Risk of Arrhythmias Associated with Inhaled Anticholinergics in Young Individuals with Asthma

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THESIS

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This thesis is dedicated to my dearest parents whose encouragement and love were vital to this journey. Amma and Daddy, thank you.

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LIST OF ABBREVIATIONS

95% CI	95% Confidence Interval
COPD	Chronic obstructive pulmonary disease
ED	Emergency department
FDA	Food and Drug Administration
HR	Hazard ratio
IAC	Inhaled anticholinergics
ICD-9	International Classification of Diseases, 9th Edition
ICS	Inhaled corticosteroids
LABA	Long acting beta (β_2) agonist
NAEPP	National Asthma Education and Prevention Program
NDC	National Drug Code
NHLBI	National Heart Lung and Blood Institute
OR	Odds ratio
PEFR	Peak expiratory flow rate
RCT	Randomized controlled trial
RR	Relative risk
SABA	Short acting beta (β2) agonist
TALC	Tiotropium Bromide as an Alternative to Increased Inhaled Corticosteroid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroids
US	United States

SUMMARY

Asthma affects 20.5 million adults and 6.5 million children in the United States (US) resulting in more than 497,000 hospitalizations and 1.8 million emergency department visits annually. With a prevalence of 9.6% in children 5-17 years old, asthma is the most common chronic condition in the pediatric population. The National Asthma Education and Prevention Program (NAEPP) guidelines recommend inhaled corticosteroids (ICS) in combination with long-acting beta-agonists (LABA) as treatment for patients with moderate to severe persistent asthma. However, concerns about LABA safety, particularly when used without ICS, highlight the importance of examining alternative therapies for asthma treatment.

Inhaled anticholinergics (IACs) are bronchodilators of choice in management of chronic obstructive pulmonary disease (COPD). Use of anticholinergics for chronic management of asthma is currently not approved. However, several studies, including the Tiotropium Bromide as an Alternative to Increased Inhaled Corticosteroid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroids (TALC) study, have shown that IACs may offer an alternative to a regimen of LABA and ICS. Notably, despite perceived safety, IACs have been associated with systematic side effects, including dry mouth, urinary retention, and tachycardia. Tachycardia and other forms of arrhythmia are of particular importance as they might herald other cerebrovascular and cardiovascular adverse events. Moreover, recent studies in COPD found IAC use was associated with increased cardiovascular adverse events such as stroke, myocardial infarction, and death.

Before anticholinergics are adopted as an alternative to LABAs in asthma, it is important to fully evaluate their risk profile, which may include cardiovascular risk. Further, the baseline

absolute risk of serious cardiac events in pediatric adolescent, and young adult populations is low, and is not likely to be detected in clinical trials. Hence, use of observational data is important in assessing whether IAC use in asthma is associated with increased cardiovascular risk.

The objective of this study was to investigate the association between IAC use and arrhythmias in young individuals with asthma. We conducted a nested case-control study within a cohort of children, adolescents, and young adults with asthma identified in a commercial health insurance claims database. The association between IACs and arrhythmias expressed in odds ratios (OR) with 95% confidence interval (95% CI) was determined using multivariate conditional logistic regression. We conducted several sensitivity analyses to evaluate the robustness of our results.

There were 283,429 individuals that met the criteria for inclusion in cohort. Within this cohort, there were 7,656 cases matched to 76,304 controls. The analytic population was mostly female (58.8%) and older than 12 years (73.3%). The median duration of follow-up was 458 (interquartile range, 180 – 913) days. Active exposure of IACs was observed in 0.69% of cases and 0.18% of controls. Active use was associated with a 1.56-fold increase in arrhythmia risk compared with non-active/nonusers (Adjusted Odds Ratio (OR_{adj}), 1.56; 95% CI, [1.08–2.25]). Risk was highest among active users of ipratropium (OR_{adj}, 1.59 [1.08–2.33]) compared with tiotropium (OR_{adj}, 1.20 [0.29–4.89]) and combination ipratropium and short-acting beta-agonists (OR_{adj}, 1.20 [0.74–1.94]). Active high dose users of IACs (>0.114mg ipratropium equivalents) had a 69% increase in risk (OR_{adj}, 1.69[1.10–2.59]) whereas the added risk for active users on low dose (≤ 0.114mg ipratropium equivalents) (OR_{adj}, 1.22 [0.53–2.65]) was not statistically significant. The increased risk of arrhythmia in active users of IACs found in the main analysis was consistent across various sensitivity analyses.

SUMMARY (continued)

Our results are consistent with literature reporting a positive association between use of IACs and cardiovascular related adverse events and deaths in patients with COPD. Our study examined the association between IACs and arrhythmias in a younger population with asthma who were at a considerably lower risk for cardiovascular diseases. The fact that we observe an increased risk lends creditability to a potential drug effect.

In this analysis we found use of inhaled anticholinergics associated with an increased risk of arrhythmia in children, adolescents, and young adults with asthma compared to other asthma controller medications. Individuals aged 12 to 24 years and those prescribed ipratropium bromide were at the highest risk for arrhythmia. It should be noted that the absolute risk was low. Nevertheless, health care providers are advised to be cautious before incorporating anticholinergics in the management of asthma. This risk may be important to consider in other populations as well where arrhythmia is more common. Clearly, further research would be helpful to more fully understand the potential risks.

1 INTRODUCTION

1.1 Statement of the Problem

Asthma is a chronic respiratory disease caused by obstruction, hyperresponsiveness and inflammation of airways.[1] A disease of exacerbation and remission, asthma is characterized by recurrent episodes of coughing, dyspnea, wheezing and tightness in chest. Asthma affects 20.5 million adults and 6.5 million children in the United States (U.S) resulting in more than 497,000 hospitalizations and 1.8 million emergency department visits per year. With a prevalence rate of 9.6% in children 5-17 years old, asthma is one among the most common chronic diseases in the pediatric population.

The primary goals in the treatment of asthma are reversal of airflow obstruction, and reduction of the likelihood of future recurrence of airflow obstruction.[2] Therapeutic agents frequently used to achieve these goals include bronchodilators (β2 – agonists; anticholinergics) and anti-inflammatory agents (systemic or inhaled corticosteroids). The National Asthma Education and Prevention Program (NAEPP) guidelines recommend the use of inhaled corticosteroids (ICS) in combination with a long-acting bronchodilator (LABA) for the treatment of patients with moderate to severe persistent asthma.[3] However, there are concerns about the safety of LABAs, particularly when used without an ICS. The use of LABAs was associated with a significant increase in asthma related morbidity and mortality. This highlights the importance of examining alternative therapies in the management of patients with asthma.[4-6]

Anticholinergics are muscarinic antagonists that offer bronchodilation.[7] They are available as inhalation formulations that are poorly absorbed and therefore perceived as to not cause any systemic effects. Although inhaled anticholinergics (IACs) are not approved for their use in asthma, several studies have indicated that the use of anticholinergics in asthma is beneficial.[8-14] The Tiotropium Bromide as an Alternative to Increased Inhaled Corticosteroid in

patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroids (TALC) study showed that IACs may offer an alternative to a regimen of LABA and ICS. [12] Despite their perceived safety, studies have demonstrated that inhaled anticholinergics cause side effects such as dry mouth, urinary retention, and tachycardia.[15] Tachycardia and other forms of arrhythmia are of particular importance as they might herald other cerebrovascular and cardiovascular adverse events such as stroke, heart failure.[16]

Inhaled anticholinergics are bronchodilators of choice in Chronic Obstructive Pulmonary Disorder (COPD) – a chronic respiratory disease that is characterized by airway obstruction and inflammation effecting older (≥ 40 years) individuals who have had a history of smoking tobacco.[17] Recent studies have indicated that the use of anticholinergics in COPD is associated with an increased risk of cardiovascular adverse events such as death, stroke or myocardial infarction.[18] However, this association is controversial in the sense that there is contradicting evidence published in literature.[8,19-22]

Little is known about the cardiovascular safety of inhaled anticholinergics in asthma. Before anticholinergics are adopted as an alternative to LABAs in asthma it is important to evaluate their risk profile. The baseline absolute risk of serious cardiac events in pediatric, adolescent and young adult populations is low. Cardiovascular risk of anticholinergics might be different in the younger asthma population and older COPD population since the COPD population shares the risk factors for cardiovascular disease such as advanced age and smoking tobacco. Understanding whether IACs use in asthma is associated with increased cardiovascular risk is important to better understand their risk-benefit profile in asthma patients. Therefore, there arises a need to determine the association between the use of inhaled anticholinergics and cardiovascular adverse events such as arrhythmias in the asthma population.

1.2 Specific Objective and Hypothesis

Our objective was to examine a sample of children, adolescents and young adults with asthma who were exposed to inhaled anticholinergics and determine the association between the exposure to anticholinergics and arrhythmias.

Corresponding to this objective, our hypothesis was as follows:

H01 (Null): Adjusting for all other characteristics, there is no association between the use of inhaled anticholinergics and risk of arrhythmia.

H11 (Alternate): Adjusting for all other characteristics, the use of inhaled anticholinergics is associated with an increased risk of arrhythmia.

1.3 Significance

Inhaled anticholinergics, when used in asthma have been shown to reduce the number of hospitalizations and improve the lung function. It is important to understand the risks associated with their use in order to perform a routine benefit-risk assessment. This study will help understand the association between inhaled anticholinergics and arrhythmias in a population that does not share majority of the risk factors for cardiovascular diseases as is the case with the COPD population

.

2 LITERATURE REVIEW

A review of the literature pertinent to stated research objectives is presented in this chapter. This review is organized into sections including the definition, epidemiology and management of asthma (2.1); the pharmacology of anticholinergics (2.2); the use of anticholinergics in asthma (2.3); comparison between obstructive airway diseases – asthma and COPD (2.4); arrhythmias (2.5); arrhythmias in the pediatric population (2.5.1); arrhythmogenic properties of anticholinergics (2.5.2); and the cardiovascular risk associated with the use of anticholinergics in COPD (2.6).

2.1 Asthma: Definition, Epidemiology, and Management

Asthma is a chronic respiratory disease that is caused by obstruction, hyperresponsiveness and inflammation of airways.[1] A disease of exacerbation and remission, asthma is characterized by recurrent episodes of coughing, dyspnea, wheezing and tightness in chest. An episode of asthma can be triggered by a variety of environmental, microbiologic, chemical, and biologic factors such as: cold air, smoke, influenza virus, pollen, drugs, exercise, and emotions. Risk factors for asthma include airway hyper-reactivity, presence of atopic diseases such as atopic dermatitis and allergic rhinitis, and increased levels of endotoxin.[23] Based on the frequency of symptom occurrence, and medication use, severity of asthma can be classified as intermittent or persistent. Persistent asthma can further be sub-classified on the same basis as mild, moderate, or severe.[24]

With a prevalence rate of 9.6% in children 5-17 years old, asthma is one of the most common chronic disorders seen in the pediatric population. [1] It is reported that 30% to 70% of children with asthma become symptom-free by early adulthood. Childhood asthma is more prevalent in males while adult asthma is more common in females. [23] The underlying cause for this gender difference has not been determined. Asthma affects 20.5 million adults and 6.5

million children in the United States and results in more than 497,000 hospitalizations and 1.8 million emergency department visits annually.[1] In 2010, asthma was projected to cost $15.6 billion in direct costs and $ 5.1 billion in indirect costs in national healthcare expenditure. [25] Factors such as lost school and work days, lost productivity place burden on the society and account for the indirect costs while cost of prescription medicines is the highest contributor to the direct costs.

The primary goals of treatment of asthma include prevention of symptoms by correction of hypoxemia and reversal of airflow obstruction, and prevention of recurrent exacerbations.[2] Medications used in the management of asthma can be classified as quick relief medications or long term control medications. **Table I** lists the medications used in the management of asthma.

TABLE I: MEDICATIONS USED IN THE MANAGEMENT OF ASTHMA[1,2]

Quick Relief Medications		
Therapeutic Class	**Generic Name**	**Mechanism of Action**
Anticholinergics	Ipratropium Bromide Tiotropium Bromide	Bronchodilation by reducing intrinsic vagal tone of airway
Short-acting β2-agonists (SABAs)	Albuterol Levalbuterol Pirbuterol	Bronchodilation by relaxing smooth muscle
Systemic corticosteroids	Hydrocortisone Prednisone Methylprednisolone Dexamethasone	Antiinflammatory – reduce mucus production, airway edema and exudation
Long Term Control Medications		
Immunomodulators	Omalizumab	Reduce the release of inflammatory mediators produced as response to allergen
Inhaled corticosteroids	BDP Budesonide Flunisolide FP MF TAA	Antiinflammatory – reduce bronchial hyperresponsiveness, mucus production, airway edema and exudation
Long-acting β2-agonists (LABAs)	Formoterol Salmeterol	Bronchodilation by relaxing smooth muscle
Leukotriene modifiers (LTMAs)	Montelukast Zafirlukast Zileuton	Antiinflammatory – reduce bronchial hyperresponsiveness
Mast cell stabilizers	Cromolyn Nedocromil	Reduce asthmatic reaction to allergens, bronchodilation by inhibiting neutrally mediated bronchoconstriction
Methylxanthines	Theophylline	Bronchodilation by relaxing smooth muscle, reduce immune/inflammatory action of specific cells

Abbreviations: BDP- beclomethasone diproprionate; FP- fluticasone proprionate; MF- mometasone furoate; TAA- triamcinolone acetonide.

The National Heart Lung and Blood Institute (NHLBI) recommends a stepwise approach to the selection of a therapeutic regimen for the management of asthma.[2] This approach is based on the severity of asthma. Severity of asthma is determined by factors such as reported frequency of symptoms, level of lung function, and the number of exacerbations requiring oral systemic corticosteroids per year.[24] Based on these factors, asthma is classified as either intermittent or persistent. Persistent asthma is further classified as mild, moderate, or severe. It is recommended to manage intermittent asthma with step 1 therapy which is a short-acting β2 agonist (SABA) on an as needed basis.[2] Mild persistent asthma is managed with step 2/ step 3 therapies. Step 2 recommends a low dose inhaled corticosteroid (ICS) or cromolyn or montelukast. Step 3 recommends medium dose ICS. Moderate persistent asthma is managed with step 4 which recommends a combination of medium dose ICS and a long acting β2 agonist (LABA) or montelukast. Severe persistent asthma is managed with step 5(high dose ICS and LABA or montelukast) and step 6(high dose ICS and LABA or montelukast and oral systemic corticosteroids) therapies.

2.2 Pharmacology of Anticholinergics

Acetylcholine mediates parasympathetic activity in the respiratory system by activating the muscarnic and nicotinic receptors present in the smooth muscles of the airways.[7,26] This activation causes constriction of bronchial smooth muscle and release of mucus into the airways, thereby causing airflow obstruction. Anticholinergics compete with acetylcholine and block the activation of muscarnic receptors in the airway smooth muscles thereby providing bronchodilation. Hence, they are referred to as muscarnic antagonists.

There are three types of muscarnic receptors in the airway smooth muscles: M1, M2, and M3.[7,26] Activation of M1 and M3 receptors by acetylcholine causes bronchoconstriction. M2 receptors are feedback inhibitory receptors meaning that they inhibit the release of acetylcholine. Blockade of M2 receptors facilitates bronchoconstriction by releasing

acetylcholine. Therefore, antagonistic agents that can selectively block M1 and M3 receptors are suitable in the therapy of obstructive lung diseases such as asthma and COPD.

Anticholinergics can be classified as short-acting (ipratropium, oxitropium) or long-acting (tiotropium).[7,26] In the US, ipratropium and tiotropium are the available inhaled anticholinergics, see **Table II**. Tiotropium is superior to ipratropium as it possesses specific kinetic selectivity for M1 and M3 receptors.[27] It is potent and long-lasting. **Table III** compares the pharmacokinetics of ipratropium and tiotropium when administered via the inhalation route.

TABLE II: INHALED ANTICHOLINERGICS[28,29]

Generic name	Trade name	Manufacturer	Approved Indication(s)
Ipratropium bromide	Atrovent	Boehringer Ingelheim	COPD Nasal discharge
Tiotropium bromide	Spiriva	Boehringer Ingelheim	COPD

TABLE III: PHARMACOKINETICS OF IPRATROPIUM VS. TIOTROPIUM[1]

	Ipratropium	Tiotropium
Onset of action	15 to 30 minutes	Less than or equal to 30 minutes
Peak effect (bronchodilation)	1 to 2 hours	1 to 4 hours
Duration of action	4 to 5 hours	Approximately 24 hours

Ipratropium bromide is available in oral inhalation and intranasal dosage forms.[28,29] The oral inhalation dosage form is indicated for use in treatment and prevention of bronchospasm associated with COPD while the intranasal dosage form is indicated for use in symptomatic relief of rhinorrhea associated with common cold or allergic/non-allergic rhinitis. Tiotropium

bromide is available in an oral inhalation dosage form and is indicated for use in long-term treatment and prevention of bronchospasm associated with COPD, chronic bronchitis and emphysema. In exacerbations of asthma, ipratropium bromide can be administered via oral inhalation or nebulization whereas tiotropium bromide is administered via the inhalation route.

Adverse events associated with the use of ipratropium and tiotropium include inhibition of gastric secretion, dry mouth, mydriasis, urinary retention and tachycardia.[26] Data from spontaneous adverse event reports indicate that chest pain, palpitation, sinus tachycardia, and other cardiac arrhythmias are experienced in users of inhaled anticholinergics.[28] However, the exact incidence of these cardiovascular adverse events has not yet been established.

2.3 The Use of Anticholinergics in Asthma

Anticholinergics are not approved by the US FDA for their use in asthma. Several studies have demonstrated that anticholinergics are beneficial in severe acute exacerbations of asthma. Effectiveness of anticholinergics for chronic asthma was also evaluated. A brief summary of these studies is presented in this section.

Studies conducted in adults with both stable and acute asthma that examined the efficacy of inhaled anticholinergics concluded that the combination regimens consisting of β2-agonists and anticholinergics were superior compared to monotherapies of either β2-agonists or anticholinergics.[8,10] Unlike β2-agonists that offer rapid bronchodilation, ipratropium produces gradual bronchodilation. Therefore, it was found not to be an effective mono-therapy in acute asthma exacerbations. Within the first hour of administration, β2-agonists show superior bronchodilation when compared to anticholinergics. Anticholinergics contribute to an additive effect in combination regimens consisting of β2-agonists and anticholinergics offering greater bronchodilation than either stand-alone regimen.

Moreover, anticholinergics might be more useful in an older patient population as sensitivity to β2-adrenergic receptors decreases with age while sensitivity to cholinergic receptors remains constant.[30-33] The synergistic effect of anticholinergics in combination therapy was independent of severity of asthma.[8,10] Also, it has been found that patients with non-allergic (intrinsic) asthma and those with longer duration of asthma episodes respond better to treatment with anticholinergics when compared to patients with allergic (extrinsic) asthma.[10,34]

Importantly, clinical trials have reported that the addition of anticholinergic to β2-agonist therapy in children with acute asthma led to significant improvement of lung function and a significant reduction in the number of hospitalizations.[14]

Plotnick and colleagues reported similar results in their systematic review of all randomized clinical trials (RCTs) comparing a polytherapy of β2-agonist plus anticholinergic to a monotherapy of β2-agonist in children ≤ 18 years old with acute asthma exacerbations in an emergency department setting.[13] Number of hospitalizations was the primary outcome analyzed. It was found that the addition of a single dose of anticholinergic to β2-agonist did not significantly reduce the risk of hospitalization (Relative Risk (RR), 0.93; 95% CI [0.65 - 1.32)]), whereas the addition of multiple doses of anticholinergic to β2-agonist reduced the risk of hospitalization by 25% [95% CI 0.62 - 0.89]. However, additional doses of anticholinergic (single or multiple) were reported to significantly improve objective measures of lung function.

However, in a systematic review of all RCTs published before 2010 in which anticholinergics were given for treatment of chronic asthma in children over 2 years of age, the authors that there was not enough evidence for the effectiveness of anticholinergics in chronic asthma in children older than 2 years.[11] Westby and colleagues conducted a systematic review of randomized trials or quasi-randomized trials evaluating effectiveness of anticholinergics versus placebo or combination therapy in the management of chronic asthma in adults.[35]

Although there was a statistically significant improvement in lung function with anticholinergics, the authors concluded that the relative clinical significance over a placebo was low.

The "Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid "(TALC) study conducted by Peters et al., is the most recent clinical trial of tiotropium bromide.[12] In this trial, adults with inadequately controlled asthma were assigned to one of the treatment groups: (i) tiotropium bromide and a low dose of glucocorticoid (beclomethasone) (ii) double dose of beclomethasone (iii) salmeterol and a low dose of beclomethasone. Peak expiratory flow rate (PEFR) – an objective measure of the degree of obstruction in airways – was the primary outcome studied in this trial. Patients receiving tiotropium bromide and a low dose of beclomethasone had a significantly higher morning PEFR when compared to those receiving double dose of beclomethasone. There was no significant difference in the morning PEFR of patients in the tiotropium and low dose beclomethasone group and the salmeterol and low dose beclomethasone group. However, patients in the salmeterol and low dose beclomethasone group had significantly higher morning PEFR when compared to patients in the double beclomethasone group. Therefore, the authors concluded that tiotropium bromide was superior to glucocorticoid treatment but not inferior to salmeterol treatment. However, these conclusions cannot be applied to clinical decisions due to the small sample size of the study (174 patients) and the short follow-up period of the study (14-weeks).

2.4 Comparison between Obstructive Airway Diseases – Asthma and COPD

Chronic Obstructive Pulmonary Disease (COPD) is an obstructive airway disease that is usually comprised of conditions such as chronic bronchitis and emphysema.[36] Bronchitis is the inflammation of airways in the lungs. It can be acute (following a respiratory infection) or chronic (as in the case of COPD). This inflammation causes symptoms like chest pain, dyspnea (shortness of breath), and sputum (cough with mucus). Emphysema is a condition in which there is progressive destruction of the lung tissue leading to airway obstruction. The fourth leading cause of death in the US, COPD is progressive in nature and is characterized by airflow obstruction that is not fully reversible meaning that the obstruction cannot be corrected with the action of bronchodilators. Tobacco smoking, exposure to occupational dusts and chemicals, and advanced age are the risk factors for COPD.[17,37]

Although both asthma and COPD are chronic respiratory disorders characterized by airflow obstruction, their pathophysiology is different.[1,36,38] While airflow obstruction and bronchial hyperresponsiveness in asthma is the result of exposure to trigger factors such as allergens or other stimuli, obstruction in COPD is chronic and developed over time. Airways of COPD patients become narrow over time and have reduced elasticity. Obstruction of airways and airflow in asthma is considered completely reversible meaning that there is an acute response to β2- adrenergic stimulation or bronchodilator action, whereas obstruction in COPD is considered only partially reversible. Patients with COPD gain little or no relief from β2-adrenergic stimulation by β2-agonists and this is the reason why inhaled anticholinergics are the bronchodilators of choice in COPD.

In asthma, airway inflammation is a response to stimuli and is reversible meaning that during a remission period there is no inflammation.[1,36,38] In COPD, inflammation occurs not only in the airway, but also extends to other areas of the respiratory system such as pulmonary vasculature and tissue and is progressive in nature. Inflammation is built up over time due to

increased oxidative stress in the lung resulting from smoking. However, patients with COPD also have acute exacerbations characterized by symptoms of upper respiratory tract infection, worsening of dyspnea, increase in sputum volume, and/or increase in sputum purulence. The cause for these exacerbations is unknown. Bronchodilators and systemic corticosteroids are used in the treatment of exacerbations. Antimicrobial agents are used only when there are signs of respiratory tract infection.

One commonality between the two diseases is the use of inhaled bronchodilators such as short-acting β2- agonists and anticholinergics for the treatment of acute exacerbations.

2.5 Arrhythmias

Cardiac arrhythmia is a disease where the normal cardiac rhythm is disturbed.[16] Clinically, cardiac arrhythmias are presented as dizziness, palpitations, syncope, or sudden death. Tachycardia is when the heart beat is too fast, while bradycardia is when the heart beat is too slow. Heart beat can be irregular and chaotic in some arrhythmias. Normally, heartbeat is initiated by a process that involves sending electrical signals from the sinoatrial node (SAN) to the atrioventricular node (AVN) which then causes blood to be pumped. In a cardiac arrhythmia, this process is disturbed.

Cardiovascular diseases such as coronary artery disease, cardiomyopathy, hypertension, and congenital heart disease and conditions such as electrolyte imbalance, obesity, and hyperthyroidism are considered as risk factors for developing arrhythmias.[39-41] Chronic alcohol abuse and excessive use of caffeine or nicotine also induce arrhythmias.

Types of arrhythmia are as follows[16]:

a) Premature/Extra beats: Premature beats are early heart beats that disrupt the rhythm of the heart. They are the most common type of arrhythmia. They are harmless and do not

cause any symptoms. Depending on the origin of the extra heart beats, premature heart beats are classified as:

1. Premature atrial contractions – origin of premature beats is in the atria.
2. Premature ventricular contractions – origin of premature beats is in the ventricles.

b) Supraventricular tachycardias: Tachycardias originating in the atria or the atrioventricular node are referred to as supraventricular tachycardias.
   1. Atrial fibrillation (AF) is characterized by fast and irregular contraction of atria. Atrial fibrillation is either paroxysmal or chronic. One of the commonly seen serious arrhythmias, AF can lead to complications such as stroke or heart failure.
   2. Paroxysmal supraventricular tachycardia (PSVT) is characterized by a fast heart beat that begins and ends abruptly, lasting a few seconds. PSVT is commonly seen in the pediatric population.

c) Ventricular arrhythmias: Tachycardias originating in the ventricles are referred to as ventricular arrhythmias. These are:
   1) Ventricular tachycardia, which is characterized by premature contraction of the lower chambers of the heart, the ventricles.
   2) Ventricular fibrillation, which is preceded by ventricular tachycardia in most cases, ventricular fibrillation is a condition in which the ventricles, instead of pumping blood, quiver rapidly due to the erratic electric signals. Ventricular fibrillation can cause death in minutes if not treated immediately.

d) Bradyarrhythmias: Often caused by preexisting heart conditions or the use of medications such as beta blockers, bradyarrhythmias are arrhythmias with a heart rate that is too slow.

Arrhythmias can sometimes occur as a side effect of medications.[16] Some drugs can induce arrhythmia by causing the heart to beat prematurely, these include bronchodilators like

ephedrine and beta agonists, stimulants of the central nervous system such as caffeine, cocaine, and methamphetamine, and medications used for common cold containing pseudoephedrine.

Long QT Syndrome is a condition in which the Q-T interval of the heart's electrical cycle is prolonged, thereby causing a ventricular tachycardia.[42-44] The long QT syndrome can be inherited genetically or acquired as an adverse effect of medications. Medications that lengthen the Q-T interval and cause arrhythmia include certain antibiotics, antidepressants, antihistamines, diuretics, anti hyperlipidemics, anti diabetes medications, antipsychotics, as well as some antifungal agents.

QT dispersion is crudely a measure of abnormality in conduction of the heart. Increased QT dispersion is known to be associated with arrhythmias and sudden death. In a randomized blinded prospective study examining the effect of standard dose albuterol (a beta agonist) versus a combination of low dose albuterol plus ipratropium bromide on QT dispersion, it was found that while there was no increment to QT dispersion post administration of the combination therapy, there was a significant increase in the QT dispersion post administration of standard dose albuterol (29.0± 3 msn vs. 40.6±5.1 msn; $p < 0.0001$; where msn indicates a QT interval parameter).[9] The authors concluded that the combination therapy had lower arrhythmogenic risk compared to the monotherapy while maintaining the bronchodilator effect.

In the systematic review of effectiveness of a combination therapy (beta agonist plus anticholinergics) versus monotherapy (beta agonists alone) in children and adults with acute asthma, Rodrigo and colleagues reported six adult trials that studied heart rate as an outcome.[14] It was found that there was no significant difference in heart rate variability between the treatment groups (weighted mean difference = -2.07; 95% CI -4.35 - 0.21; $p = 0.07$).

In a community-pharmacy based survey of 1,351 asthma patients aged between 18 and 50 years old in France, 21.1% of the respondents indicated that they have experienced palpitations that they perceived were a consequence of the medications they were using for their asthma.[45]

2.5.1 Arrhythmias in the Pediatric Population

The overall incidence of arrhythmias was reported at 13.9 per 100,000 emergency department (ED) visits and 55.1 per 100,000 pediatric ED visits while the prevalence of supraventricular tachycardia was reported to be 1 in 25,000 children.[46,47]

Sacchetti and colleagues reported that the incidence of clinically significant arrhythmias was 22.5 per 100,000 pediatric ED visits.[46] The most common arrhythmias identified by them were sinus tachycardia, supraventricular tachycardia, non-specific arrhythmias, bradycardia, and atrial fibrillation. A noteworthy observation in their research was the bimodal distribution of arrhythmias by age. The distribution demonstrated an infant peak, dropped in early childhood, and peaked again in later childhood and adolescence. This was attributed to the subject's ability to recognize and communicate a health problem –in this case, chest pain or palpitations. The distribution peak observed in infants can be attributed to continuous monitoring.

Arrhythmia induced chest pain in children can be considered as a sign of cardiac arrest. Ventricular tachycardia and bradycardia can manifest as chest pain in children.[48] A study that retrospectively examined pediatric patient charts for the causes of cardiac chest pain reported that 37% (9/24) of the children had a chest pain due to cardiac arrhythmia (supraventricular tachycardia, long QT syndrome, ventricular tachycardia).[49] Supraventricular tachycardia in children is clinically presented as a heart rate of approximately 200 beats, hypotension, and syncope. Children with ventricular tachycardia have a heart rate of 120-240 beats per minute. When not treated, this fast rhythm can deteriorate into ventricular fibrillation.[50]

2.5.2 Arrhythmogenic Properties of Anticholinergics

Acetylcholine, a parasympathetic neurotransmitter, has the following effects on the cardiovascular system: decrease in cardiac rate, decrease in the rate of conduction in SAN and AVN, vasodilation, and reduction in force of contraction.[7] These effects are mediated via muscarnic receptors present in the cardiac muscle. Anticholinergics competitively block the activation of muscarnic receptors by acetylcholine, therefore producing antagonistic effects such as increase in heart rate (tachycardia).

Inhaled anticholinergics are poorly absorbed into systemic circulation. Therefore, the occurrence of systemic side effects is thought of to be rare.[7,26] However, there were two studies identified which reported that treatment with inhaled anticholinergics was associated with an increased risk of developing side effects such as dry mouth, urinary retention, and sinus tachycardia.[15,51] These findings indicate that there still is a possibility of inhaled anticholinergics exerting systemic side effects. Accelerated heart rate results in cardiac strain. Cardiac strain is associated with an increased risk of adverse cardiovascular events such as congestive heart failure, myocardial infarction, stroke, and sudden cardiac death.[16]

Exacerbations in obstructive lung diseases are characterized by multiple pathophysiological events such as hypoxia, hypercapnia, acid-alkali disturbances, increased anxiety, and elevated intrathoracic pressures that in turn have an effect on cardiac blood return.[52,53] Therefore, exacerbations of childhood asthma carry a theoretical arrhythmogenic risk. Additionally, medications used in the treatment of these exacerbations such as β2-agonists, and methylxanthines are said to have potential cardiotoxic effects.[54]

A nested case-control analysis aimed to examine the association between the use of respiratory medications (oral and inhaled steroids, β2-agonists, anticholinergics, theophylline, cromoglycate, and antibiotics) in asthma and COPD and the risk of cardiac arrhythmias was

conducted by Huerta et al., using a population database.[55] This study showed that the long-term use of anticholinergics was associated with an increased risk for supraventricular tachycardias (RR, 1.7 [0.7 - 4.1]). However, the study population included patients with asthma and/or COPD.

It has been shown that cardiovascular diseases and COPD share risk factors such as advancing age and smoking of tobacco.[37,39] Therefore, the nature of the association between inhaled anticholinergics and cardiac arrhythmia in asthma remains unclear.

2.6 Cardiovascular Risk Associated with the Use of Inhaled Anticholinergics in COPD

Inhaled anticholinergics are the bronchodilators of choice in the treatment of COPD.[20] The use of these agents has been shown to reduce COPD-related hospitalization and death. Patients have been reported to adhere to anticholinergic treatment better than placebo. Between the two anticholinergic agents used, tiotropium is more effective than ipratropium owing to its selectivity for specific muscarnic receptors, and longer duration of action.

However, the cardiovascular safety of these agents is unclear. There has been conflicting evidence published in the literature on this issue. While some observational studies have shown that the use of anticholinergics is associated with an increased risk of cardiovascular adverse events[18,56-62], pooled analysis of safety data from clinical trials shows otherwise[63-69]. The FDA released an early warning in March 2008 saying that the use of tiotropium was associated with a small excess risk of stroke when compared to placebo in patients with COPD[70]. Later in that year, there were several studies that demonstrated an increased risk of cardiovascular morbidity and mortality with the use of tiotropium[18,59]. However, a 4-year pivotal trial (UPLIFT) demonstrated that there was no increased risk of adverse cardiovascular events associated with the use of tiotropium when compared to placebo.[69] Advisory committees unanimously agreed that the data from UPLIFT trial adequately addressed

the potential stroke and cardiovascular signal and in early 2010, the FDA released a follow-up stating that there was no association between the use of tiotropium and stroke.

Evidence published in the literature supporting an increased risk of cardiovascular adverse events with the use of inhaled anticholinergics is summarized in **Table IV**. Published literature reporting no evidence of increased risk of cardiovascular adverse events with the use of inhaled anticholinergics is summarized in **Table V**.

TABLE IV: EVIDENCE SUPPORTING INCREASED CARDIOVASCULAR RISK WITH ANTICHOLINERGIC USE IN COPD

Study (Year)	Study Type/Design	Treatment Groups	No. of patients in study	Cardiovascular outcome measured	Result	Measure of association [95% CI]
1. Guite (1999)	Obs – nested case-control	-	2,242	CV death	Death more common in pts with ipra Rx.	OR, 3.55 [1.05 - 11.94]
2. Anthonisen [Lung Health Study] (2002)	Clin Trial – R, DB, placebo-controlled	Smoking cessation + ipra vs smoking cessation + placebo vs usual care	5,887	CV death	More deaths in ipra compared to placebo	p = 0.027
3. Ringbaek (2003)	Obs – longitudinal cohort	Ipra vs Others (LABA, CS)	1,100	All-cause mortality	More deaths in ipra	RR_{COPD}, 1.6[1.2-2.1]; RR_{Asthma}, 2.4[1.2-5.0]
4. Barr (2006)	Meta-analysis	Tio vs placebo; Tio vs ipra; Tio vs LABA	8,002	Frequency of arrhythmia	More arrhythmia cases in tio than placebo	OR, 2.33 [1.11-4.88]
5. Wedzicha [INSPIRE] (2008)	Clin Trial – R, DB	Sal/Flu vs Tio	1,323	Fatal cardiac events	More fatal events in tio than sal/flu	3% in tio had fatal cardiac events vs. 1 % in sal/flu
6. Lee (2008)	Obs – nested case control	-	11,897(cause specific mortality subgroup)	CV death	Ipra associated with more CV deaths	OR,1.34[1.22-1.47]
7. Singh (2008)	Meta-analysis	AC vs placebo; AC vs beta agonists or CS	14,783	Composite outcome of CV morbidity and mortality;	AC's increased risk of composite outcome;	RR, 1.58 [1.21-2.06]
8. Ogale (2010)	Obs – cohort	-	82,717	CV events	Increased risk of CV events	≤4 30-day equivalents of cumulative exposure: HR, 1.40 [1.30-1.51];> 4 30-day equivalents: HR,1.23 [1.13-1.36]

Abbreviations: CV- cardiovascular; pts – patients; ipra – ipratropium; Rx – prescription; OR – odds ratio; R – randomized; DB: double-blinded; LABA – long-acting beta agonists; CS – corticosteroids; COPD – chronic obstructive pulmonary disorder; tio – tiotropium; Sal – salmeterol; Flu – fluticasone; AC – anticholinergics; RR – relative risk; HR – hazard rati

TABLE V: EVIDENCE FOR NEGATIVE ASSOCIATION BETWEEN ANTICHOLINERGICS AND CARDIOVASCULAR RISK IN COPD

Study (Year)	Type/Design	Treatment Groups	No. of patients in study	Cardiovascular outcome measured	Result	Measure of association [95% CI]
1. Kesten (2006)	Pooled safety analysis	Tio vs. placebo	12,819	CV mortality	Lower risk for CV mortality in tio users	Rate Ratio, 0.57 [0.26 - 1.26]
2. deLuise (2007)	Obs- cohort	-	10,603	Hospitalizations due to CV events; CV mortality	Tio users were at reduced risk (small)	Results were imprecise
3. Jara (2007)	Obs – cohort	Tio vs. LABA	2,862	Cardiac adverse events	Tio and LABA users had similar risk profile	HR_{Angina}, 0.77[0.37 - 1.59] $HR_{Tachycardia}$,0.66[0.29 -1.51]
4. Oba (2008)	Meta-analysis	AC vs. placebo; AC vs beta agonists or CS	10,249	Composite outcome of CV morbidity and mortality;	Non-significant increased risk associated with AC users	RR,1.07 [0.95 - 1.21]
5. Tashkin [UPLIFT] (2008)	Clin Trial – R, DB, placebo-controlled	Tio vs. placebo	5,993	Serious adverse cardiac events	Tio users at reduced risk for serious adverse cardiacevents	RR,0.84 [0.73 - 0.98]
6. Grosso (2009)	Obs – self-controlled case series	Tio	1,043	Incident stroke	No evidence of increased risk for stroke among tio users	Rate Ratio, 1.1[0.9 - 1.3]
7. Rodrigo (2009)	Meta-analysis	Tio vs placebo; Tio vs LABA+CS; Tio vs LABA	18,111	Composite adverse CV events; CV death	No diff between tio and control in CV events; CV death;	CV events – tio vs control: 3.6% vs. 4% CV death – tio vs. control: 1.7% vs. 1.9%
8. Celli (2010)	Pooled safety analysis	Tio vs. placebo	19,545	Composite outcome of CV morbidity and mortality;	Tio associated with reduction of risk for CV events, mortality	Rate Ratio, 0.83 [0.71 - 0.98]

Abbreviations: CV- cardiovascular; R – randomized; DB: double-blinded; LABA – long-acting beta agonists; CS – corticosteroids; COPD – chronic obstructive pulmonary disorder; tio – tiotropium; Sal – salmeterol; Flu – fluticasone; AC – anticholinergics; RR – relative risk; HR – hazard rat

A retrospective observational pharmacoepidemiologic study examining the association between the use of anticholinergics and risk of arrhythmias has not been performed previously. In order to determine the relationship between anticholinergics and cardiovascular adverse events in a population that does not share very many risk factors for cardiovascular disease, we examined a sample of children, adolescents, and young adults with obstructive lung disease (asthma) who have been on controller medications for the treatment of their asthma. In determining this relationship, we compared cases and controls exposed to anticholinergics with those who were not exposed previously and compute measures of association.

3 METHODS

The objective of this study was to investigate the association between the use of IACs and arrhythmias in children, adolescents, and young adults with asthma. A nested case-control study was conducted within a cohort of children, adolescents, and young adults with asthma. These individuals were identified from a commercial health insurance claims database.

3.1 Data Source

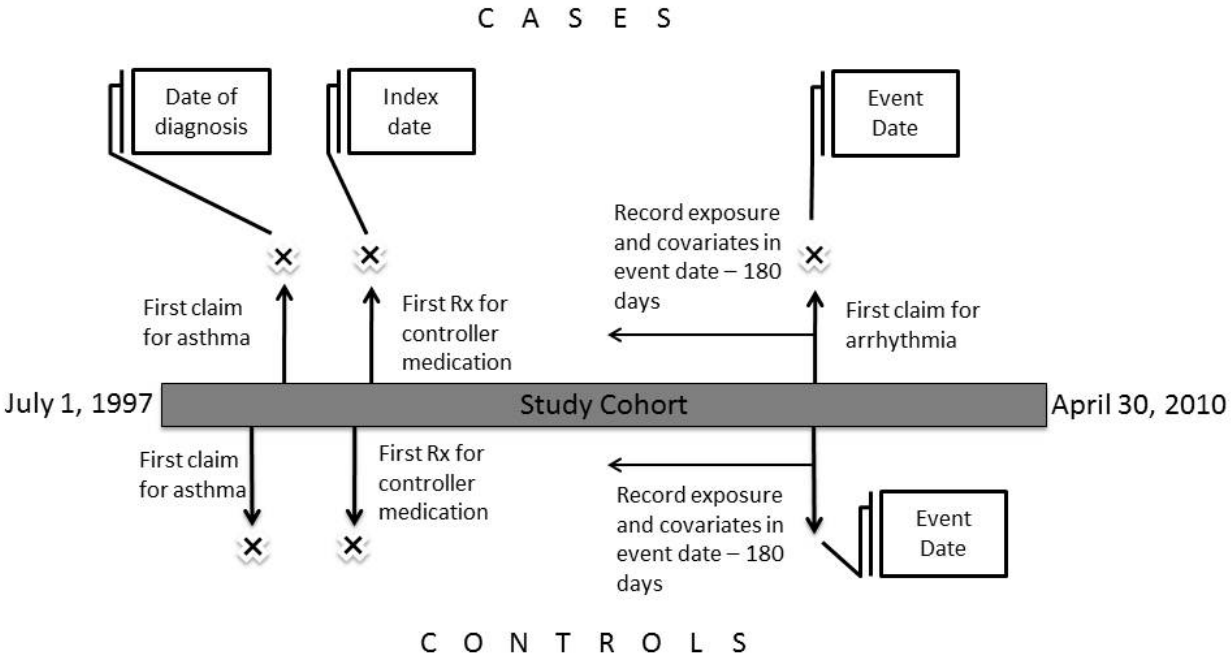
Data for this study were obtained from the IMS LifeLink™ Health Plan Claims Database. The database consisted of medical and pharmaceutical claims for more than 60 million patients from over 98 commercial health insurance plans across the United States. Enrollees in the database have average enrollment duration of 2.5 years. Information from medical claims in the dataset consisted of inpatient and outpatient diagnoses recorded in the International Classification of Diseases, 9th Edition (ICD-9) format, and medical procedures in the Current Procedural Terminology (CPT-4) and Health Care Common Procedure Coding System (HCPCS) formats. Information from retail and mail order prescriptions included the National Drug Code (NDC) and the quantity of medication dispensed. Dates of service for all medical and pharmaceutical claims were available. Additionally, the dataset had demographic data on members (e.g. age, gender, and geographic region) and dates of health plan enrollment.

The base cohort was an extract from the IMS data which consisted of medical and pharmaceutical claims for 1,653,126 individuals with a diagnosis of asthma (ICD-9 code 493.xx) on or after 1st January, 1997. The individual's age on at least one of the claims was between 5 and 24.

3.2 Study Cohort

The study cohort was limited to individuals with an asthma diagnosis followed by a first time prescription for a controller medication between July 1, 1997 and April 30, 2010. Inhaled corticosteroids, long-acting beta agonists, leukotriene modifying agents, xanthines, immunomodulators, mast cell stabilizers, and inhaled anticholinergics were the medication classes included in the definition of a controller medication. The index prescription date was defined as the date individuals first received a controller medication. This date served as the cohort entry date. The cohort was limited to those between 5 and 24 years old on their index date. Individuals were excluded if they were not continuously enrolled in the database for at least 6 months prior to the index prescription date. Individuals with a history of arrhythmia prior to the index prescription date or with congenital heart disease were also excluded. Starting from their index prescription date, individuals in the study cohort are followed until their first event of arrhythmia or their last date of enrollment (**Figure 1**).

Figure 1. Study design illustration



3.3 Identification of Cases and Controls

A case was defined as an event with a diagnosis of arrhythmia during the follow-up period identified by the following algorithm:

a) Out-patient visit, admission or discharge with diagnosis for cardiac arrhythmias identified by ICD-9 codes: 427(cardiac dysrhythmia), 427.0(paroxysmal supraventricular tachycardia), 427.1(paroxysmal ventricular tachycardia), 427.2(paroxysmal tachycardia, unspecified), 427.3(atrial fibrillation and flutter), 427.31(atrial fibrillation), 427.32(atrial flutter), 427.4(ventricular fibrillation and flutter), 427.41(ventricular fibrillation), 427.42(ventricular flutter), 427.5(cardiac arrest), 427.6(premature beats), 427.60(premature beats, unspecified), 427.61(supraventricular premature beats), 427.69(other premature beats), 427.8(other specified cardiac dysrhythmias), 427.81(sinoatrial node dysfunction), 427.89(other rhythm disorders), and 427.9(cardiac dysrhythmias, unspecified)
b) Out-patient visit, admission or discharge with symptoms involving cardiovascular systems identified by ICD-9 codes: 785.0 (tachycardia, unspecified), and 785.1 (palpitations)
c) Sudden death identified by ICD-9 codes: 798(sudden death, cause unknown), 798.1(instantaneous death), and 798.2(Death occurring in less than 24 hours from onset of symptoms, not otherwise explained)

This algorithm has been previously used to identify arrhythmias and was reported to have a high diagnostic accuracy.[71] The date of arrhythmia was defined as the event date. Cases were further categorized as severe or not severe. Severe cases were defined as those that required an inpatient hospitalization or an emergency department visit for arrhythmia. An emergency department visit was identified by the following CPT-4 procedure codes: 450, 451, and 452(emergency room); 99281, 99282, 99283, 99284, 99285, and 99288 (emergency

department visit). An inpatient hospitalization was identified by the presence of a confinement number which served as a unique ID for an event that led to hospitalization or confinement of an individual. While the main analysis included all cases, sensitivity analyses included stratified analyses by severity of the case.

Potential controls were individuals in the cohort who were at risk on the event date of the corresponding case. Up to 10 controls were randomly matched from the at risk population using the incidence density sampling approach.[72,73] The incidence density sampling scheme involves selecting multiple matched controls for each case from all persons at risk at the time of case occurrence (also referred to as the risk set), excluding the case. Since the cases and controls were essentially time-matched, it was possible for a cohort member serving as a control at one point to become a case later on in the study. It was also possible for one cohort member to be selected as a control for more than one case at different time points. Controls were matched on category of age (5-11 years, 12 and above), gender, geographic region, and cohort entry quarter and year to the cases. Controls were assigned the same event date as their corresponding cases.

3.4 Exposure

Exposure to inhaled anticholinergics was determined in the 180 days prior to the event date. Inhaled anticholinergics were identified by NDCs for:

(i) Ipratropium bromide ('00054840211', '00054840213', '00054840221', '00054840411', '00054840413', '00054840421', '00172640744', '00172640749', '00378698962', '00378698964', '00378698966', '00472075123','00472075130', '00472075160', '00472075323' ,'00472075330', '00472075360', '00487980101', '00487980102', '00487980125', '00487980130', '00487980160', '00597008062', '00597008214', '00597008218', '16252009822', '16252009833' '16252009866', '49502068503', '49502068524', '49502068526', '49502068529', '49502068530', '49502068531',

'49502068533', '49502068560', '49502068561', '49502068562', '55045193005', '55175138201', '60505080601', '65271000125', '65271000130', '65271000160', '66794000225', '66794000230', '66794000260', '00597008717', '00093672373', '00093672374', '00185732213', '00185732230', '00185732260', '00378698858', '00378698891', '00378698893', '00487020101', '00487020103', '00487020160', '00591343330', '00591343360', '00597001314', '16252054733', '16252054766', '49502067230', '49502067231', '49502067260', '54569460000', '54868422500', '54868597400')

(ii) Tiotropium bromide ('00597007506', '00597007537', '00597007541', '00597007547', '00597007575'), and

(iii) Ipratropium bromide – albuterol combination ('00093672373', '00093672374', '00185732213', '00185732230', '00185732260', '00378698858', '00378698891', '00378698893', '00487020101', '00487020103', '00487020160', '00591343330', '00591343360', '00597001314', '16252054733', '16252054766', '49502067230', '49502067231', '49502067260', '54569460000', '54868422500', '54868597400') administered via inhalation.

Based on exposure to any inhaled anticholinergic, individuals were classified as active users (sufficient days supply to cover the event date), immediate past users (prescription ended ≤30 days before the event date), past users (prescription ended 30 – 180 days before the event date), or nonusers (no prescription in 180 days before the event date). Dose was calculated in milligrams of ipratropium equivalents for active exposure. The calculation of ipratropium equivalents depended on the formulation of the drug. Tiotropium is supplied as dry powder capsules for inhalation. Total dose was determined by multiplying the quantity dispensed times the unit dose of tiotropium in a capsule. This dose was then converted to ipratropium equivalents by multiplying by a conversion factor of 7.5 which was obtained by equating recommended daily doses of ipratropium and tiotropium in COPD management. Ipratropium (monotherapy or in combination with albuterol) is supplied as metered-dose inhalers or as a

solution for nebulization. For metered-dose inhalers, total number of puffs was determined by multiplying the number of canisters (quantity dispensed/ package size) with number of puffs per canister. Total dose was calculated by multiplying the total number of puffs with the unit dose of ipratropium in a puff. For nebulizers, total dose was calculated by multiplying the quantity dispensed with the strength of the solution. The average daily dose was calculated and categorized into low (≤114 mg), and high (>114mg). Exposure to individual inhaled anticholinergics – ipratropium, ipratropium-albuterol combination, and tiotropium - was also identified.

3.5 Covariates

Potential confounders in the association between exposure to inhaled anticholinergics and arrhythmias were identified in the 180 days prior to the event date. These included:

a) Comorbidities

Hyperthyroidism, rheumatic fever, obesity, myocarditis, cardiomyopathy, and ischemic heart disease are all conditions that have a disease association with arrhythmia.[39-41] Indicator variables were created to record the presence of these conditions in the study period. Presence of a condition was defined as having at least one claim with a diagnosis including any of the following ICD-9 codes: 242.xx (hyperthyroidism), 390.xx – 392.xx (rheumatic fever), 278.xx (obesity), 422.xx (myocarditis), 425.xx (cardiomyopathy), 410.xx-414.xx (ischemic heart disease).

b) Concomitant active use of other asthma medications

Indicator variables were created to record the active use of other asthma medications. Active use was defined as having a prescription with days supply covering the event date. Classes of medications included were short acting beta-agonists (SABA), oral corticosteroids, inhaled

corticosteroids, long-acting beta-agonists, leukotriene modifying agents, mast cell stabilizers, immunomodulators, and xanthines.

c) Concomitant active use of medications with anticholinergic effects

Antiarrhythmic agents, antibacterials, antidepressants, antiemetics, antihistamines, antimalarial agents, antimigraine agents, antipsychotics, calcium channel blockers, cough/cold/allergy medications, and opioid analgesics are classes of medications that either produce systemic anticholinergic effects or are known to induce QT prolongation.

d) Severity of asthma

Severity of asthma in the 180 days prior to the event date was assessed using previously established proxy measures, including the number of emergency department visits with a diagnosis of asthma, the number of SABA canisters dispensed, the use of oral corticosteroids, and the number of acute asthma exacerbations.[74,75] An event of acute asthma exacerbation was identified by a prescription for an oral corticosteroid filled within 7 days of an outpatient encounter for asthma.[75] Number of SABA canisters dispensed was calculated by dividing the quantity of the SABA dispensed by the package size. Package size information was available with the NDC.

3.6 Descriptive Statistics

Summary statistics were calculated for all covariates in the study cohort. Means, medians, ranges and standard deviations were used to summarize continuous variables such as age and duration of follow-up. Counts and percentages summarized categorical variables. Covariates were compared between cases and controls. Study variables are described in **Table VI**.

TABLE VI: STUDY VARIABLES

Variable	Measure	Operation
Outcome variable		
Case status	Individual is a case if they have an event of arrhythmia, control otherwise	Binary: 1 = Case 0 = Control
Exposure variable(s)		
Active user of any IAC	Whether or not an individual was an active user of IAC at the time of event	Binary: 1 = Yes 0 = No
Active user of ipratropium	Whether or not an individual was an active user of ipratropium at the time of event	Binary: 1 = Yes 0 = No
Active user of tiotropium	Whether or not an individual was an active user of tiotropium at the time of event	Binary: 1 = Yes 0 = No
Active user of combination IAC (ipratropium-albuterol)	Whether or not an individual was an active user of combination IACs at the time of event	Binary: 1 = Yes 0 = No
Covariates		
Hyperthyroidism	Whether or not an individual had a claim for hyperthyroidism in the 180 days before the event	Binary: 1 = Yes 0 = No
Rheumatic fever	Whether or not an individual had a claim for rheumatic fever in the 180 days before the event	Binary: 1 = Yes 0 = No
Obesity	Whether or not an individual had a claim for obesity in the 180 days before the event	Binary: 1 = Yes 0 = No
Myocarditis	Whether or not an individual had a claim for myocarditis in the 180 days before the event	Binary: 1 = Yes 0 = No
Ischemic heart disease	Whether or not an individual had a claim for ischemic heart disease in the 180 days before the event	Binary: 1 = Yes 0 = No
Cardiomyopathy	Whether or not an individual had a claim for cardiomyopathy in the 180 days before the event	Binary: 1 = Yes 0 = No
Active user of SABA	Whether or not an individual was an active user of SABA at the time of the event	Binary: 1 = Yes 0 =No
Active user of OCS	Whether or not an individual was an active user of OCS at the time of the event	Binary: 1 = Yes 0 =No
Active user of ICS	Whether or not an individual was an active user of ICS at the time of the event	Binary: 1 = Yes 0 =No
Active user of LABA	Whether or not an individual was an active user of LABA at the time of the event	Binary: 1 = Yes 0 =No

TABLE VI: STUDY VARIABLES (continued)

Variable	Measure	Operation
Active user of LTMA	Whether or not an individual was an active user of LTMA at the time of the event	Binary: 1 = Yes 0 =No
Active user of MCS	Whether or not an individual was an active user of MCS at the time of the event	Binary: 1 = Yes 0 =No
Active user of immunomodulators	Whether or not an individual was an active user of immunomodulators at the time of the event	Binary: 1 = Yes 0 =No
Active user of xanthines	Whether or not an individual was an active user of xanthines at the time of the event	Binary: 1 = Yes 0 =No
Active user of antiarrhythmic agents	Whether or not an individual was an active user of antiarrhythmic agents at the time of the event	Binary: 1 = Yes 0 =No
Active user of antibacterials	Whether or not an individual was an active user of antibacterials at the time of the event	Binary: 1 = Yes 0 =No
Active user of antidepressants	Whether or not an individual was an active user of antidepressants at the time of the event	Binary: 1 = Yes 0 =No
Active user of antiemetics	Whether or not an individual was an active user of antiemetics at the time of the event	Binary: 1 = Yes 0 =No
Active user of antihistamines	Whether or not an individual was an active user of antihistamines at the time of the event	Binary: 1 = Yes 0 =No
Active user of antimalarial agents	Whether or not an individual was an active user of at the time of the event	Binary: 1 = Yes 0 =No
Active user of antimigraine agents	Whether or not an individual was an active user of antimalarial agents at the time of the event	Binary: 1 = Yes 0 =No
Active user of antipsychotics	Whether or not an individual was an active user of antipsychotics at the time of the event	Binary: 1 = Yes 0 =No
Active user of calcium channel blockers	Whether or not an individual was an active user of calcium channel blockers at the time of the event	Binary: 1 = Yes 0 =No
Active user of cough/cold/allergy medications	Whether or not an individual was an active user of cough/cold/allergy medications at the time of the event	Binary: 1 = Yes 0 =No
Active user of opioid analgesics	Whether or not an individual was an active user of opioid analgesics at the time of the event	Binary: 1 = Yes 0 =No

TABLE VI: STUDY VARIABLES (continued)

Variable	Measure	Operation
Asthma related ED visits	Number of asthma related ED visits in the 180 days before event date	Categorical: 0 = No visits 1 = ≤ 3 visits 2 = ≥ 4 visits
SABA canisters	Number of SABA canisters dispensed in the 180 days before event date	Categorical: 0 = No canisters 1 = ≤ 3 canisters 2 = ≥ 4 canisters
Acute asthma exacerbations	Number of acute asthma exacerbations in the 180 days before event date	Categorical: 0 = No exacerbations 1 = ≤ 3 exacerbations 2 = ≥ 4 exacerbations
Use of OCS	Whether or not an individual had at least one prescription claim for OCS in the 180 days before event date	Binary: 1 = Yes 0 =No

Abbreviations: IAC – inhaled anticholinergics; SABA – short-acting beta agonists; OCS – oral corticosteroids; ICS – inhaled corticosteroids; LABA – long acting beta agonists; LTMA – leukotriene modifying agents; MCS – mast cell stabilizers; ED – emergency department

3.7 Statistical Analysis

The association between inhaled anticholinergics and arrhythmias expressed in odds ratios (OR) with 95% confidence interval (95% CI) was determined using multivariate conditional logistic regression. In developing the adjusted model, all covariates individually associated with both exposure and outcome in univariate analyses were first selected. Covariates that modified the OR estimate for exposure to anticholinergics by ≥ 10% were included in the final adjusted model.[76] Covariates in the final model included measures for severity of asthma (number of asthma related emergency department visits, number of events of acute asthma exacerbations, use of oral corticosteroids, number of SABA canisters dispensed), concomitant use of other asthma medications (SABA, inhaled corticosteroids, oral corticosteroids), comorbid conditions (ischemic heart disease, cardiomyopathy), and concomitant use of systemic drugs with anticholinergic effects (antibacterials, antidepressants, cough/cold/allergy medications, opioid analgesics). Separate analyses were conducted to determine OR estimates for exposure to ipratropium, tiotropium, and combination (ipratropium-albuterol) anticholinergics. The absolute risk of arrhythmia was assessed by two calculations: incidence rate of arrhythmia in the cohort during the observation period and the number needed to be treated for one additional patient to be harmed (NNTH). The overall incidence rate of arrhythmia in the cohort was obtained by dividing the number of arrhythmia events by the total person time from index prescription date to the last enrollment date. The NNTH is a concept of expressing the magnitude of adverse effects observed in case-control studies.[77] This number is a reflection of the number of people that need to be exposed to a treatment over a follow-up period such that one additional person is harmed by experiencing the adverse effect of the treatment.

The NNTH is calculated as follows:

$$\text{NNTH} = \frac{1}{[(OR-1)Unexposed\ event\ rate]}$$

In the formula above, OR is the adjusted odds ratio estimated and the unexposed event rate is the incidence rate of the adverse effect among the unexposed group. Unexposed event rate was calculated as the number of arrhythmia events in the IAC naïve group divided by the total person time of the group from the index prescription date to the last enrollment date.

Datasets for this analysis were generated using were generated using SAS software, Versions 9.1 and 9.2 (SAS Institute Inc., Cary, NC); all statistical analyses were conducted using STATA software, Version 11.0 (STATA Corp., College Station, TX).

3.8 Sensitivity Analysis

We conducted several sensitivity analyses to evaluate the robustness of our results from the main analysis. First, we limited the analysis to only the severe and non-severe cases of arrhythmia, to examine if IACs may be more associated with one or the other. Second, we excluded individuals who switched to inhaled anticholinergics after using a SABA in the immediate past. The assumption here was that active users of IACs who used SABA in the immediate past may be at increased risk for an arrhythmia. Specifically, we were concerned that prescribers may have switched these patients because of symptoms suggesting SABA-associated palpitations. We also re-determined the association in severe and non-severe cases excluding immediate past SABA users. Third, to account for the difference in the prevalence of cardiovascular risk factors between cases and controls, we excluded individuals with ischemic heart disease and cardiomyopathy. Fourth, in order to investigate effect modification by age, we stratified the analytic cohort by age category. Fifth, in order to determine whether the exposure to anticholinergics was associated with other systemic anticholinergic effects, we defined cases

as individuals with urinary tract infections (UTIs) (ICD-9 599.xx) and repeated the analysis. Last, in order to rule-out the possibility that our main results were influenced by unmeasured confounders or other bias we examined an outcome that we assumed would have no possible association with IAC use. Here we defined cases as individuals with a diagnosis of dental caries (ICD-9 521.xx)

4 RESULTS

4.1 Analytic Population

We identified 283,429 asthmatics who were new users of an asthma controller medicine between July 1, 1997 and April 30, 2010. Within this cohort, there were 7,656 cases of arrhythmia matched to 76,304 controls. **Figure 2** demonstrates the entry of eligible individuals into the study cohort and the attrition observed at each criterion. The analytic population was mostly female (58.8%) and older than 12 years (73.3%). Characteristics of the analytic population are described in **Table VII**. The mean (SD) age was 14.9 (5.2) years in cases and 14.1 (4.9) in controls. The median duration of follow-up for the analytic population was 458 (interquartile range, 180 – 913) days. Cases were more likely to have comorbidities that increased the risk of arrhythmias. Cases had a greater utilization of healthcare resources for asthma compared to controls. Healthcare utilization serves as a proxy measure of severity of asthma. Cases were more likely to have at least one emergency department visit for asthma (28.27% vs. 15.86% controls) and at least one acute exacerbation (14.04% vs. 7.92% controls). Compared to controls, cases were more commonly receiving other asthma medications (**Table VIII**) and also systemic drugs with anticholinergic effects as shown in **Table IX**.

Figure 2. Study cohort entry

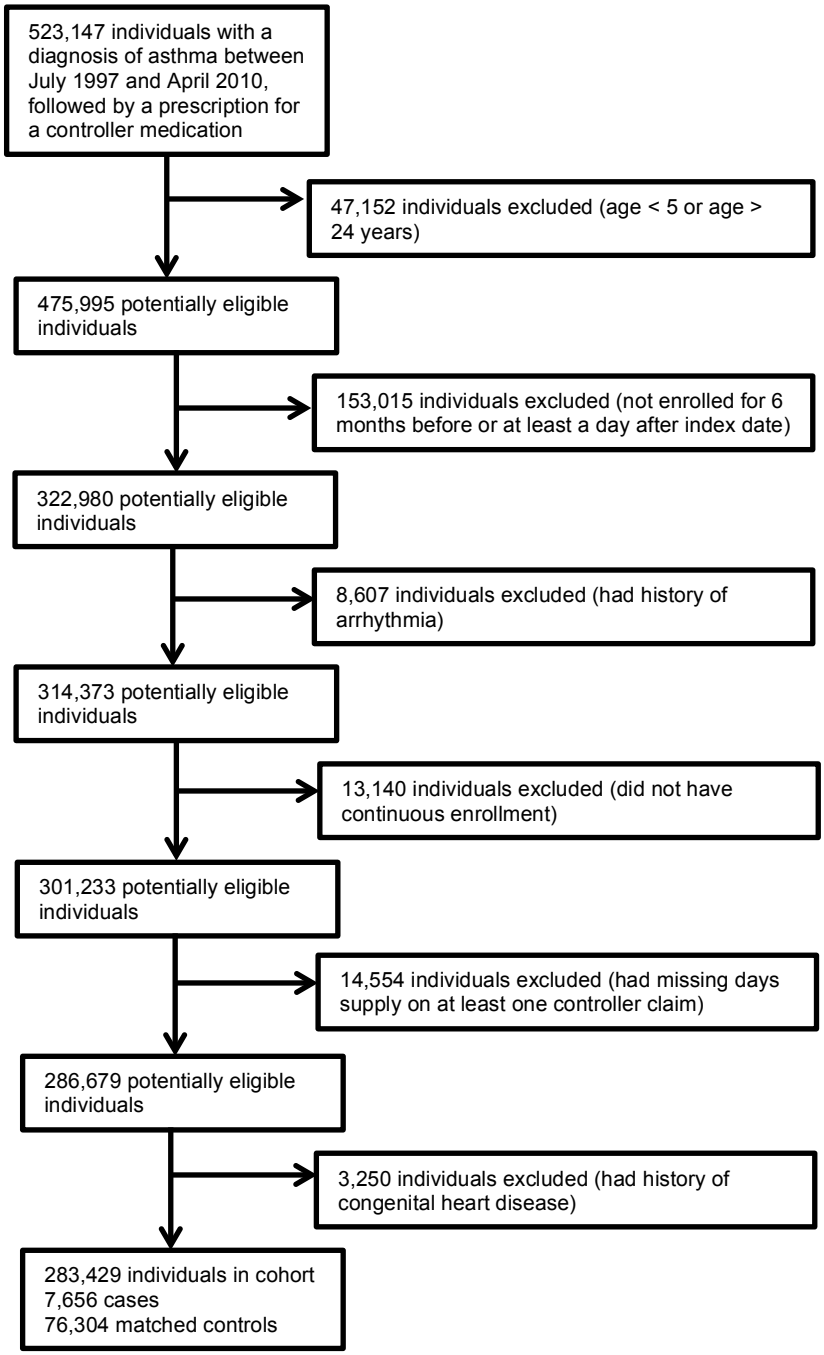


TABLE VII: CHARACTERISTICS OF THE ANALYTIC POPULATION AND ASSOCIATION WITH ARRHYTHMIA

Characteristic	Cases (n, %)	Controls (n, %)	$OR_{unadjusted}$ (95% CI)
No. of patients	7,656	76,304	--
Age, years			
5 – 11	2,044 (26.7%)	20,406 (26.7%)	--
>12	5,612 (73.3%)	55,898 (73.26%)	--
Gender			
Male	3,155 (41.21%)	31,448 (41.21%)	--
Female	4,501 (58.79%)	44,856 (58.79%)	--
Comorbidities			
Hyperthyroidism	49 (0.64%)	102 (0.13%)	4.81 (3.42 – 6.78)
Rheumatic Fever	7 (0.09%)	12 (0.02%)	5.07 (1.96 – 13.14)
Obesity	296 (3.87%)	1,317 (1.73%)	2.30 (2.02 – 2.62)
Myocarditis	2 (0.03%)	2 (0.0026%)	10 (1.40 – 70.99)
Ischemic Heart Disease	60 (0.78%)	50 (0.07%)	12.16 (8.33 – 17.74)
Cardiomyopathy	27 (0.35%)	11 (0.01%)	24.54 (12.17 – 49.48)
Components of Asthma Risk Score			
Emergency Department Visits			
0	5,492 (71.73%)	64,205 (84.14%)	Reference
<6	1,828 (23.88%)	10,946 (14.35%)	1.99 (1.88 – 2.11)
>=6	336 (4.39%)	1,153 (1.51%)	3.62 (3.18 – 4.11)
SABA Canisters			
< 6	7,500 (97.96%)	75,183 (98.53%)	Reference
>=6	156 (2.04%)	1,121 (1.47%)	1.39 (1.17 – 1.65)
Oral Corticosteroid Use	1,507 (19.68%)	9,710 (12.73%)	1.72 (1.62 – 1.83)
Marker of Asthma Severity			
Number of Acute Asthma Exacerbations			
0	6,581 (85.96%)	70,261 (92.08%)	Reference
<6	577 (7.54%)	4,564 (5.98%)	1.40 (1.28 – 1.53)
>= 6	498 (6.5%)	1,479 (1.94%)	3.75 (3.37 – 4.18)

TABLE VIII: CONCOMITANT USE OF ASTHMA MEDICATIONS AND THEIR ASSOCIATION WITH ARRHYTHMIA

Asthma medications	**Cases (n, %)**	**Controls (n, %)**	**p-Value**	**$OR_{unadjusted}$ (active use vs. others) (95% CI)**
SABA	1,144 (14.94%)	6,613 (8.67%)	<0.0001	1.97 (1.83 – 2.11)
OCS	344 (4.49%)	578 (0.76%)	<0.0001	6.64 (5.77 – 7.64)
ICS	909 (11.87%)	6,757 (8.86%)	<0.0001	1.48 (1.36 – 1.60)
LABA	496 (6.48%)	3,776 (4.95%)	<0.0001	1.37 (1.23 – 1.51)
LTMA	680 (8.88%)	5,391 (7.07%)	<0.0001	1.30 (1.19 – 1.42)
Mast Cell Stabilizers	13 (0.17%)	107 (0.14%)	0.5138	1.21 (0.68 – 2.17)
Immunomodulators	2 (0.03%)	9 (0.01%)	--	2.22 (0.48 – 10.28)
Xanthines	4 (0.05%)	24 (0.03%)	--	1.67 (0.58 – 4.80)

Abbreviations: SABA – short-acting beta agonists; OCS – oral corticosteroids; ICS – inhaled corticosteroids; LABA – long acting beta agonists; LTMA – leukotriene modifying agents;

TABLE IX: CONCOMITANT USE OF DRUGS WITH ANTICHOLINERGIC EFFECTS AND THEIR ASSOCIATION WITH ARRHYTHMIA

Drugs with anticholinergic effects	Cases (n, %)	Controls (n, %)	p-Value	$OR_{unadjusted}$ (active use vs. others) (95% CI)
Antiarrhythmic Agents	1 (0.01%)	0 (0%)	--	--
Antibacterial Agents	835 (10.91%)	3,537 (4.64%)	<0.0001	2.57 (2.37 – 2.80)
Antidepressants	701 (9.16%)	2,623 (3.44%)	<0.0001	2.87 (2.63 – 3.14)
Antiemetics	39 (0.51%)	38 (0.05%)	<0.0001	10.62 (6.75 – 16.71)
Antihistamines	506 (6.61%)	3,679 (4.82%)	<0.0001	1.41 (1.28 – 1.55)
Antimalarial Agents	11 (0.14%)	56 (0.07%)	0.0379	1.89 (0.98 – 3.63)
Antimigraine Agents	35 (0.46%)	106 (0.14%)	<0.0001	3.30 (2.25 – 4.83)
Antipsychotics	171 (2.23%)	470 (0.62%)	<0.0001	3.71 (3.10 – 4.43)
Calcium Channel Blockers	23 (0.30%)	48 (0.06%)	<0.0001	4.79 (2.91 – 7.87)
Cough/Cold/Allergy Medications	264 (3.45%)	1,416 (1.86%)	<0.0001	1.91 (1.67 – 2.19)
Opioid Analgesics	199 (2.60%)	466 (0.61%)	<0.0001	4.36 (3.68 – 5.15)

The top 3 arrhythmia diagnoses among cases were palpitations (36.8%), tachycardia (23.8%), and cardiac dysrhythmia (17.5%). **Table X** shows a complete listing of the arrhythmia diagnosis among cases. The majority of these events (83.1%) were diagnosed during or resulted in outpatient visits, the remainder being inpatient hospitalizations (8.9%) or emergency department visits (8.0%). Of the 7,656 events of arrhythmia, 1,295 were classified as severe events.

TABLE X: DIAGNOSIS OF ARRHYTHMIA IN CASES

Diagnosis in Cases	Number (%)
Atrial fibrillation	94(1.23%)
Atrial flutter	8(0.10%)
Cardiac arrest	49(0.64%)
Cardiac dysrhythmia	1(0.01%)
Cardiac dysrhythmias, unspecified	1,338(17.48%)
Instantaneous death	1(0.01%)
Other premature beats	82(1.07%)
Other rhythm disorders	1,081(14.12%)
Other specified cardiac dysrhythmias	7(0.09%)
Palpitations	2,816(36.78%)
Paroxysmal supraventricular tachycardia	104(1.36%)
Paroxysmal tachycardia, unspecified	20(0.26%)
Paroxysmal ventricular tachycardia	35(0.46%)
Premature beats, unspecified	29(0.38%)
Sinoatrial node dysfunction	115(1.50%)
Sudden death, cause unknown	3(0.04%)
Supraventricular premature beats	46(0.60%)
Tachycardia, unspecified	1,818(23.75%)
Unexplained death within 24h of symptoms	3(0.04%)
Ventricular fibrillation	3(0.04%)
Ventricular flutter	3(0.04%)

Active exposure to any IAC was observed in 0.69% cases and 0.18% controls (**Table XI**). Active exposure to ipratropium was observed in 0.65% cases and 0.16% controls. Active exposure to tiotropium was observed in 0.04% cases and 0.02% controls. Active exposure to combination anticholinergics was observed in 0.37% cases and 0.12% controls. Among the active users of any IAC, 0.53% cases and 0.12% controls were on a high average daily dose (>0.114mg ipratropium equivalents).

TABLE XI: EXPOSURE TO INHALED ANTICHOLINERGICS

Exposure	Cases (n, %)	Controls (n, %)
Use of Any Inhaled Anticholinergic		
Active Users	53 (0.69%)	137 (0.18%)
Immediate Past Users	32 (0.42%)	154 (0.20%)
Past Users	69 (0.9%)	418 (0.55%)
Use of Ipratropium		
Active Users	50 (0.65%)	125 (0.16%)
Immediate Past Users	29 (0.38%)	146 (0.19%)
Past Users	66 (0.86%)	400 (0.52%)
Use of Tiotropium		
Active Users	3 (0.04%)	12 (0.02%)
Immediate Past Users	3 (0.04%)	8 (0.01%)
Past Users	3 (0.04%)	19 (0.02%)
Use of Combination Anticholinergic (Ipratropium-Albuterol)		
Active Users	28 (0.37%)	94 (0.12%)
Immediate Past Users	18 (0.24%)	104 (0.14%)
Past Users	37 (0.48%)	253 (0.33%)
Dosage (measured in Ipratropium equivalents, mg;1 mg Ipratropium = 1.32*10-4 mg Tiotropium)		
Active Exposure (Average daily dose)		
Low dose (≤ 0.114mg)	10 (0.13%)	40 (0.05%)
High dose (>0.114mg)	41 (0.54%)	93 (0.12%)
Missing	2	4

4.2 Association between Use of Inhaled Anticholinergics and Arrhythmias

Results from the main analysis assessing the association between active use of inhaled anticholinergics and the risk of arrhythmias are listed in **Table XII**. Compared with nonusers, active users of any IACs were at an increased risk of arrhythmia (OR_{adj}, 1.56, 95% CI [1.08-2.25]) after adjusting for confounding factors. A dose response relationship was established among the active users of IACs. Those who received more than 0.114mg of ipratropium equivalents as an average daily dose were at the highest risk for arrhythmia (OR_{adj}, 1.69 [1.10-2.59]) while those who received less than or equal to 0.114mg ipratropium equivalents were at a non-significant increased risk (OR_{adj}, 1.22 [0.53-2.65]) compared to nonusers. Risk of arrhythmia differed by specific anticholinergic, with ipratropium users at a higher risk (OR_{adj}, 1.59 [1.08–2.33]) compared to tiotropium users (OR_{adj}, 1.20 [0.29–4.89]) and combination ipratropium and SABA users (OR_{adj}, 1.20 [0.74–1.94]).

TABLE XII: RISK OF ARRHYTHMIA ASSOCIATED WITH IAC USE

Exposure	**Cases (n,%)**	**Controls (n,%)**	**$OR_{Unadjusted}$ (95% CI)**	**$OR_{Adjusted}$ (95% CI)**
Exposure to IAC				
Nonusers	7,502 (97.98%)	75,595 (99.07%)	Reference	Reference
Active Users	53 (0.69%)	137 (0.18%)	3.95 (2.86 – 5.44)	1.56 (1.08-2.25)
Immediate Past	32 (0.42%)	154 (0.20%)	2.10 (1.43 – 3.09)	1.24 (0.82 – 1.87)
Past Users	69 (0.9%)	418 (0.55%)	1.66 (1.28 – 2.15)	1.16 (0.88 – 1.52)
Exposure to Ipratropium				
Nonusers	7,511 (98.10%)	75,633 (99.12%)	Reference	Reference
Active Users	50 (0.65%)	125 (0.16%)	4.08 (2.92 – 5.68)	1.59 (1.08 – 2.33)
Immediate Past	29 (0.38%)	146 (0.19%)	2.00 (1.34 – 3.00)	1.16 (0.75 – 1.79)
Past Users	66 (0.86%)	400 (0.52%)	1.66 (1.27 – 2.16)	1.15 (0.87 – 1.52)
Exposure to Tiotropium				
Nonusers	7,647 (99.88%)	76,265 (99.94%)	Reference	Reference
Active Users	3 (0.04%)	12 (0.02%)	2.50 (0.70 – 8.85)	1.20 (0.29 – 4.89)
Immediate Past	3 (0.04%)	8 (0.01%)	3.75 (0.99 – 14.13)	2.52 (0.62 - 10.08)
Past Users	3 (0.04%)	19 (0.02%)	1.58 (0.46 – 5.33)	1.33 (0.38 – 4.63)
Exposure to Combination IAC				
Nonusers	7,573 (98.91%)	75,853 (99.40%)	Reference	Reference
Active Users	28 (0.37%)	94 (0.12%)	3.01 (1.96 – 4.60)	1.20 (0.74 – 1.94)
Immediate Past	18 (0.24%)	104 (0.14%)	1.74 (1.05 – 2.88)	1.02 (0.60 – 1.75)
Past Users	37 (0.48%)	253 (0.33%)	1.47 (1.03 – 2.08)	1.05 (0.73 – 1.52)
Dosage of Active Exposure				
Not Exposed	7,605 (99.33%)	76,171 (99.82%)	Reference	Reference
Low Dose (≤0.114mg)	10 (0.13%)	40 (0.05%)	2.55 (1.27 – 5.11)	1.22 (0.53 – 2.65)
High Dose (>0.114mg)	41 (0.53%)	93 (0.12%)	4.50 (3.10 – 6.52)	1.69 (1.10 – 2.59)

We created two alternate exposure windows to assess the association between IACs and arrhythmias. In one analysis, we defined individuals as exposed if they were a recent user of any IAC (i.e. they were either an active or an immediate past user). Compared to past users and those who have never used any IAC, recent users were at an increased risk for arrhythmia (OR_{adj}, 1.41 [1.07 - 1.85]). In another analysis, we defined individuals as exposed if they ever used any IAC (i.e. they were either an active or an immediate past or a past user). Compared to those who have never used any IAC, those who have ever used any IAC were at an increased risk for arrhythmia (OR_{adj}, 1.28 [1.05 - 1.55]) as shown in **Table XIII** below.

TABLE XIII: RISK OF ARRHYTHMIA ASSOCIATED WITH IAC USE (ALTERNATIVE DEFINITIONS OF EXPOSURE)

Alternative definition of exposure to any IAC	**Cases, n (%)**	**Controls, n (%)**	**$OR_{Unadjusted}$ (95% CI)**	**$OR_{Adjusted}$ (95% CI)**
Past use or never	7,571 (98.89%)	76,013 (99.62%)	Reference	Reference
Recent (Active or immediate past use)	85 (1.11%)	291 (0.38%)	3.00 (2.3 - 3.84)	1.41 (1.07 - 1.85)
Never	7,502 (97.99%)	75,595 (99.07%)	Reference	Reference
Ever (Active or immediate past or past use)	154 (2.01%)	709 (0.93%)	2.22 (1.86 – 2.65)	1.28 (1.05 – 1.55)

Overall, the absolute risk of arrhythmia in our cohort was low. Incidence rate in the cohort (n = 283,429) during the observation period between the index prescription date and the last enrollment date was 1.314 in 100 person years. The unexposed event rate in this study cohort was the incidence of arrhythmia in the IAC naïve group in 1 person year, which was 0.0127 Therefore, 140.6 people need to be treated with IACs in 1 person year for 1 person to experience an arrhythmia event

4.3 Sensitivity Analyses

The increased risk of arrhythmia in active users of IACs as determined in the main analysis was observed across various sensitivity analyses (**Figure 3**). Active use of IAC had a higher magnitude of increased risk of arrhythmia in severe events of arrhythmia (OR_{adj}, 3.39 [1.39-8.24]) compared to non-severe (OR_{adj}, 1.38 [0.91-2.10]) events. In the analysis excluding SABA to IAC switchers, we identified 11 individuals (5 cases (2 severe, 3 non-severe) and 6 controls) who have used SABA within 30 days of the event but were active users of IAC at the time of the event. After excluding these individuals, active users of IAC were still at an overall increased risk of arrhythmia (OR_{adj}, 1.39 [0.95-2.04]), though non-significant. However, the magnitude of effect differed in severe and non-severe events, with active exposure having a larger effect in severe events (OR_{adj}, 2.96 [1.15-7.60]) than in non-severe events (OR_{adj}, 1.26 [0.82-1.96]).

There were 148 individuals with ischemic heart disease or cardiomyopathy. The prevalence of these diseases varied among cases and controls with cases being more likely to have these diseases. Excluding the 148 individuals (87 cases) with ischemic heart disease or cardiomyopathy, the OR_{adj} for active use of IACs was 1.52 [1.05-2.21].

To investigate potential effect modification by age, we stratified the analytic cohort by age category. The younger cohort (age 5-11 years) comprised of 2,044 cases and 20,406

controls. Active exposure to any IAC was observed in 0.39% cases and 0.12% controls. The older cohort (ages 12 and above) comprised of 5,612 cases and 55, 898 controls. Active exposure was observed in 0.80% cases and 0.20% controls. In the analyses, we found that increased risk of arrhythmias among active users of IACs had a higher magnitude among individuals aged 12 and older (OR_{adj}, 1.72 [1.15-2.57]) compared to those in the 5-11 years category (OR_{adj}, 1.03 [0.41-2.60]).

In order to determine the association between urinary tract infections and exposure to IAC, 18,457 cases and 183,881 controls were drawn from a cohort of 269,303 eligible individuals built using the same criteria as used in the primary study cohort. Active exposure to IACs was observed in 0.33% cases and 0.18% controls. Adjusting for confounding factors identified in the main model, the OR_{adj} for active use of IACs was 1.09 [0.80-1.49].

For determining the association between dental caries and exposure to IAC, 1,401 cases and 13,961 controls were identified from a cohort of 292,256 eligible individuals built using the same criteria as used in the primary study cohort. Active exposure to IACs was observed in 0.36% cases and 0.21% controls. Adjusting for confounding factors identified in the main model, active exposure to IAC was associated with a slightly reduced but not significant risk of dental caries (OR_{adj}, 0.92 [0.27-3.16])

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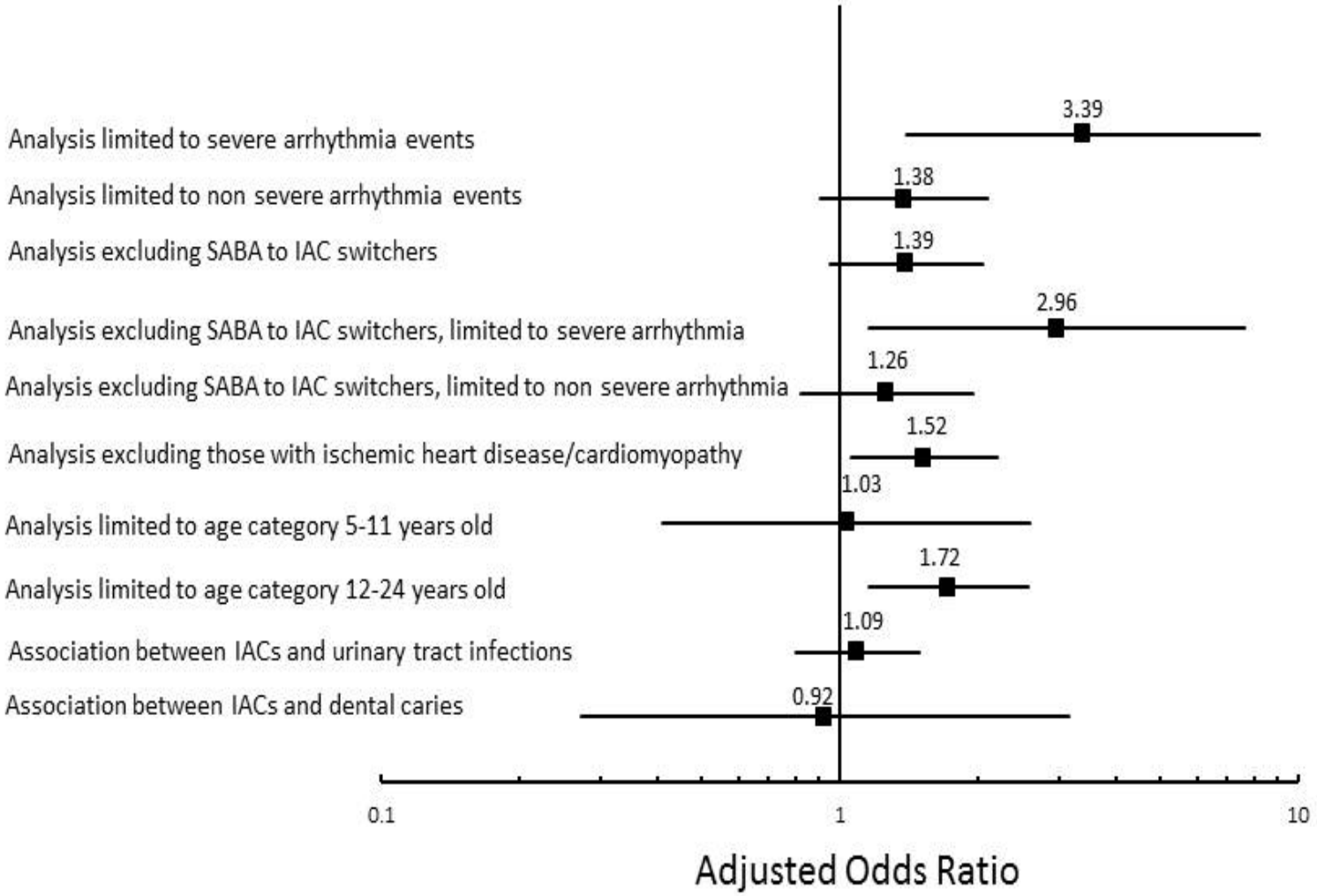
Figure 3: Results from various sensitivity analyses



5 DISCUSSION

5.1 Discussion of the Results

In a cohort of patients aged 5 to 24 with asthma that were new users of controller medicines, we found that active use of IACs was associated with an increase in the risk of arrhythmia. The effect was stronger in individuals aged 12 to 24, and was more strongly associated with severe events of arrhythmia. Further, among individuals who were actively exposed to IACs, those on a higher average daily dose were at greater risk for arrhythmia. One can speculate that the dose response relationship demonstrated is indicative of a drug effect. We also found that active users of ipratropium were at a higher risk (OR_{adj}, 1.59 [1.08–2.33]) than those on tiotropium (OR_{adj}, 1.20 [0.29–4.89]). However, our ability to identify a difference in their association with arrhythmias was limited due to low sample size with respect to tiotropium.

Both ipratropium and tiotropium have a rapid onset of action. While ipratropium is short acting (duration of action ~ 5 hours; elimination half-life ~ 2 hours), tiotropium is long acting (duration of action ~ 24 hours; elimination half-life ~6 days). Therefore, we speculated that any potential systemic drug effect leading to arrhythmias would largely be observed among those who were actively exposed. Consistent with our speculations, we found that the effect gradually diminished and even became non-significant in those who were immediate past or past users. This was also true in the analysis where alternative definitions of exposure were employed. The overall effect was lower for recent users compared to active users and least for those who were ever exposed to IACs in the 180 days before the event date.

Our results are consistent with recent literature reporting a positive association between the use of IACs and cardiovascular related adverse events and deaths in patients with COPD. For example, the Lung Health Study reported an increase in the occurrence of supraventricular

tachycardia and cardiovascular deaths (p = 0.027) among smokers randomized to smoking cessation and ipratropium bromide compared to placebo.[56] In a retrospective cohort study of patients with newly diagnosed COPD, Ogale et al reported a 29% increase in risk of cardiovascular adverse events of acute coronary syndrome, heart failure, or dysrhythmia (HR_{adj},1.29 [1.21-1.38]) associated with exposure to anticholinergics.[60] Barr et al in a systematic review reported a higher frequency of arrhythmias in tiotropium exposed compared to placebo (OR_{adj} 2.33, [1.11-4.88]).[57] A meta-analysis conducted by Singh and colleagues reported an increased risk of myocardial infarction (OR_{adj},1.52 [1.04-2.22]), and cardiovascular death (OR_{adj},1.92 [1.23-3.00]) among COPD patients on IACs.[18] However, these studies were conducted on COPD patients with inherent cardiovascular risk factors, such as advanced age and smoking histories.

Our study tested the association between IACs and arrhythmias in a younger population with asthma who were at a considerably lower risk for cardiovascular diseases. The fact that we still observe an increased risk lends creditability to a potential drug effect.

SABAs are the bronchodilators of choice in asthma. It has been shown that some people are more prone to experiencing cardiovascular effects of beta-agonists compared to others. A genetic polymorphism causes some individuals to be homozygous for arginine at the beta adrenoreceptors which in turn causes them to have an altered pharmacological response to beta agonists.[78-81] Therefore, individuals who are switched to IAC therapy from SABAs could potentially be systematically different than those not so treated. Specifically, we were concerned that any effect observed with anticholinergics may be due to confounding by indication where those patients using an IAC were at highest risk for events. This may be particularly true among patients that were switched to an IAC because they may have experienced cardiovascular side effects from their SABA. To evaluate this, we excluded patients switching from SABA to IAC in our analysis. We found that our effect estimates went down by 17% and were no longer

statistically significant. This does not exclude the possibility of confounding by indication explaining the results. However, when this was repeated for severe versus non-severe cases, severe cases were still found to be at a significant increased risk associated with active exposure to IACs pointing towards a potential anticholinergic drug effect.

Generating further evidence pointing toward a drug effect were results from our analysis excluding individuals with comorbid heart disease. These individuals are at a higher risk for arrhythmia. There were more cases with ischemic heart disease and cardiomyopathy than controls. Therefore we were concerned that the association could be confounded by inherent risk factors. However, on excluding them, active exposure to IACs was still associated with a 52% increased risk for arrhythmia.

UTIs may be indicative of systemic anticholinergic effect as anticholinergics have been shown to induce urinary obstruction by impairing muscle contraction[82] and one of the risk factors for developing urinary tract infections is urinary obstruction.[83] Moreover, there is evidence in the literature that shows a positive association between the use of anticholinergics and urinary retention and urinary tract infections.[15,84,85] When we examined UTIs as an outcome, we found that active exposure to IACs was associated with a non-significant 9.4% increase in risk. A significant positive association in this analysis could have strengthened our conclusions of a drug effect. However, it must be noted that the overall exposure to inhaled anticholinergics was low. The low sample size in the exposed group may have rendered our study under powered to detect an association. Moreover, we recorded the same covariates that were confounders in the association between inhaled anticholinergics and arrhythmias and ran the same model in assessing the relationship between urinary tract infections and inhaled anticholinergics. Significant risk factors such as diabetes, auto-immune disorders, sickle cell disease were not accounted for in this analysis.

5.2 Study Limitations

There are several limitations to our study and our findings need to be interpreted with caution. First, we defined exposure based on prescription fills recorded in administrative data which is not indicative of the actual use of drugs. We classified active users of anticholinergics into low and high dose groups based on the quantity dispensed. Hence, it is possible that individuals were misclassified if they were not taking the medication as dispensed. However, it is not likely that this misclassification was different between cases and controls.

Second, we did not have either lung function information or frequency of symptoms which is a true measure of asthma severity, itself a confounder in the association between IACs and arrhythmia. Exacerbations of asthma carry a theoretical arrhythmogenic risk owing to multiple pathophysiological events in an episode of exacerbation such as hypoxia, hypercapnia, elevated intrathoracic pressures which in turn have an effect on cardiac blood return. We did however adjust for proxy measures such asthma related emergency department visits, SABA canisters dispensed, and number of acute exacerbations in the 180 days before the event date.

Third, while we adjusted for potential confounders in our study design, we cannot be certain of the absence of potential biases resulting from unknown and unmeasured confounding. We conducted a sensitivity analysis that determined the association between IACs and an outcome that was known not to be associated with IACs – dental caries, expecting to see a null effect. We found an 8% decrease in risk. This risk is small and not statistically significant but at the same time, it does not render our main analysis to be free from unknown and unmeasured confounding.

5.3 Study Strengths and Implications

The findings in this study are particularly important given recent efforts focused on evaluating tiotropium efficacy in treating patients with asthma. The TALC study found that combination tiotropium and ICS was superior to doubling the dose of ICS but not inferior to combination LABA and ICS.[12] Thus, providers may begin to consider tiotropium as an alternative to increasing dose of ICS in patients with inadequately controlled asthma. While the TALC results are promising from an efficacy standpoint, the sample size is inadequate for alleviating potential safety concerns associated with anticholinergic treatment in asthma. Given the event rate observed in this analysis and that TALC included 174 patients, it is not surprising there were not any cardiovascular adverse events reported in the TALC study. While our investigation was observational in nature, it was conducted using a large population-based dataset that included a broader range of patients and a longer duration of follow-up compared to randomized controlled trials investigating the effectiveness of IACs in chronic asthma management. Therefore when coupling our findings with recent efficacy evidence, it is clear more evidence is needed on IAC safety in asthma patients prior to widespread adoption for chronic asthma management.

Importantly, TALC focused on tiotropium and not ipratropium which was the predominant medication in this analysis. We had limited sample size with respect to patients exposed to tiotropium. Nevertheless, our results raise important questions about the cardiovascular safety profile of anticholinergics in patients with asthma.

5.4 Conclusions

In this study we found that the use of inhaled anticholinergics is associated with an increased risk of arrhythmia in children, adolescents, and young adults with asthma. Individuals aged 12 to 24 years and those prescribed ipratropium bromide were at the highest risk for arrhythmia. Anticholinergics have previously been shown to increase the risk of cardiovascular

adverse events in the COPD literature. The fact that we observed an increased risk in a population that is comparatively at a lower cardiovascular risk points toward a probable drug effect. It is also important to note that we found a low absolute risk of arrhythmia. Nevertheless, this is a potentially significant adverse effect, and health care providers need to be advised before incorporating anticholinergics in the management of asthma. Further research needs to be conducted in other study populations where arrhythmias are more common to fully understand potential risks.

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