this study, we were not able to measure the actual doses were taken by patients. However, ICS strength may serve as proxy for doses.

There also are key strengths of this research. First, this research addressed questions that were never answered in older adult populations as older adults with chronic diseases are systematically excluded from clinical trials. We believe that the paucity of knowledge regarding asthma treatments in older adults is a contributing factor to the poor health outcomes in this population. Second, the use of fee for service (FFS) Medicare beneficiaries claims data makes our results generalizable and representative for the older adult population. FFS enrollees accounted for approximately 66% of the total Medicare population in 2010 [136]. Third, in the

effectiveness and safety study (Chapter 4), we used the augmented inverse propensity weighting estimator to model both the outcome and the treatment probability. This method is considered "doubly robust" since only one of the two models must be correctly specified to consistently estimate the treatment effects [110]. Finally, this is a large observational cohort study of older asthmatic adults in which we accounted for many predisposing, medical need and enabling factors that may affect both treatment and health care utilization.

6.5 FUTURE DIRECTIONS

Further subgroup analysis with adequate sample size is needed to find out which patients may be at highest risk for CV adverse events when treated with LABA add-on treatment. Similarly, subgroup analysis is needed to identify which patients may benefit most from LTRA add-on treatment.

Results from this research indicate that ICS+LTRA may be more effective in controlling asthma in the absence of COPD comorbidity. Future studies should include adequate numbers of asthmatic older adults without COPD to address this point.

Future research with adequate sample of incident users would provide valuable information regarding early treatment effects associated with these add-on treatments and will increase the internal validity of the results.

Finally, further research expanding on our discontinuation design with longer follow up periods is warranted. This is of importance to measure treatment effect in patients compliant with filling their prescriptions. In particular, this is crucial to understand weather the inferior effectiveness of ICS+LTRA combination in the primary analysis was due to real inferior effectiveness of the combination or due to lower compliance with the ICS part of the combination.

APPENDIX A

Table 1: Likelihood-ratio test for adding the interaction between treatment group and the presence of preexisting CVD. CVD: ischemic heart disease, congestive heart failure, myocardial infarction, atrial fibrillation or stroke/transient ischemic attack.

Outcome	p value
Effectiveness outcomes	
Asthma Hospitalizations or ED visits	0.009
Asthma related oral corticosteroid or antibiotic prescriptions	0.54
Any asthma exacerbation	0.02
SABA use	0.312
Cardiovascular safety	
CV hospitalization/ED	0.961
Other outcomes	
Change treatment	0.68
All-cause death	0.567

ED: emergency department; CV: cardiovascular;
SABA: short acting beta agonists.

Treatment effects on asthma hospitalizations/ED visits and any asthma exacerbation were different by the presence of major CVDs.

Table 2: Likelihood-ratio test for adding the interaction between treatment group and the presence of preexisting CVD. CVDs were categorized into three levels: having no preexisting CVD; having preexisting ischemic heart disease, acute myocardial infarction, or stroke/transient ischemic attack (ischemic diseases); and having congestive heart failure or atrial fibrillation (CHF/AF diseases).

Outcome	p value
Effectiveness outcomes	
Asthma Hospitalizations or ED visits	0.028
Asthma related oral corticosteroid or antibiotic prescriptions	0.824
Any asthma exacerbation	0.064
SABA use	0.458
Cardiovascular safety	
CV hospitalization/ED	0.465
Other outcomes	
Change treatment	0.11
All-cause death	0.681

ED: emergency department; CV: cardiovascular;
SABA: short acting beta agonists.

Treatment effects on asthma hospitalizations/ED visits and any asthma exacerbation were different by the presence of major CVDs (categorized to ischemic diseases and CHF/AF diseases)

Table 3: Likelihood-ratio test for adding the interaction between treatment group and the presence of preexisting COPD.

Outcome	p value
Effectiveness outcomes	
Asthma Hospitalizations or ED visits	0.0152
Asthma related oral corticosteroid or antibiotic prescriptions	0.0202
Any asthma exacerbation	0.0142
SABA use	<0.001
Cardiovascular safety	
CV hospitalization/ED	0.5124
Other outcomes	
Change treatment	0.053
All-cause death	0.4301

ED: emergency department; CV: cardiovascular;
SABA: short acting beta agonists.

Treatment effects were different by the presence of major COPD for asthma hospitalizations/ED visits, asthma related oral corticosteroids or antibiotics, SABA use, any asthma exacerbation and treatment change.

Secondary analysis: The effect of LABA Add-on strength (as a proxy for dose).

Table 4: Effect of different LABA add-on strengths versus LTRA add-on.

	Low LABA strengths versus LTRA			**Medium- high LABA strengths versus LTRA**		
	OR	p value	Favor	OR	p value	Favor
Effectiveness outcomes						
Asthma Hospitalizations or ED visits	0.75	<0.000	LABA	0.72	<0.000	LABA
Asthma related oral corticosteroid or antibiotic prescriptions	0.77	0.001	LABA	0.67	<0.000	LABA
Any asthma exacerbation	0.72	<0.000	LABA	0.631	<0.000	LABA
SABA use (RR)	0.7	<0.000	LABA	0.66	<0.000	LABA
Cardiovascular safety						
CV hospitalization/ED	1.07	0.304	Neither	1.13	0.044	LTRA
Other outcomes						
Change treatment	0.76	0.016	LABA	0.95	0.58	Neither
All-cause death	1.06	0.645	Neither	1.21	0.089	Neither

Multivariable logistic regression/ Poisson regression were used and were adjusted for all covariates mentioned in chapter 4.
Abbreviations: ED: emergency department; SABA: short acting beta agonists; CV: cardiovascular, LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist; ICS: inhaled corticosteroids; OR: odds ratio; RR: rate ratio.

Among the total of 12,940 patients who were receiving the LABA add-on treatment, 3,029 were receiving low strengths and 9,911 were receiving medium to high strengths at the time of starting the follow up. All LABA add-on strengths were associated with lower odds of asthma exacerbations and lower SABA use compared to LTRA add-on. Only medium to high strengths LABA add-on were associated with statistically significant higher likelihood of CV events compared with LTRA add-on (however, both strength were associated with statistically significant higher likelihood of CV events in the discontinuation design Appendix B: Table 6) . Further, lower strengths LABA-add-on were associated with lower odds of changing the treatment compared with LTRA add-on whereas medium to high strengths LABA did not show this effect (**Table 4**).

Table 5: incident user design: study population characteristics by total and add-on medication group

	Total sample n= 1338 (%)		LABA add-on n= 1154 (%)		LTRA add-on n= 184 (%)		p value[1]
Age							
65-70	270	(20.2)	230	(19.9)	40	(21.7)	0.669
70-75	347	(25.9)	295	(25.6)	52	(28.3)	
75-80	316	(23.6)	278	(24.1)	38	(20.7)	
80+	405	(30.3)	351	(30.4)	54	(29.4)	
Female gender	985	(73.6)	842	(73.0)	143	(77.7)	0.174
Race							
Non-Hispanic white	1,044	(78.2)	896	(77.8)	148	(80.9)	0.436
Black	131	(9.8)	119	(10.3)	12	(6.6)	
Hispanic	91	(6.8)	77	(6.7)	14	(7.7)	
Others	69	(5.2)	60	(5.2)	9	(4.9)	
Geographic region							
Northeast	315	(23.5)	267	(23.1)	48	(26.1)	0.037
Midwest	353	(26.4)	317	(27.5)	36	(19.6)	
South	395	(29.5)	328	(28.4)	67	(36.4)	
West	275	(20.6)	242	(21.0)	33	(17.9)	
Asthma duration							
<6 months	71	(5.3)	67	(5.8)	4	(2.2)	0.194
6-12 months	91	(6.8)	78	(6.8)	13	(7.1)	
1-2 years	147	(11.0)	129	(11.2)	18	(9.8)	
>2 years	1,029	(76.9)	880	(76.3)	149	(81.0)	
Disability	221	(16.5)	203	(17.6)	18	(9.8)	0.008
Major prescriber specialty asthma drugs							
Asthma	298	(22.3)	254	(22.0)	44	(23.9)	0.922
General	844	(63.1)	729	(63.2)	115	(62.5)	
Non-physician	82	(6.1)	71	(6.2)	11	(6.0)	
Others	114	(8.5)	100	(8.7)	14	(7.6)	
Rural Urban							
Metro	1,059	(79.8)	903	(78.9)	156	(85.7)	0.089
Urban	226	(17.0)	203	(17.7)	23	(12.6)	
Rural	42	(3.2)	39	(3.4)	3	(1.7)	
Low income enrollment	629	(47.0)	559	(48.4)	70	(38.0)	0.009
Using beta blockers	524	(39.2)	455	(39.4)	69	(37.5)	0.619
Medium to high ICS strength in the pre-index period	807	(60.3)	700	(60.7)	107	(58.2)	0.519
Outpatient physician visits in the pre-index period. means (SE)	4.0	(0.09)	3.9	(0.1)	4.3	(0.3)	0.101
Number of unique asthma prescribers mean (SE)	1.8	(0.02)	1.8	(0.03)	1.7	(0.06)	0.315
Study population Comorbidities							
Alzheimer	239	(17.9)	210	(18.2)	29	(15.8)	0.423

Acute myocardial infarction	95 (7.1)	89 (7.7)	6 (3.3)	0.029
Anemia	888 (66.4)	774 (67.1)	114 (62.0)	0.173
Atrial fibrillation	288 (21.5)	255 (22.1)	33 (17.9)	0.202
Cancers (other than lung cancer)	175 (13.1)	152 (13.2)	23 (12.5)	0.802
Cataract	1,034 (77.3)	891 (77.2)	143 (77.7)	0.879
Chronic kidney disease (CKD)				
No CKD	950 (71.0)	807 (69.9)	143 (77.7)	0.063
CKD, no ESRD	379 (28.3)	338 (29.3)	41 (22.3)	
ESRD	9 (0.7)	9 (0.8)	0 (0)	
Chronic obstructive pulmonary disease	1,058 (79.1)	928 (80.4)	130 (70.7)	0.002
Congestive heart failure	692 (51.7)	608 (52.7)	84 (45.7)	0.076
Depression	579 (43.3)	497 (43.1)	82 (44.6)	0.703
Diabetes	582 (43.5)	516 (44.7)	66 (35.9)	0.025
Glaucoma	375 (28.0)	321 (27.8)	54 (29.4)	0.668
Hip fracture	69 (5.2)	63 (5.5)	6 (3.3)	0.21
Hyperlipidemia	1,088 (81.3)	939 (81.4)	149 (81.0)	0.899
Benign Prostatic Hyperplasia	198 (14.8)	171 (14.8)	27 (14.7)	0.959
Hypertension	1,211 (90.5)	1,055 (91.4)	156 (84.8)	0.004
Hypothyroidism	350 (26.2)	294 (25.5)	56 (30.4)	0.155
Ischemic heart	903 (67.5)	786 (68.1)	117 (63.6)	0.224
Lung cancer	61 (4.6)	53 (4.6)	8 (4.4)	0.882
Osteoporosis	460 (34.4)	396 (34.3)	64 (34.8)	0.901
Rheumatoid arthritis, Osteoarthritis	938 (70.1)	806 (69.8)	132 (71.7)	0.602
Stroke, transient ischemic attack	262 (19.6)	237 (20.5)	25 (13.6)	0.027
Counties level health care access variables calculated as mean per 10,000 older adults (SE)				
Primary care physicians	57.0 (0.76)	56.6 (0.83)	59.5 (1.91)	0.184
Medical specialty physicians	78.2 (2.12)	77.2 (2.32)	84.9 (4.91)	0.208
Allergy immunology specialty	1.1 (0.04)	1.1 (0.04)	1.2 (0.08)	0.438
Cardiovascular specialty	5.9 (0.17)	5.8 (0.19)	6.5 (0.39)	0.136
Pulmonary specialty	2.8 (0.08)	2.7 (0.09)	3.0 (0.18)	0.328
Emergency medicine specialty	8.3 (0.21)	8.2 (0.24)	8.9 (0.45)	0.24
Preventive medicine specialty	0.47 (0.02)	0.46 (0.02)	0.50 (0.06)	0.589
Hospitals number	1.6 (0.05)	1.6 (0.05)	1.3 (0.07)	0.026
Hospitals with emergency department	0.92 (0.03)	0.94 (0.03)	0.79 (0.06)	0.08
Average household size	2.6 (0.01)	2.6 (0.01)	2.6 (0.02)	0.451
Percent below poverty	11.2 (0.13)	11.1 (0.14)	11.2 (0.38)	0.858

1 Variables were compared between the two treatment groups using bivariate analysis (un-adjusted).
ESRD: End stage renal disease; LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist; ICS: inhaled corticosteroids; SE: standard error.

Table 6: Evaluating covariate balance between the two treatment groups after propensity score weighting

	After weighting		
	LABA add-on (%)	**LTRA add-on (%)**	**p value ***
Age			0.42
65-70	19.6	16.5	
70-75	26.9	31.5	
75-80	23.7	21.1	
80+	29.8	30.8	
Female gender	72.2	68.9	0.5
Race			0.36
Non-Hispanic white	77.7	74.7	
Black	8.8	8	
Hispanic	8.4	12.4	
Others	5	4.9	
Geographic region			0.092
Northeast	21.7	27.4	
Midwest	22.6	18.9	
South	36.2	28.9	
West	19.6	24.9	
Asthma duration			0.37
<6 months	5.3	4.2	
6-12 months	6.4	5.1	
1-2 years	11.5	13.5	
>2 years	76.8	77.2	
Disability	17	20.3	0.51
Major prescriber specialty asthma drugs			0.46
Asthma	19.8	18.6	
General	63.6	67.2	
Non-physician	6.9	5.9	
Others	9.7	8.4	
Rural Urban			0.23
Metro	78.6	81.8	
Urban	18.6	16.2	
Rural	2.8	2	
Low income enrollment	45.7	49.2	0.43
Using beta blockers	39.9	36.5	0.36

Medium to high ICS strength at index prescription	76.4	74.5	0.63
Outpatients physician visits in the 4 months wash in period Means (SE)	4.68 (0.03)	4.74 (0.28)	0.85
Number of unique asthma prescribers Mean (SE)	1.47 (0.01)	1.48 (0.05)	0.82
Study population Comorbidities			
Alzheimer	17.9	16.8	0.58
Acute myocardial infarction	7.3	7.7	0.81
Anemia	67.9	72.8	0.07
Atrial fibrillation	20.4	22.8	0.63
Cancers (other than lung cancer)	15.4	12.3	0.06
Cataract	77.8	79.6	0.49
Chronic kidney disease (CKD)			0.34
No CKD	71.2	67.4	
CKD, no ESRD	28	32.1	
ESRD	0.9	0.5	
Chronic obstructive pulmonary disease	77.7	80.4	0.19
Congestive heart failure	51.4	53.7	0.59
Depression	43	45.2	0.61
Diabetes	45.4	51.1	0.19
Glaucoma	26.6	25.9	0.81
Hip fracture	5	8	0.12
Hyperlipidemia	83.4	83.7	0.92
Benign Prostatic Hyperplasia	15.7	21.1	0.28
Hypertension	91	92.8	0.06
Hypothyroidism	27.1	29.6	0.53
Ischemic heart	68.5	71.7	0.26

Lung cancer	3.5	2.7	0.25
Osteoporosis	34	36.5	0.56
Rheumatoid arthritis, Osteoarthritis	70	67	0.53
Stroke, transient ischemic attack	20.4	19.4	0.69
Counties level health care access variables calculated as mean per 10,000 older adults (SE)			
Primary care physicians	55.7 (0.2)	59.1(2.5)	0.19
Medical specialty physicians	72.3 (0.59)	80.2 (7.3)	0.28
Allergy immunology specialty	1.0 (0.01)	1.1 (0.1)	0.36
Cardiovascular specialty	5.5 (0. 05)	6.1 (0.6)	0.29
Pulmonary specialty	2.6 (0.02)	2.8 (0.2)	0.4
Emergency medicine specialty	7.8 (.06)	8.1 (0.3)	0.3
Preventive medicine specialty	0.43 (0.01)	0.5 (0.04)	0.4
Hospitals number	1.6 (0.01)	1.6 (0.05)	0.14
Hospitals with emergency department	1.0 (0.01)	0.9 (0.05)	0.21
Average household size	2.6 (0.002)	2.5 (0.01)	0.49
Percent below poverty	11.3 (0.04)	10.9 (0.3)	0.21

1 Variables were compared between the two treatment groups using bivariate analysis (un-adjusted).
ESRD: End stage renal disease; LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist;

ICS: inhaled corticosteroids; SE: standard error.

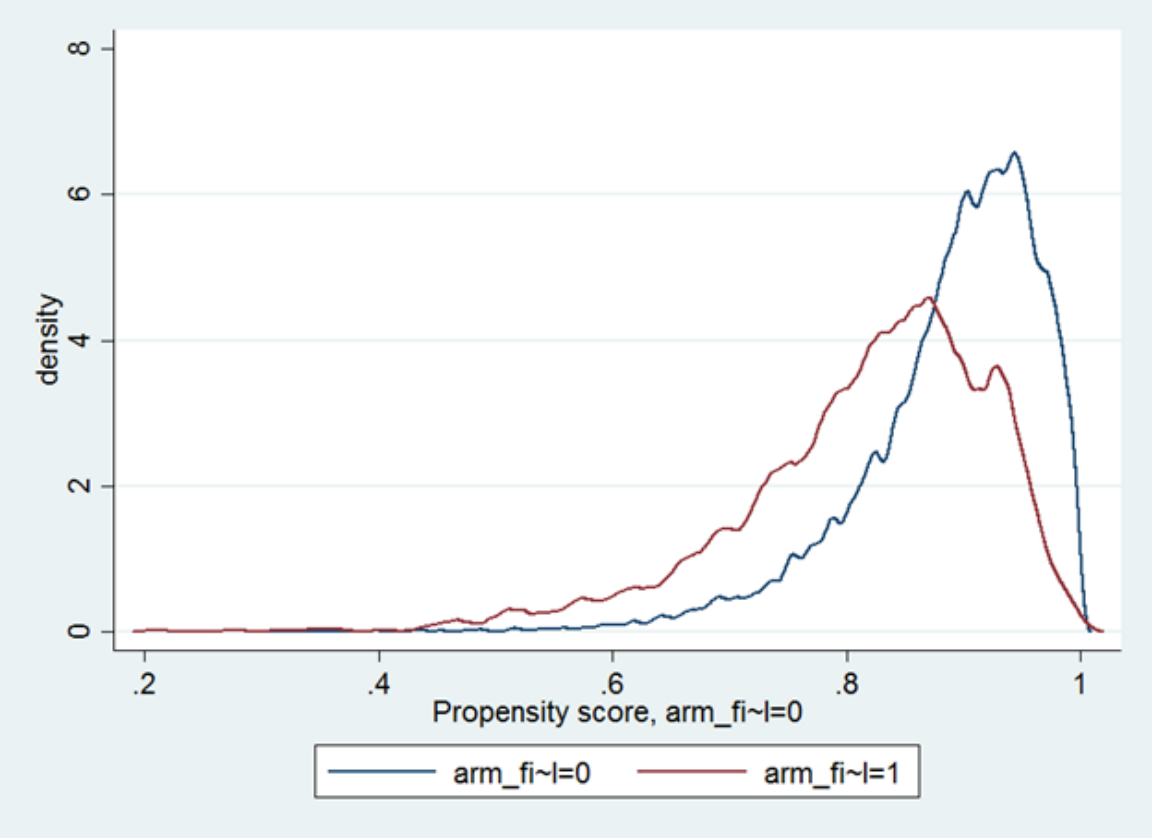

Figure 1 T**he overlap plot** displays the estimated densities associated with predicted probabilities that an ICS+LABA treated patient is an ICS+LABA treated and an ICS+LTRA treated patient is an ICS+LABA treated. In both plots, most of their respective masses are in regions in which they overlap each other. Accordingly, there is no evidence that the overlap assumption is violated.

APPENDIX B

Table 1: Discontinuation design: Likelihood-ratio test for adding the interaction between treatment group and the presence of preexisting CVD. CVD: ischemic heart disease, congestive heart failure, myocardial infarction, atrial fibrillation or stroke/transient ischemic attack.

Outcome	p value
Effectiveness outcomes	
Asthma Hospitalizations or ED visits	0.179
Asthma related oral corticosteroid or antibiotic prescriptions	0.253
Any asthma exacerbation	0.055
SABA use	0.050
Cardiovascular safety	
CV hospitalization/ED	0.33
Other outcomes	
Change treatment	0.794
All-cause death	0.551

ED: emergency department; CV: cardiovascular;
SABA: short acting beta agonists.

Treatment effects on any asthma exacerbation and SABA use were different (marginally significant) by the presence of major CVDs.

Table 2: Discontinuation design: Stratified analysis by the presence of major cardiovascular diseases (CVD). Results are shown for outcome models in which treatment effect is different by the presence of CVDs.

	With CVD (ischemic heart disease, congestive heart failure, myocardial infarction, atrial fibrillation or stroke/transient ischemic attack)					Without CVD				
Sample size	11,301 (ICS+LTRA: 1,077, ICS+LABA: 10,224)					3,065 (ICS+LTRA: 421, ICS+LABA: 2,644)				
	OR	**Adjusted probability LABA add-on**	**Adjusted probability LTRA add-on**	**p value**	**Favor**	**OR**	**Adjusted probability LABA add-on**	**Adjusted probability LTRA add-on**	**p value**	**Favor**
Any asthma exacerbation	1.4	0.13	0.17	0.001	LABA	1.1	0.13	0.14	0.594	Neither
SABA use (RR)	1.93	0.8	1.54	<0.001	LABA	1.81	0.7	1.25	0.008	LABA

ORs were calculated based on adjusted probabilities estimated by the augmented inverse propensity weighting estimator.
RRs were calculated based on adjusted rates estimated by the augmented inverse propensity weighting estimator.
Abbreviations: ED: emergency department; CVD: cardiovascular disease, LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist; ICS: inhaled corticosteroids; OR: odds ratio; RR: rate ratio.

The odds ratio of any asthma exacerbation (ICS+LTRA vs ICS+LABA) was not statistically significant in the absence of CVD. The RR of SABA use (ICS+LTRA vs ICS+LABA) was attenuated but still significant in the absence of CVD.

Table 3: Discontinuation design: Likelihood-ratio test for adding the interaction between treatment group and the presence of preexisting CVD. CVDs were categorized into three levels: having no preexisting CVD; having preexisting ischemic heart disease, acute myocardial infarction, or stroke/transient ischemic attack (Ischemic diseases group); and having congestive heart failure or atrial fibrillation (CHF/AF group).

Outcome	p value
Effectiveness outcomes	
Asthma Hospitalizations or ED visits	0.365
Asthma related oral corticosteroid or antibiotic prescriptions	0.358
Any asthma exacerbation	0.072
SABA use	0.093
Cardiovascular safety	
CV hospitalization/ED	0.59
Other outcomes	
Change treatment	0.92
All-cause death	0.79

ED: emergency department; CV: cardiovascular;
SABA: short acting beta agonists.

Treatment effects were not different by the presence of major CVDs (categorized into ischemic diseases and CHF/AF diseases) for all outcomes.

Table 4: Discontinuation design: Likelihood-ratio test for adding the interaction between treatment group and the presence of preexisting COPD.

Outcome	p value
Effectiveness outcomes	
Asthma Hospitalizations or ED visits	0.746
Asthma related oral corticosteroid or antibiotic prescriptions	0.003
Any asthma exacerbation	0.048
SABA use	<0.001
Cardiovascular safety	
CV hospitalization/ED	0.016
Other outcomes	
Change treatment	0.9
All-cause death	0.88

ED: emergency department; CV: cardiovascular;
SABA: short acting beta agonists.

Treatment effects were different by the presence of COPD for asthma related oral corticosteroids or antibiotics, SABA use, any asthma exacerbation and CV hospitalization/ED.

Table 5: Discontinuation design: Stratified analysis by the presence of COPD. Results are shown for outcome models in which treatment effect is different by the presence of COPD.

	With COPD					Without COPD				
Sample size	11,198 (ICS+LTRA: 1,041, ICS+LABA: 10,157)					3,168 (ICS+LTRA: 457, ICS+LABA: 2,711)				
	OR	**Adjusted probability LABA add-on**	**Adjusted probability LTRA add-on**	**p value**	**Favor**	**OR**	**Adjusted probability LABA add-on**	**Adjusted probability LTRA add-on**	**p value**	**Favor**
Asthma related oral corticosteroid or antibiotic prescriptions	1.56	0.05	0.07	<0.001	LABA	0.79	0.08	0.06	0.223	Neither
Any asthma exacerbation	1.43	0.12	0.15	<0.001	LABA	0.96	0.13	0.12	0.787	Neither
SABA use (RR)	1.65	0.68	1.13	<0.001	LABA	2	0.35	0.71	<0.001	LABA
CV hospitalization/ED	0.73	0.22	0.17	0.001	LTRA	1.2	0.08	0.09	0.321	Neither

Multivariable logistic regression was used due to propensity scores modelling issues (not concave)
Abbreviations: ED: emergency department, COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids; LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist; OR: odds ratio; RR: rate ratio.

ICS+LTRA associated asthma related oral corticosteroids or antibiotics prescriptions as well as any asthma exacerbations were not significantly different from those associated with ICS+LABA in the absence of COPD. Further, CV exacerbations were not significantly different between the two groups in the absence of COPD. SABA use was even higher in patients treated with ICS+LTRA compared to those treated with ICS+LABA in the absence of COPD.

Table 6: Discontinuation design: Effect of different LABA add-on strengths versus LTRA add-on.

	Low LABA strengths versus LTRA			Medium- High LABA strengths versus LTRA		
	OR	p value	Favor	OR	p value	Favor
Effectiveness outcomes						
Asthma Hospitalizations or ED visits	0.85	0.196	Neither	0.86	0.167	Neither
Asthma related oral corticosteroid or antibiotic prescriptions	0.82	0.105	Neither	0.77	0.014	LABA
Any asthma exacerbation	0.8	0.02	LABA	0.78	0.002	LABA
SABA use (RR)	0.58	<0.000	LABA	0.57	<0.000	LABA
Cardiovascular safety						
CV hospitalization/ED	1.24	0.024	LTRA	1.24	0.01	LTRA
Other outcomes						
Change treatment	0.95	0.865	Neither	1.8	0.01	LTRA
All-cause death	1.2	0.563	Neither	1.3	0.642	Neither

Multivariable logistic regression/ Poisson regression were used and were adjusted for all covariates mentioned above.
Sample size: Low LABA strengths: 3029; Medium- High LABA strengths: 9839.
Abbreviations: ED: emergency department; SABA: short acting beta agonists; CV: cardiovascular, LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist; ICS: inhaled corticosteroids; OR: odds ratio; RR: rate ratio.

Both LABA add-on strengths were associated with significantly lower odds of any asthma exacerbation and treatment change and with lower SABA use compared with LTRA add-on. Also, both LABA strengths were associated with significantly higher likelihood of CV events compared with LTRA add-on.

Table 7: Discontinuation design: Incident users' design. ORs and RRs for asthma, cardiovascular and other outcomes by treatment group: ICS + LTRA vs ICS + LABA.

	OR	CI	Adjusted probability LABA add-on	Adjusted probability LTRA add-on	p value	Favor
Effectiveness outcomes						
Asthma Hospitalizations or ED visits	0.68	0.27 - 1.69	0.08	0.06	0.404	Neither
Asthma related oral corticosteroid or antibiotic prescriptions	1.48	0.61 - 3.56	0.04	0.05	0.385	Neither
Any asthma exacerbation	1.02	0.52 - 2.01	0.14	0.15	0.952	Neither
SABA use (RR)	0.82	0.66 - 1.04	0.88	0.73	0.097	Neither
Cardiovascular safety						
CV hospitalization/ED	0.85	0.45 - 1.62	0.2	0.18	0.63	Neither

Multivariable logistic regression/ Poisson regression were used and were adjusted for all covariates mentioned above.
Total sample size= 655 (106 on ICS+LTRA and 549 on ICS+LABA).
Average follow up periods = 0.37+ 0.34 person years.
Abbreviations: ED: emergency department; SABA: short acting beta agonists; CV: cardiovascular, LABA: long acting beta agonist; LTRA: leukotriene receptor antagonist; ICS: inhaled corticosteroids; OR: odds ratio; RR: rate ratio.
For all cause death; model failed "not concave"

Analysis of incident users showed no significant difference for all outcomes between the two treatment groups.

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