Arrhythmia risk associated with the use of bronchodilators in patients with chronic obstructive pulmonary disease: cohort studies and methodological issues

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ABSTRACT

Whereas first line therapy for chronic obstructive pulmonary disease (COPD) usually includes a short-acting bronchodilator, there are suggestions that these agents may increase the risk of cardiac arrhythmias. In this thesis, we first assessed the risks associated with short-acting β-agonists (SABA), long-acting β-agonists (LABA), ipratropium bromide (IB), and methyl xanthines (MX) within a cohort of COPD patients using the health databases of Saskatchewan. In order to confirm these findings and to address some methodological issues we then replicated this analysis within a larger cohort of patients using the health databases of Quebec.

Our first study cohort consisted of 6,018 adults aged 55 and older, newly treated with bronchodilator medications. We found that new users of both IB and LABA increased the risk of arrhythmia (RR 2.39 [95% CI 1.42-4.05] and (RR 4.55 [95% CI 1.43-14.45] respectively). When the cohort was restricted by excluding subjects who had recently either been hospitalised or experienced an exacerbation, the elevated risk associated with the new use of IB persisted (RR 3.65 [95% CI 1.72-7.74]), an effect was detected with new use of MX (RR 5.17 [95% CI 1.38-19.30]), but there was insufficient power to detect an effect associated with the new use of LABA.

Due to both power issues and the limited availability of LABA within the Saskatchewan data, we replicated the analysis in a larger new-user cohort of 76,661 Quebec adults aged 67 and over. This study confirmed our earlier results, with an elevated risk of arrhythmia associated with the new use of both IB and LABA (RR 1.43 [95% CI 1.08-1.88]) and (RR 1.54 [95% CI 1.00-2.36]) respectively, as well as with new use of SABA (RR 1.28 [95% CI 1.02-1.61]).

Finally, using marginal structural models, we demonstrated that both exacerbations of COPD as well as minor non-event arrhythmias were moderate time-dependent confounders within this setting.

In conclusion, we found that new use of bronchodilators in COPD, particularly IB and LABA, was associated with an increase in the risk of cardiac arrhythmias. We also demonstrated the method by which the time-dependent confounder status of specific model covariates may be evaluated.

RÉSUMÉ

Puisque la thérapie de première ligne pour la Maladie Pulmonaire Obstructive Chronique (MPOC) inclut normalement l'utilisation d'un bronchodilatateur à action rapide, il a été suggéré que ces agents pourraient augmenter le risque d'arythmie cardiaque. Dans cette thèse nous avons évalué dans un premier temps, et ceci grâce à la banque de données sur la santé de la Saskatchewan, les risques associés aux agonistes β à action rapide (BACA), ceux à action prolongée (BALA), le bromide d'ipratropium (BI), et les méthylxanthines (MX) à l'intérieur d'une cohorte de patients souffrant de MPOC. Dans le but de confirmer ces observations et d'adresser certains problèmes méthodologiques particuliers aux données de la Saskatchewan, nous avons ensuite répété cette analyse au sein d'une cohorte plus nombreuse de patients issus des banques de données sur la santé du Québec.

Notre première cohorte était formée de 6,018 adultes âgés de 55 ou plus et nouvellement traités avec des médicaments bronchodilatateurs. Nous avons trouvé un risque accru d'arythmie cardiaque chez les nouveaux usagers d'BI et de BALA (RR 2.39 [95% IC 1.42-4.05]et RR 4.55 [95% IC 1.43-14.45 respectivement]) Lorsque la cohorte a été restreinte par le biais de l'exclusion des sujets qui avaient soit été hospitalisés ou qui avaient eu une exacerbation de leur MPOC, le risque accru associé au nouvel usage de bromide d'IB a persisté (RR 3.65 [95% IC 1.72-7.74]) et un effet associé au nouvel usage d'MX a été décelé RR 5.17 [95% IC 1.38-19.30]). Pourtant, il n'y avait pas assez de puissance pour déceler un effet associé au nouvel usage de BALA.

À cause des problèmes de puissance et le fait que les BALA étaient listés sous le programme de médicaments d'exception aux sein des donnés de Saskatchewan, nous avons répété cette analyse au sein d'une plus grande cohorte de nouveaux usagers consistant de 76,661 Québécois adultes âgé de 67 ou plus. Cette analyse de la cohorte québécoise a confirmé nos résultats antérieurs avec un risque accru

d'arythmie associé avec un nouvel usage d'BI et de BALA (RR 1.43 [95% IC 1.08-1.88]) et (RR 1.54 [95% CI 1.00-2.36] respectivement, et par ailleurs, signale une augmentation du risque associé avec le nouvel usage de BACA (RR 1.28 [95% IC 1.02-1.61]).

Dans le troisième article, nous avons démontré, grâce aux modèles structurels marginaux, qu'en ce contexte, les exacerbations de MPOC ainsi que les mineures silencieuses ont étés les variables confondantes qui varient dans le temps.

En conclusion, nous avons trouvé que le nouvel usage de bronchodilatateurs pour la MPOC, plus particulièrement avec le BI et les BALA, était associé à une augmentation du risque d'arythmies cardiaques. Nous avons aussi démontré la méthode grâce à laquelle il est possible d'évaluer si les covariables spécifiques à un modèle sont en réalité les variables confondantes qui varient dans le temps.

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PREFACE

Outline

This thesis consists of seven chapters, including an introduction, a review of the literature, methodological considerations, three manuscripts intended for publication in peer-reviewed journals, and an overall summary and conclusion.

The three manuscripts will be submitted to various clinical and methodological journals. As a result, some material which is presented in the introduction, the review of the literature and the methods sections is repeated in the manuscripts. In order to facilitate reading, one comprehensive bibliography to cover references contained within all chapters has been produced and is located at the end of this document. Supplementary tables are placed in the Appendix.

This thesis was prepared in accordance with the McGill University rules and regulations for manuscript-based theses from the "Thesis, e-Thesis, Non-thesis Information" section of the Graduate and Postdoctoral Studies Office (GPSO), entitled "Thesis Preparation and Submission Guidelines." found at: http://www.mcgill.ca/gps/current/programs/thesis/guidelines/preparation/

Contributions of Authors

This thesis is the result of research which I initiated and developed. It is a manuscript-based thesis which includes three co-authored papers. In all cases, I (the candidate) was responsible for conceptualizing, designing, analysing, and reporting research results. Dr. Samy Suissa, my supervisor, secured funding for and made available the two large databases which formed the source populations from which each of my two cohorts were assembled. Study design, cohort assembly, variable creation, database management and all statistical analyses for the purposed of each of the three studies presented here were entirely performed by me. My co-authors, all of whom were members of my thesis committee, provided me with methodological and clinical advice throughout the process.

I, the candidate, therefore accept all responsibility for the scientific quality of the research.

Statement of Originality

Several aspects of the work presented in this thesis represent original contributions to the literature. This thesis includes the first observational studies to specifically examine the risks of cardiac arrhythmias associated with the use of bronchodilators within a COPD population. These first two studies are also, to the best of my knowledge the first observational COPD pharmacoepidemiological study of cardiovascular risks explicitly designed in order to avoid both immortal and immeasurable time-biases. The third paper in this thesis is an original attempt to provide a method by which the time-dependent confounder status of specific model covariates may be evaluated. Finally, this third paper also represents the first time that a marginal structural model has been used to assess risks associated with the use of respiratory medications

Disclaimer

This thesis is based in part on non-identifiable data provided by the Saskatchewan Department of Health and by the Régie de l'assurance Maladie du Québec (RAMQ). The interpretation and conclusions contained herein do not necessarily represent those of the RAMQ, the Government of Québec, the Government of Saskatchewan, or the Saskatchewan Department of Health.

Acknowledgements

As my friend and esteemed colleague, Dr. Helen McNamara has said, "It takes a village to produce a PhD thesis", and my experience has been no different. There are, therefore quite a few people who deserve acknowledgment and thanks.

First and foremost, I must thank my supervisor, Dr. Samy Suissa without whom none of this would have been possible. He is an excellent teacher who is passionate about pharmacoepidemiology which drove me in pursuit of excellence. Dr. Suissa was unconditionally supportive throughout this process and I am immensely grateful for having had the opportunity to have had him as my mentor.

I would like to thank my clinical committee members, Dr. Pierre Ernst and Dr. James Brophy whose collaboration and expertise in matters both clinical and methodological contributed substantially to the improvement of this research. I am also grateful to them for helpful suggestions they have made in preparing the manuscripts for publication.

I would like to thank Dr. Robert Platt, who in addition to being on my committee has also been my teacher and mentor for many years. Since the early days when I approached him as a student interested in conquering General Estimating Equations (which resulted in the creation of the student/faculty workgroup on clustered and correlated data), Dr. Platt has always been a resource for learning, support, and encouragement. Whenever I became excited about a novel methodological technique, he would assist me in finding a project in which it could be explored. He has made significant contributions to this thesis and to my development as a researcher, and I can not thank him enough for all his efforts on my behalf.

I also must thank Chris Delaney for sharing his enthusiasm for epidemiology, and for being someone with whom to this day I can always discuss all things "epi". In addition to being a good friend, for the past four years he has played a pivotal role in my development as a researcher. It was Chris who convinced me to attend my first meeting of the causal inference work group which, by chance, was a presentation by Dr. Ian Shrier titled "Confounders vs. confounding". In a nutshell, it turned my epidemiology world on its head, and spawned the first MSM project in the department (conducted by myself, Chris, and Sheila McDonald and Dr. Platt). Clearly, I would have a very different third manuscript in this thesis if it had not been for him.

I would like to thank all the members of the Department of Epidemiology, Biostatistics, and Occupational health for providing such a stimulating and challenging learning environment. A special thank you to Dr. Claire Infante-Rivard for her wonderful teaching and for reminding me what it was that I loved about epidemiology.

I would like to thank Caroline Hebert for both taking the time to translate the previous version of my thesis abstract into French, and as well for having been there as a peer, my comprehensive exam study partner as well as my partner for several years in departmental politics within the Epidemiology and Biostatistics Students' Society (EBSS), for being so kind to get pregnant with her first child within days of my doing same so that we could experience yet another life-defining event together, and for being my long-running office mate at the RVH.

I would like to thank Diane Gaudreau, Dr. Suissa's long-standing assistant, and expert in all things administrative for helping me navigate the Hospital and University waters all these years, and for being a friend. A special thank you also goes out to Sophie Dell'Aniello for always taking the time to share her knowledge and experience with the various databases with which we, at the Pharmacoepidemiology Unit, are so fortunate to work.

Before coming to McGill, I was a PhD student in health Management at Ben Gurion University of the Negev. A health economist working in Israel, I was funded by my place of work, Maccabi Healthcare Services, to pursue a PhD. I would be therefore be completely remiss if I did not thank them as well as Dr. Dov Chernichovsky for convincing me to return to academia and for agreeing to supervise my research. I must also thank Drs. Ilana Shoham-Vardi and Drora Fraser at BGU for being my first epidemiology mentors and for encouraging me to pursue pharmacoepidemiology here at McGill.

I would like to thank Dr. Pierre Tousignant at the Direction de la santé publique for offering me my first research job in Montreal. I would also like to thank Dr. Robyn Tamblyn for her mentorship during my earlier years in the programme.

Several funding agencies deserve mention. I would first like to thank the McGill University Health Centres Research Institute (formerly Royal Victoria Hospital Research Institute) for awarding me my first research fellowship at the start of this thesis journey. I must thank the Canadian Institutes of Health Research (Formerly, the Medical Research Council of Canada) for funding me through a doctoral research award and for the grant through which database acquisition was made possible for this research. I would also like to thank the Fonds de la Recherche en santé du Québec (FRSQ) for supporting the Phamacoepidemiology Unit at the Royal Victoria Hospital.

To my wonderful mother Dr. Marilyn Wilchesky, and my in-laws Bob and Karen Nathan, and to my extended family, thank you for all the help and support you have provided me over the past years in pursuit of this degree.

Finally, to my husband Lorne and daughter Samantha, thank you for all your love and encouragement, and for always believing in me, even when I didn't think I could persevere. Thank you for all the times that you didn't complain when I had to work instead of play. My name may be on this thesis, but we did this together.

DEDICATION:

This thesis is dedicated in loving memory to my father,
Dr. Isaac Leonard Wilchesky, MD, CCFP, FCFP
1933-2004

He was a healer and wonderful human being.
As a child, I distinctly remember him lamenting the frustration he felt in trying
to diminish the suffering of his patients with COPD.
His clinical input in this research was sorely missed,
and I, of course, will miss him forever.

1 Chapter 1: Introduction

1.1 Chronic Obstructive pulmonary disease

Chronic Obstructive pulmonary disease (COPD) is the term that's been given for a group of chronic respiratory conditions that obstruct the airways in the lungs. Predominantly related to past smoking behaviour, this disease is devastating: once symptoms of breathlessness begin, the damage to the lungs, for the most part can not be reversed, and there is no cure. Treatments for COPD focus primarily on controlling symptoms and preventing further damage. Recently termed "an orphan condition" due to it having been largely overlooked by scientists and governments,[1] COPD represents a major health issue in Canada and will likely remain so for decades[2].

An estimated $123 million dollars were spent on medications for COPD in Canada in 1998, with respiratory drugs representing 12% of all drug expenditures in Canada in 1998, second only to the 19% spent on drugs for cardiovascular diseases.[3] While these drugs are prescribed in the hopes of improving the quality of life of these patients, it is possible that these medications can increase the risk of cardiovascular outcomes such as arrhythmia.

1.2 Pharmacoepidemiology

Before being approved, drugs must be tested by the manufacturer according to strict procedures. After a given drug receives approval for use in Canada, the monitoring of its effectiveness and side effects (called adverse drug reactions, or ADRs) continues. In some cases, an ADR can be uncommon in which case it may not be detected during clinical trials, but only after the drug has been marketed and subsequently prescribed to the larger group of total users within a population.[4-6]

To further complicate matters, in some cases, drugs may be developed for the treatment of one disease, but then used post-market in the treatment of others. This is the case for drugs used in the treatment of COPD which were first developed as therapeutic agents for asthma. The efficacy of these agents in the younger asthmatic populations with less comorbidity and less severe more reversible airflow obstruction was easy to demonstrate given the size of the benefit that could be obtained.[7]When these same medications were transposed for drug therapy of COPD, however, the benefits were less obvious and the side effects more frequent.

Pharmacoepidemiology is the discipline which studies the use of and the effects of drugs in large numbers of people.[8] It was borne out of an increase in public concern regarding drug safety which highlighted the importance of drug surveillance and the application of epidemiologic techniques used to measure drug risks.[9] Since most (if not all) drugs have at least some adverse effects, the purpose of pharmacoepidemiological research is to detect and share information about them such that prescribing practices may be optimized and public health is protected. It is in this spirit that we set out to conduct this research.[10]

1.3 Rationale and Objectives

This body of research relates to the issue of post marketing evaluation of the safety of drug use using observational designs. More specifically, our goal is to evaluate the arrhythmia risk associated with the use of bronchodilators, the class of drugs which provide symptomatic benefit, in patients with COPD.

This thesis consists of three manuscripts, the first two of which set out to answer this specific study question within two separate COPD populations. Specifically, the risks associated with three temporal categories of drug use are compared to no use for short and long-acting β-agonists, short-acting anticholinergics, and methyl xanthines within two new user COPD cohorts generated from databases from the

Provinces of Saskatchewan and Québec. In the third manuscript, we address a methodological issue pertaining to exacerbations of COPD as well as minor arrhythmias which are both important risk factors for serious cardiac arrhythmias. These two variables could hypothetically fulfill the definition of a time-dependent confounder, seeing that they are (a) a time-dependent risk factors for the outcome that also predict exposure, and (b) past history of exposure also affects subsequent level of the risk factor. We suggest a method for determining time-dependent exposure status using marginal structural models and comment on whether or not it would be appropriate to include these covariates within a model used to answer our original research question using standard statistical techniques.

2 Chapter 2: Review of the Literature

2.1 COPD, Definition

Chronic obstructive pulmonary disease (COPD) is a disease spectrum caused by an abnormal inflammatory response in the lungs to noxious particles and gases.[11] It is characterized by progressive airflow obstruction that is not fully reversible in response to bronchodilators, systemic manifestations, and increasing frequency and severity of exacerbations.[12;13] The two main components of COPD are two related diseases, chronic bronchitis and emphysema, with these two conditions often occurring concomitantly, at least to some degree.[14]

Emphysema is characterized by destruction of the alveoli, distal airways, and surrounding lung tissue. The walls between the alveoli become distended, lose their elasticity and rupture, allowing air to become trapped in the enlarge spaces. This leads to poor lung function in which the exchange of gases (oxygen taken into the bloodstream, and carbon dioxide released) is impaired.[15] Patients with emphysema typically experience shortness of breath on exertion. In comparison, chronic bronchitis is characterized by hypertrophy of the mucous glands in the trachea, bronchi and bronchioles which results in excessive mucous production, inflammation of airway walls, and smooth muscle hypertrophy.[16] The resulting cough with sputum production and narrowing of the airways causes difficulty in breathing (dyspnea) and a higher susceptibility to more frequent infections.[15]

The diagnosis of COPD is based on clinical, functional, radiographic, biochemical, and cellular/histopathologic findings[11]. Although no single and uniform clinical standard for the definition of COPD exists, one functional definition suggested by the Canadian Thoracic Society guidelines is that it is represented by a ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) of < 0.7.[17;18] Using spirometry data as a basis for stratifying the disease as to severity, mild, moderate and severe COPD is classified by comparing actual FEV1 to predicted values.

2.2 COPD burden, epidemiology

Chronic obstructive pulmonary disease (COPD), represents a major health issue in Canada and will likely remain so for decades.[2] COPD is listed by Statistics Canada as being the fourth leading cause of death in Canada after cancers, diseases of the heart, and cerebrovascular disease,[19] and further evidence suggests that COPD as a cause of death has been significantly under-reported. Worldwide, it is expected by 2020 to be the third leading cause of death.[20] Although it has been estimated that approximately 714,000 Canadians have been diagnosed with the disease, evidence also suggests that more than 50% of patients remain undiagnosed in the community.[2]

Morbidity and mortality from COPD is continuing to rise and the resulting economic burden is enormous.[12] The results of the *Confronting COPD International Survey*[21] estimated the direct cost of the disease at $1,997.81 per patient with over half this amount due to hospitalizations. With an additional indirect cost component to the economy of $1,198.18, the total cost per COPD patient to society per year is $3,195.97.[22] When multiplied by our conservatively estimated number patients with COPD, the cost to our nation is 2.3 billion dollars annually.

2.3 Aetiology and natural history of COPD

Risk factors for COPD include both environmental exposures as well as host factors, with the disease usually resulting from a host/environmental interaction.[23] Environmental factors include air pollution (both indoor and outdoor), poverty, low socioeconomic status,, alcohol, and exposure to occupational dusts and chemicals[23] however, COPD has often been tagged *a smokers disease* owing to the fact that the most powerful environmental exposure at cause is tobacco smoke. The absolute risk of developing clinically significant COPD among continuous smokers without initial disease has been recently estimated to be at least 25%,

which is larger than previously reported [24] with smokers losing lung function at an annual rate approximately twice that of nonsmokers.[25]

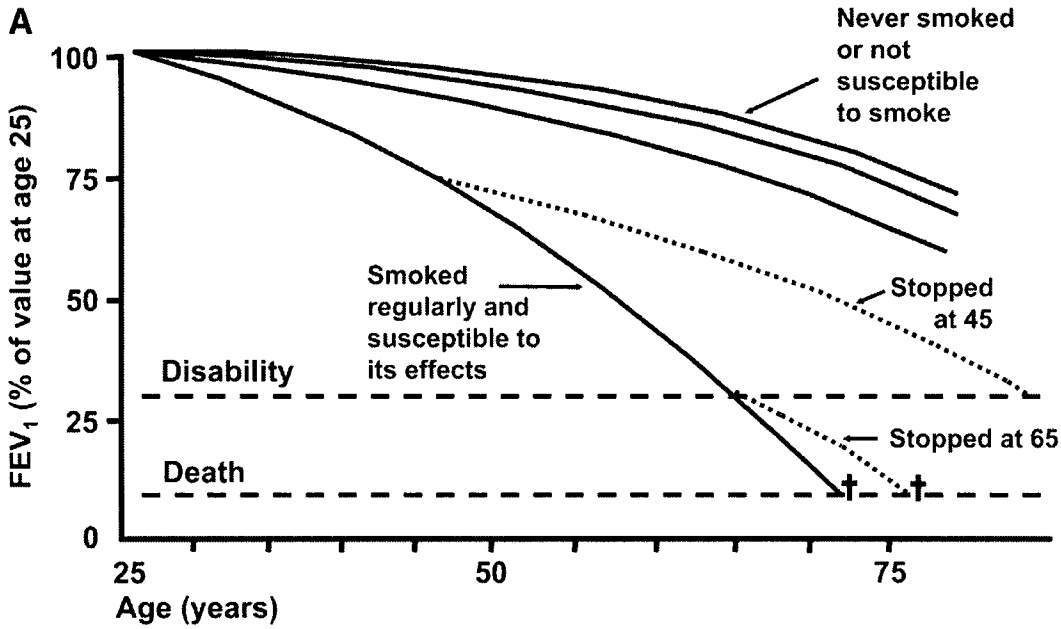


Figure 2-1 The natural history of lung function as measured by FEV1. Lung function usually peaks at approximately 25 years of age and then declines by 20-30mL/year. The rate of decline is accelerated in smokers but that rate returns to normal after stopping to smoke. The graph shows that the FEV1 of a 50-year old smoker is at approximately 70% of that predicted for a 5-year old, and indicates an approximate lung age of an individual in their early 70s. (Reproduced with written permission from the *British Medical Journal*, this graph was originally published in Fletcher C and Peto R. The natural history of chronic airflow obstruction. *BMJ* 1977;1:1645-1648).

Among the host factors, the best established is α_1-antitrypsin (AAT) deficiency, where AAT is a protein which protects the lungs from neutrophil elastase, an enzyme released from white blood cells.[23;26] The risk of panlobular emphysema, for instance, is increased in individuals with low AA concentrations, particularly when they are exposed to other environmental factors, such as smoking.[27] Other host factors include low birth weight, childhood respiratory infection, high IgE (Atopy), bronchial hyper-responsiveness and a family history of COPD.[28]

More and more, COPD is being regarded in a broader context as being more than a disease of the lungs.[29] The associated systemic inflammation[30] is related to chronic heart failure, metabolic syndrome and other chronic diseases, which may contribute to the clinical manifestations and natural history of COPD[29]. In other

words, in its later stages, COPD becomes a challenging and complex multisystem disorder requiring multi-modal interventions and pharmacotherapy. [31]

2.4 Exacerbations

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) have a range of clinical consequences including progressive respiratory failure,[32-35] and their prevention is now recognised as a primary goal of COPD therapy.[36] The term essentially implies a perception on the part of the patient as being in a worse state than usual,[37] but they are a state for which there was no universally accepted definition by the end of our study follow up. Clinical trials which measure exacerbations as their primary outcome have been inconsistent in their definition, and by extension their identification of AECOPD which has lead to conflicting and biased results.[38] Most published definitions encompass some combination of three clinical findings: worsening dyspnea, increase in sputum purulence, and increase in sputum volume.[39] In 2003, the Canadian Thoracic Society proposed that AECOPD be defined as "a sustained worsening of dyspnea, cough or sputum production leading to an increase in the use of maintenance medications and/or supplementation with additional medications" where the term "sustained" is used in order to distinguish these episodes from the normal day-to day variations in symptoms.[12]

Exacerbations are a feature of moderate to severe COPD,[40] as they tend to occur infrequently in the earlier stages of the disease.[41;42] They are independently associated with increased mortality[43] and with accelerated rates of decline in pulmonary function,[44;45] and they are a relevant factor in determining quality of life among this population[46]. It is expected that on average, COPD patients will experience two to three disease exacerbations per year requiring either a health care provider visit, an emergency department (ED) visit, or a hospitalization.[46;47]

Current evidence indicates that bacterial infection (either primary or secondary to an antecedent viral infection of the lower airway) causes approximately 40–50% of AECOPD, [48] with an increased risk associated with non-typeable haemophilus influenzae, streptococcus pneumoniae and moraxella catarrhalis[49]. It is believed that another 30% have a viral etiology, with rhinoviral infections influenza, parainfluenza, respiratory syncytial virus, and adenovirus being implicated.[48] The remainder are thought to be cause by reactions to environmental stimuli, or other pathophysiologic processes. [50]

In conjunction with changes to bronchodilator therapy, pharmacological treatment of AECOPD usually involves a 7-10 day course of antibiotics[36;50-56] in order to address the bacterial component of AECOPD. A 7-14 day course of oral or parenteral corticosteroid therapy is usually prescribed in most moderate to severe patients.[55;56]

2.5 How COPD differs from Asthma

COPD and asthma are similar with respect to some of the outward clinical symptoms such as coughing and wheezing. They are, however, two distinct conditions which can be compared in terms of disease onset, frequency of symptoms, characteristics of exacerbations and reversibility of airway obstruction.

2.5.1 Age at Onset

The onset of COPD most usually occurs among patients who are 40 years of age or older[18] and who are either current or former smokers. The onset of asthma, in comparison, typically occurs during childhood or adolescence.[57]

2.5.2 Reversibility

With treatment, asthma patients often have near-normal lung function and are symptom-free between exacerbations[57] often presenting with spirometry values that normalize during their disease course[18]. COPD patients, experience progressive worsening of their condition with exacerbations, and whereas their

spirometry values may improve, they do not normalize, and patients experience persistent symptoms.[18] Where the airflow obstruction associated with COPD is only partially reversible with bronchodilator use,[58] smoking cessation is the only intervention that has been shown to affect the natural history of COPD.[25;59] Smoking cessation, however, has limited benefit among patients presenting with advanced disease and severe airflow obstruction, underlining the importance of early detection of COPD.

2.5.3 Characteristics of Exacerbations:

Exacerbations of asthma, characterized by recurrent wheezing, shortness of breath, chest tightness and cough, often have identifiable triggers such as allergens, viral agents, cold air or exercise.[57] In contrast, at least one-half of exacerbations in COPD patients are either caused by infection or caused by viral agents which in turn cause infection, with other triggering factors including congestive heart failure, pulmonary embolism, and irritants.[18]

2.5.4 First-Line Pharmacotherapy:

Most asthma patients are treated with inhaled corticosteroids (ICS) with the addition of a bronchodilator on an as-needed basis to control symptoms.[57] In contrast, first-line maintenance therapy for COPD patients consists of bronchodilators, with the role of ICS alone in COPD being controversial.[18] Randomized clinical trials have been unable to establish a protective effect of ICS monotherapy on lung function decline in COPD.[40-42;60] Although some observational studies have reported a reduction in all cause death[61] and hospital readmission[62] from ICS monotherapy, they have been found to suffer from immortal time bias, a fundamental methodological flaw which renders their results questionable.[63-65]

2.5.5 Effect of anticholinergics

The often greater bronchodilating effect of anticholinergic drugs compared with adrenergic agents in COPD is opposite to the result in patients with asthma. It has been hypothesized that this greater response to anticholinergics among patients

with COPD vs. asthma might be due to increased parasympathetic tone in the airways, increased mucociliary clearance, or the decrease in bronchial secretions.[66] In addition, there has been an observed decline in response to SABA among the elderly[66] which may result from a progressive loss of beta receptors with age[67].

2.5.6 Poorly Reversible Asthma Is Not COPD

Although the primary distinction between COPD and asthma pertains to reversibility, there are cases when untreated or undertreated airway inflammation in asthma results in some degree of "fixed" or non-nonreversible airway obstruction.[68-70] Asthma with a non-reversible airway obstruction component, however, should not be confused with COPD as their histologies have been found to be distinct. Although activated T-lymphocytes play a central role in the pathogenesis of both conditions, the predominant T-lymphocyte subset in asthma is the CD4+ type-2, while in COPD it is the CD8+ type-1.[71] Indeed there are also patients who suffer from both COPD and asthma.

COPD and asthma can therefore be shown to be quite distinct disease entities. Despite these differences, however, COPD is often misdiagnosed as asthma, resulting in inappropriate treatment and suboptimal patient outcomes.[72] A 1993 survey of 75 Canadian primary care physicians revealed that they had a low level of suspicion for COPD and that they prescribe similar medications for COPD and asthma even though the appropriate treatments differ.[73]

2.6 The role of bronchodilators in COPD

The goal of COPD therapy is to improve patient-centered outcomes of dyspnea, activity limitation, and quality of life. Pharmacotherapy can not prevent the development of COPD or slow down the rate at which pulmonary function deteriorates,[59] which is why interventions such as smoking cessation, vaccination against influenza (in order to prevent exacerbations), and pulmonary rehabilitation are crucial to any comprehensive COPD management programme.[28;55;56;74;75] Bronchodilator medications, which relax the muscles around the bronchi to

improve expiratory flow and lung emptying with each breath, however, are central to the symptomatic management of COPD[12;17].

While structural abnormalities that lead to fixed irreversible airflow obstruction comprise part of the COPD disease definition, it is the reversible airflow component that serves as the basis for bronchodilator therapy.[76] Unfortunately, the pattern of response to bronchodilators among individual patients can be inconsistent and may vary a great deal[77] even on a day-to day basis[78]. Even if the response to bronchodilator therapy is at best moderate, it should be noted that among patients with severe obstruction, even small improvements in airflow can be regarded as clinically beneficial, particularly if it reduces the effort of breathing by decreasing gas trapping and hyperinflation.[79]

One means by which airway smooth muscle tone is maintained is by balancing activity between the sympathetic (adrenergic) and parasympathetic (cholinergic) autonomic nervous systems.[80] One can achieve bronchodilation, therefore, either by stimulating the adrenergic receptors with sympathomimetic drugs, or by inhibiting the action of acetylcholine at muscarinic receptors with anticholinergic agents.

Bronchodilators come in either short or long-acting formulations, the former which are active for about 4 to 6 hours and are now used mostly when needed for the relief of persistent or worsening symptoms, and the latter which last about 12 or more hours and are generally prescribed for daily use in order to prevent or reduce symptoms. Administration can be via both inhaled and oral routes (methyl xanthines, for example, can only be administered orally), but inhaled therapy is generally preferred as this directly targets the airways and is usually associated with fewer adverse effects.[12]

The three major classes of bronchodilators for use in COPD are β-agonists (sympathomimetics), anticholinergics and methyl xanthines with (as stated

previously) inhaled bronchodilators are often preferred because of the rapid response and minimal systemic side effects as compared with oral agents.[79]

2.6.1 Bronchodilators by Class:

Table 2-1 presents the list of bronchodilators by class and by duration of action:

Table 2-1 Bronchodilators by drug class

Bronchodilator Class	Drugs
Short-acting β_2-Agonists (SABA)	Fenoterol Isoproterenol Orciprenaline Metaproterenol Pirbuterol Procaterol Salbutamol (Albuterol) Terbutaline
Long-acting β_2-Agonists (LABA)	Formoterol Salmeterol Aformoterol†
Short-acting Anticholinergics	Ipratropium Bromide Oxitropium Bromide†
Long-acting Anticholinergics	Tiotropium Bromide†
Methyl Xanthines	Theophylline Aminophylline Oxtriphylline

† These bronchodilators were not available for study.

2.6.1.1 Short-acting β_2-agonists:

The adrenergic system consists of adrenergic receptors which can be divided into α- and β- receptors on the basis of their response to various adrenergic activating and blocking agents[81]. Both β_1 and β_2- receptors are found in varying concentrations in the heart and lung, as well as in peripheral tissues throughout the body, but β_2- receptors are predominately located in bronchial and vascular smooth muscle, peripheral leukocytes, and adrenergic nerves.[82] β_2-agonists bind with these β_2 receptors which line the cell walls of the lungs and the bronchioles thereby resulting in opening the airways and reducing dyspnea.

Short-acting inhaled β_2– agonists have a rapid onset of action in terms of increasing forced FVC and mean FEV1[83] and produce bronchodilatation within minutes reaching a peak at 15–30 min.[28] Results from two similar meta-analyses which included crossover-design randomized trials of this class of drugs found that regular use of inhaled SABA for the management of stable COPD was associated with improvements in post-bronchodilator lung function, and a decrease in breathlessness.[84;85] There were no significant differences detected, however, when comparing SABA use to placebo in either sputum production, cough, or exercise tolerance.[85]

SABA are generally regarded as appropriate first or second-line therapy, and are prescribed on a PRN (as needed) basis or as maintenance therapy, depending on the severity of symptoms. In fact, a 2002 systematic review of worldwide COPD clinical practice guidelines determined that 59% of all guidelines recommended SABA as first line monotherapy in patients with intermittent symptoms or during 'early phase' COPD.[86]

2.6.1.2 Long-acting β_2-agonists:

One of the advantages of treatment with long-acting agents is the convenience it provides by reducing the number of doses required per day, which in turn might increase adherence.[87;88] Salmeterol and formoterol are two such drugs which comprise the class of potent long-acting β_2 -agonists (LABAs) and have a 12-hour or greater duration of action.[89-92] Their onset of action are 20 minutes and less than 10 minutes respectively with peak effects occurring at between one to two hours for both compounds.[93;94]

LABAs have been associated with more sustained improvements in pulmonary function,[89;91;95-98] chronic dyspnea,[91;96-98] and quality of life[96;99] when compared with short-acting bronchodilators, although no significant difference in exercise tolerance has been detected[91;100;101]. Perhaps the most promising finding

pertaining to these drugs, however, is that they have been associated with a reduction in the number of exacerbations among patients with stable, poorly reversible COPD.[102]

2.6.1.3 Short-acting anticholinergics:

Ipratropium bromide, a short-acting anticholinergic drug, is a synthetic atropine-like compound which inhibits the constriction of bronchial smooth muscle by competitive antagonism with muscarinic receptors.[103] Ninety percent of the inhaled drug remains in the upper airways and mouth and is eventually excreted by the body, making it a drug that is poorly absorbed and thereby resulting in fewer unintended systemic effects.[104] Ipratropium does not cross the blood-brain barrier, it possesses a wide margin of safety, and no major acute or chronic toxicity has been observed in patients treated with doses within the therapeutic range. [104] The onset of action of ipratropium is somewhat slower when compared to that of short-acting β-adrenergic agents with peak bronchodilation occurring at 60-90 minutes (as compared with SABA which reach a peak at 15–30 min).

Several COPD studies conducted in the 1980s indicated that the level of bronchodilatation achievable with anticholinergic agents was at least equal to or greater than that produces by SABAs.[105-107] with ipratropium producing a longer duration of action [108] A 1991 review conducted by Chapman et al pointed out that of 38 published studies which compared anticholinergic agents and SABA on various spirometric parameters, that all but two found the anticholinergic agents to be at least equal or superior.[109] The results of the Lung Health Study, however showed that regular treatment with ipratropium resulted in only a relatively small improvement in FEV_1 which was not sustainable after treatment was discontinued, and that ipratropium did not affect the long-term decline in FEV1[59].

The 2006 Cochrane Systematic Review, (a meta-analysis including eleven randomized controlled trials which were published predominantly in the 1990s)

comparing ipratropium and SABA therapy in patients with stable COPD concluded that no major differences between the responses to either class of bronchodilator were evident either when prescribed alone or in combination, and recommended that the prescribing choice be individualized based on which agent results in the most symptomatic improvement.[110] This conclusion corresponds in most part with Canadian Thoracic Society guidelines recommendations regarding short-acting bronchodilator choice. [12;18;74]

An important benefit of this class of bronchodilator was determined by a large retrospective study which found that the inclusion of ipratropium bromide as part of a COPD drug treatment regimen was associated with a lower rate of exacerbations.[111] The most frequently cited benefit of treatment with short-acting anticholinergics, however, is the fact that they had been found to be associated with fewer side effects.[112] For all these reasons, ipratropium bromide is often considered to be an advantageous initial therapy choice for maintenance regimens.

Oxitropium bromide is an other anticholinergic medication with a slightly longer duration of action than ipratropium (at least 8 hours versus 4-6 hours).Skorodin, 1986 1413 /id} It should be noted, however, that the company which manufactures Oxitropium bromide never made application for its approval in North America.[113]

2.6.1.4 Long-acting anticholinergics:

Tiotropium bromide is a new, once-daily long-acting anticholinergic bronchodilator which reduces dyspnea and chronic obstructive pulmonary disease exacerbation frequency and improves health status in COPD.[114] Tiotropium has been shown to have a greater impact on improving lung function, reducing the frequency of exacerbations, the need for rescue medications, and quality of life as compared with placebo,[114] ipratropium bromide,[115;116] and salmeterol[117;118]. This drug was approved for use in the USA in September 2002,[119] and in Canada in January 2003[120].

2.6.1.5 Methyl Xanthines:

Methyl xanthines, the class of bronchodilators which includes include theophylline, aminophylline, and oxtriphylline, were among the first bronchodilators to be used to treat obstructive lung diseases[121], but have fallen out of favor in recent years and relegated to third-line therapy [122;123]. Although the bronchodilating effects of these drugs are well established, the mechanism by which these effects occur are not yet fully understood. The major therapeutic benefit of theophylline, for example, has been attributed to its phosphodiesterase inhibitor activity, which inhibits the degradation of cyclic adenosine monophosphate (cAMP).[124] Some other hypothesized mechanisms of action, however, include the inhibition of prostoglandins, increased cellular calcium uptake and distribution, stimulation of release of endogenous catecholamines, increases in endogenous secretion of cortisol, "positive inotropic" effect on the heart.

The 2002 Cochrane systematic Review which examined the benefits of oral theophylline in COPD from twenty randomized controlled trials concluded that while it has a modest effect on FEV1 and FVC as well as levels of oxygen and carbon dioxide, that there is limited information on its effect on symptoms, exercise capacity or quality of life.[124]

2.6.1.6 Combination therapy:

In addition to mono therapy, different classes of bronchodilator or a bronchodilator and an inhaled corticosteroid can be combined with one another in the pursuit of improved symptomatic relief.

The combination of both ipratropium and SABA has proven to take advantage of both the rapid onset of action of the adrenergic agents and the prolonged action of the anticholinergic[125], resulting in maximum reversibility of airflow obstruction[126]. In addition, since (for example) combinations of anticholinergics

and β_2-agonists at sub maximal doses will produce an additive effect,[127-129] it is possible to prescribe each component bronchodilator using a reduced dose thereby avoiding unintended side-effects.[125]

In the mid to late 1990s, products combining LABAs with an inhaled corticosteroid were approved for use and distributed in Canada. In three large studies it was found that the combination of either budesonide/formoterol or salmeterol/fluticasone in a single inhaler improved lung function, decreased symptom scores, and reduced the number of exacerbations per patient per year than either agent alone or than placebo.[130-132] Finally, the recently published results of the TORCH study suggested that the combination of salmeterol 50μg plus fluticasone may reduce the rate of decline of FEV_1 in patients with moderate to severe COPD, thus slowing disease progression.[133]

2.7 Guidelines- controversy, options, changes over time

The last twenty years have seen dramatic changes in both the availability of bronchodilators for use in pharmacotherapy as well as in the published guidelines for the management of patients with COPD. A 2002 article which compared published international guidelines concluded that the level of variation and ambiguity pertaining to specific recommendations might contribute to both the under diagnosis and suboptimal treatment of COPD.[86]

Figure 2-2 presents a timeline of first line COPD pharmacotherapy clinical guidelines eminating from the Canadian Thoracic Society (CTS)[12;79], the American Thoracic Society (ATS)[55;58;134;135], the British Thoracic Society (BTS)[136], The European Respiratory Society (ERS)[28;55] as well as from Global Initiative for Chronic Obstructive Lung Diseases (GOLD)[17]. The first practice guidelines were published by the American Thoracic Society in 1986 and recommended that first-line treatment for stable COPD with a SABA with the addition of a xanthine or an inhaled anticholinergic if necessary.

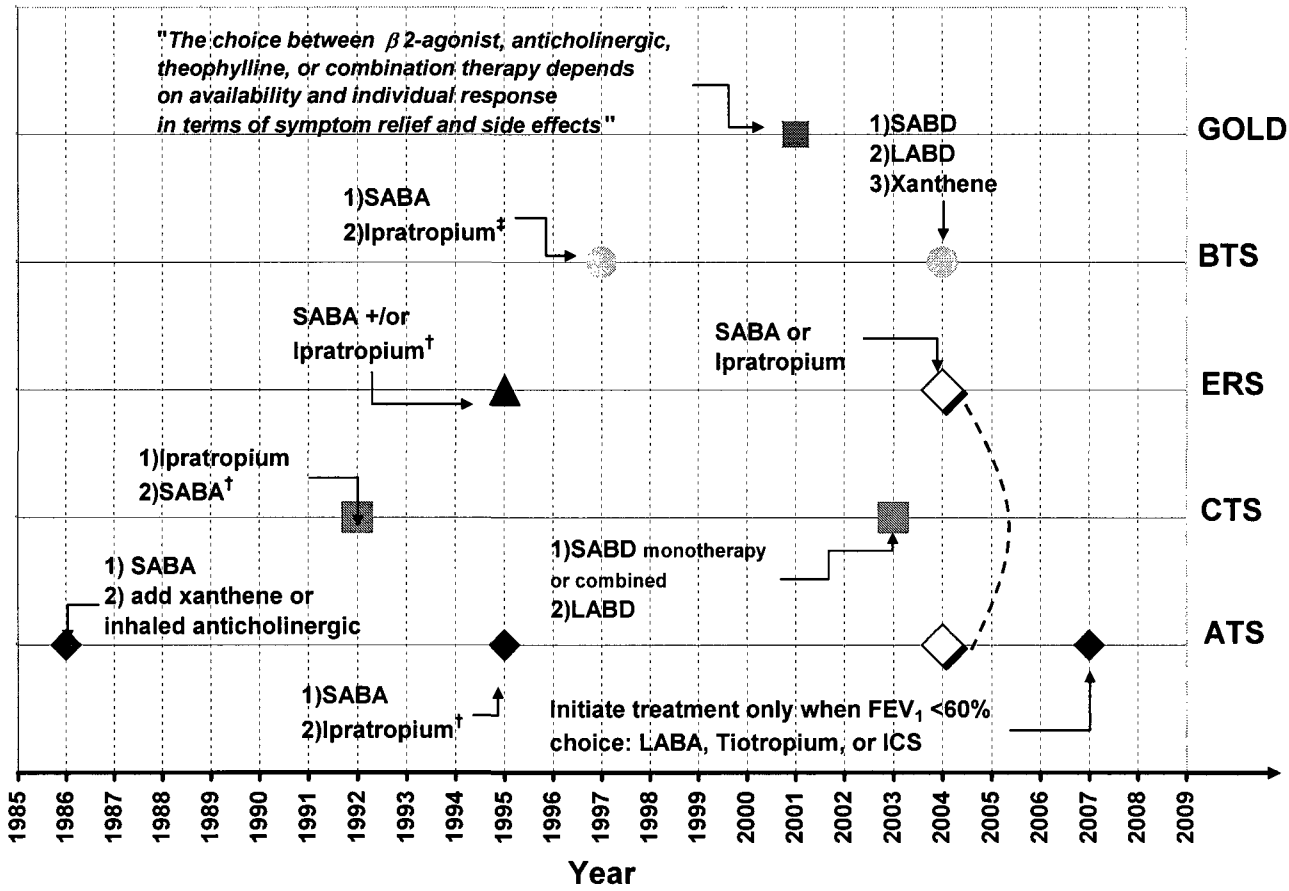


Figure 2-2 Timeline of relevant COPD clinical guidelines and their recommendations for initial therapy 1986-2007 Ordering signifies preference for intial treatment, if stated; † indicates that xanthene therapy is recommended; ‡ indicates that there is no firm recommendation regarding xanthene therapy. The 2004 guidelines produced by the ATS and the ERS were a joint statement and therefore corresponds to one document.

During the 1990s, the increasing role of ipratropium bromide featured prominently, with ipratropium recommended as either first or second line therapy. Long-acting bronchodilators saw mention beginning in 2001 as per the GOLD guidelines, which included both short and long-acting β_2-agonists as agents which should be tried using a stepwise increase in treatment depending on disease severity. Current Canadian guidelines state that optimal pharmacotherapy of COPD is guided on an individual basis by assessment of level of disease severity and frequency of exacerbations.[18]

2.8 Arrhythmia- a brief overview

The heart is a four chambered muscular organ that serves as the primary pump or driving force within the circulatory system. The heart's ability to pump blood is produced via an intrinsic electrical conduction system which causes the chambers of the heart to contract in proper sequence. [137]

Cardiac arrhythmia is the name for different conditions that cause the heart to beat too slowly, too quickly, or irregularly. Arrhythmias are usually categorised by two features: 1) the area of the heart from which the event originates; and 2) the rhythm and speed with which the heart beats. Ventricular arrhythmias originate in the two lower chambers (called the ventricles) of the heart, and supraventricular arrhythmias originate in the structures above the ventricles, mainly the atria, which comprise the hearts upper two chambers. In terms of the heart rate itself, bradycardia is the term given to a slow heart rate of less than 60 beats per minute. Conversely, tachycardia implies a very fast heart rate, and is defined by the heart beating faster than 100 beats per minute. Fibrillation is the term given to a most serious form of arrhythmia, which is characterised by rapid uncoordinated beats, which are produced via contractions of individual heart-muscle fibres.

The electrocardiogram (ECG) is a recording of the electrical activity of the heart[138], and is most commonly conducted cardiovascular diagnostic procedure, particularly for the diagnosis of acute coronary syndromes, intraventricular conduction disturbances and arrhythmias.[139] Essentially all cells located within the heart can originate their own electrical activity which is then transmitted along a conduction pathway of specialized cells.[138] As the heart undergoes cycles of wave activity called depolarization and repolarisation, the generated electrical currents are spread not only within the heart, but also throughout the body, which is then detected by the ECG. The different waves that comprise the ECG are labeled by the letters P through U, each representing a portion of the sequence of depolarization and re-polarization of the atria and ventricles. Normally, as the electrical impulse moves through the heart, this results in the heart contracting at a

rate of about 60 to 100 times a minute, with each contraction of the ventricles representing one heartbeat.[140] A typical ECG tracing is shown in Figure 2-3 which illustrates the P-wave, the PR interval, the QRS complex, the J-joint, ST-segment, T-wave, and the Q-T interval.

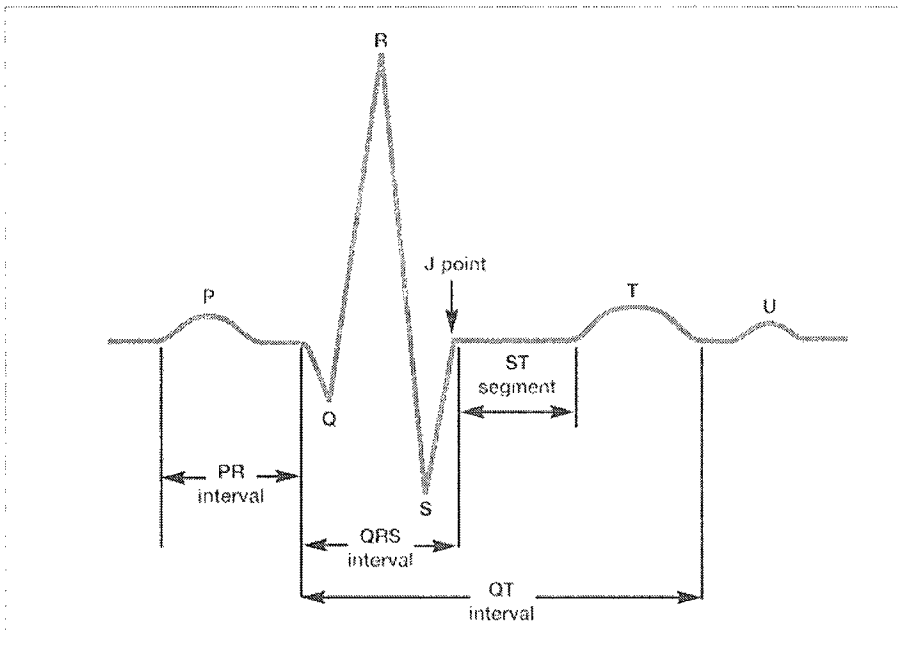


Figure 2-3 The basic pattern of electrical activity across the heart as shown via electrocardiogram.

Atrial fibrillation(AF) is the term for the arrhythmia characterised by the quivering rather than contracting of the atria, rendering the heart unable to pump all the blood. AF is the most prevalent sustained cardiac arrhythmia,[141] with an estimated hospitalisation rate of 582.7 per 100,000 population in Canada[142], and an incidence which has been shown to increase sharply with age[143;144]. Adding to the burden is the fact that AF causes significant morbidity and mortality, including heart failure, and stroke, the latter which occurs when the un-pumped produces blood clots in the chambers of the heart.

Whereas atrial arrhythmias are more prevalent, the more dangerous arrhythmias are those which originate from the ventricles. The most lethal of arrhythmias are

ventricular tachycardia and ventricular fibrillation, as they have been shown to cause approximately 84% of cases of sudden death among ambulatory patients who died while wearing Holter monitor devices.[145] An additional 16% of sudden deaths among these subjects were found to be the result of bradyarrhythmias.[145]

A detailed description of the twelve most common arrhythmia types including information pertaining to their epidemiology, risk factors, etiology and prognosis are provided at the end of this chapter in Table 2-3.

2.9 The Cardiovascular disease (CVD) / COPD connection

Cardiovascular diseases and COPD share several significant risk factors, such as smoking, and advanced age.[146] Furthermore, there is strong epidemiologic evidence to indicate that reduced FEV_1 which is a measure of lung function reflecting the severity of COPD, is itself a significant independent risk factor for cardiovascular (CVD) mortality.[147;148] Some sources, in fact, suggest it may be as strong a predictor of mortality from CVD as total serum cholesterol.[149] In addition, the reduction in physical activity caused by respiratory illness can also be a risk factor for CVD.

In a recent Canadian study, it was estimated that after adjustment for cardiovascular risk, the odds ratios (95% confidence interval) of arrhythmia, angina, acute myocardial infarction and congestive heart failure associated with having COPD were 1.8 (1.6-1.9), 1.6 (1.5-1.8), 1.6 (1.4-1.8), and 3.8 (3.6-4.1) respectively.[150] The fact that CVD is more frequent in COPD patients than in the general population may represent a burden greater than that of lung disease itself.[146] Symptoms of chronic bronchitis have been shown to predict the risk of coronary disease independently from known cardiovascular risk factors,[147] and patients with daily cough and sputum production were found to 43% more likely to die from cardiovascular events than those without any respiratory symptoms after adjustment for age.[151] It is unclear from these studies, however, whether and

to what extent medications taken for the symptomatic control of breathlessness may play a role on these CVD outcomes.

2.9.1 COPD Exacerbations and Arrhythmia

The lungs and the heart share a close anatomic and physiologic relationship, and as a result, COPD patients are at higher risk of arrhythmias than those in the general population.[152] The risk of arrhythmia in patients with COPD is a function of disease severity, with the highest risk of arrhythmias occurring during periods of COPD exacerbations.[153-155] COPD exacerbations which are accompanied by changes in blood gases, abnormalities in pulmonary function, and changes in hemodynamics (resulting in pulmonary hypertension) can all lead to the development of arrhythmia.[156] More specifically, several possible clinical pathways for this association have been proposed, including:

1. Acidosis:[152] the accumulation of acid and hydrogen ions or depletion of the alkaline reserve (bicarbonate content) in the blood and body tissues, resulting in a decrease in pH[157] ;
2. Hypoxemia:[154;155] the state in which there is an inadequate supply of oxygen in the blood; and
3. Cor pulmonale:[158] An abnormal cardiac condition with hypertrophy of the right ventricle of the heart, caused by hypertension of the pulmonary circulation[159].

That there exist biological mechanisms which would predispose exacerbated patients to arrhythmia is clear. What is not clear, however, is whether or not the studies performed to date have sufficiently untangled these biological effects from those associated with drugs prescribed in the treatment of AECOPD.

2.10 Bronchodilators and Cardiovascular outcomes

COPD patients who are already at higher risk of CVD are treated with bronchodilators which are known in and of themselves to have several side effects with potential effects on cardiac function.[160] The following is a brief review of the

literature pertaining to cardiovascular outcomes associated with each bronchodilator class.

2.10.1 Methyl Xanthines

Xanthine toxicity is dose-related and is associated with life threatening arrhythmias and seizures.[56] Whereas the arrhythmogenicity of methyl xanthines such as theophylline[161;162] and aminophylline,[163;164] has been well documented, cardiac toxicity is not limited to this class of bronchodilator alone.

2.10.2 β_2- Agonists

Since β_1 and β_2 receptors are found in varying concentrations in both the heart and lung, the potential for cardiovascular effects from β-agonists is not surprising.[165] β-blockers, the β-agonists analogue, are a class of drug used to treat patients with ischemic heart disease, myocardial infarction, congestive heart failure, cardiac arrhythmias, and hypertension.[82;166-168] The potential for inhaled β-agonists to be absorbed systemically can produce an increase in cardiac output due to peripheral vasodilatation and afterload reduction.[169]

β-agonists have been shown to impact cardio vascular function causing tachycardia, decreased peripheral vascular resistance,[170] and increased QTc dispersion[171]. In a study which compared the pulmonary and cardiovascular effects of formoterol and salbutamol, neither was found to prolong the QTc interval when compared to placebo, but there was a tendency for both β_2-agonists to decrease T-wave amplitude.[172] In another study which examined the cardiovascular effects among COPD patients with preexisting cardiac arrhythmias and hypoxemia, high doses of formoterol was associated with supraventricular or ventricular premature beats and a higher heart rate when compared with salmeterol or lower doses of formoterol.[173]

2.10.3 Anticholinergics

It has been written that ipratropium bromide is poorly absorbed after inhalation and consequently produces no atropine-like side effects and no significant measurable cardiovascular effects.[112] There is some emerging evidence, however to suggest otherwise.

In a study of pediatric asthma, an increase in QTc dispersion was detected which was more prominent with the use of a standard dose of salbutamol compared to low dose salbutamol plus ipratropium therapy.[174] In addition, there exists a 1989 case report of a 71 year old patient who developed a supraventricular tachycardia after the administration of nebulised ipratropium bromide.[175] In that report, it was published that the UK Committee on Safety of Medicines had been aware of two cases of tachycardia which might have been attributable to inhaled ipratropium bromide, and that the drug manufacturer was aware of an additional nine such cases.[175] The report advises that nebulised ipratropium bromide be given with caution (and with cardiac monitoring) to patients who are known to be at risk of cardiac arrhythmias.

Current information on cardiovascular effects of the newer long-acting anticholinergic agent tiotropium bromide has been somewhat conflicting. A recently published population-based cohort study which identified cardiovascular and respiratory hospitalizations and mortality among COPD users of tiotropium failed to find an association between cardiac mortality or cardiovascular hospitalisations.[176] Another study which published pooled clinical trial results pertaining to tiotropium safety, however showed a rate ratio (95% CI) of 2.71 (1.10-6.65) for the risk of cardiac arrhythmias other than tachycardia or atrial fibrillation associated with tiotropium use compared with placebo,[177] and pooling of the table information suggests that the rate ratio (95% CI) for all arrhythmias is 1.48 (1.10-2.41). The 2004 version of the tiotropium bromide product monograph itself lists both atrial fibrillation and supraventricular tachycardia among the 356 adverse events observed in the clinical trials with an incidence of <1%.[178] In

addition, according to the 2007 product monograph revision, post-marketing adverse cardiovascular events include reports of chest pain, atrial fibrillation, myocardial infarction, angina pectoris, tachycardia, arrhythmia, and cardiac failure.[179]

2.11 The *Lung Health Study*

The Lung Health Study (LHS), the first large-scale clinical intervention trial in respiratory medicine,[180] was a multi-center randomized clinical trial designed to determine whether a program combining smoking cessation and daily use of inhaled ipratropium bromide could slow the decline in lung function in middle-aged cigarette smokers[181]. A total of 5,887 smokers aged 35 to 60 years of age with clinical indication of early pulmonary function impairment were randomized at 10 participating clinical centers between 1986-1989 to one of the following three study treatment arms[182]:

1. Smoking intervention (SI) plus inhaled ipratropium bromide;
2. SI plus placebo inhalers; and
3. Usual care.

Study subjects were then followed for 5 years to determine the rate of decline in FEV_1, the incidence of respiratory and cardiovascular morbidity, and the rate of mortality[182].

When trial results pertaining to hospitalizations and mortality outcomes were published in 2002, it was revealed that no differences among treatment groups for all-cause mortality, lung cancer, or hospitalizations for respiratory disease had been found.[182] There was, however, a trend towards a higher risk of death and hospitalisation for cardiovascular and coronary artery disease in the SI plus ipratropium bromide group as compared to the SI plus placebo inhaler group. Table 2-2 is adapted from Table 5 of *Hospitalizations and Mortality in the Lung Health Study* which reported first cardiovascular events among study participants.

Table 2-2 Arrhythmias as first cardiovascular events as reported from the Lung Health Study[182]

	SI plus Ipratropium		SI plus Placebo		Usual Care	
First Cardiovascular Events	#	%	#	%	#	%
Fatal Arrhythmia	0	0.00	0	0.00	1	0.05
Non-fatal Arrhythmia	11	0.56	3	0.15	3	0.15
Total Arrhythmia	11	0.56	3	0.15	4	0.20

The study noted the high frequency of arrhythmia as a cause of hospitalization (but not death) in the SI plus ipratropium group. Upon individual case review, the majority of these arrhythmias were found to be cases of supraventricular tachycardia (SVT), with SVT counts of 9, 3, and none in the SI plus ipratropium, SI plus placebo, and usual care groups respectively. Since the majority of these SVT cases were deemed to have been unusually compliant, thereby ruling out misclassification of exposure as an explanation for this unexpected result, the authors concluded that supraventricular tachycardia was a plausible side-effect of ipratropium and that the excess SVT hospitalizations represented a drug effect. [182]

2.12 Previous studies which have examined the association between bronchodilator use and arrhythmia or other serious cardiovascular outcomes in COPD

To date there have been two observational studies, and one meta-analysis which have examined the association between bronchodilator use and arrhythmia in COPD. The timing of these studies is worth noting, as the first was published a full year after our own research had begun, and the last two studies were both published within a few weeks of the submission of this thesis. The following is a critical appraisal of these studies.

2.12.1 Observational Study #1

In 2005, Huerta et al published results from their study titled "Respiratory medications and the risk of cardiac arrhythmias", in which apart from a weak association with current short-term use of theophylline was detected (RR 1.8 [95% CI 1.0 to 3.3]), the risk of cardiac arrhythmias was found to be unrelated to current use of bronchodilators .[183] It must be underlined at the outset that the Huerta study did not address the question specifically within the framework of COPD, but rather assembled a cohort comprised of both asthma and COPD patients aged 10-74. In addition to this noteworthy difference, however, it is probable that this study suffered from methodological flaws which could have biased their findings and explain their subsequent results.

The first serious methodological issue pertains to the fact that in this nested-case control study, instead of using risk-set sampling, the authors randomly sampled 5000 age and sex frequency-matched controls from the study cohort and randomly assigned an index date to controls from their eligible person-time, implying that the Huerta study was not time-matched. Although they did adjust for calendar year in their analyses, this would most probably be insufficient to control for the strong temporal trends in prescribing that occurred during their study period (1994-2000), and most certainly does not begin to address seasonality, a factor which is strongly associated with COPD exacerbation[37].

Secondly, COPD exacerbation is a crucial confounder in any study looking at respiratory medications and arrhythmia risk, and great care needs to be taken in order to effectively identify AECOPD. Whereas the authors did control for exacerbations of the underlying illness during the past year identified by means of hospital and outpatient diagnoses, these diagnoses probably had insufficient sensitivity to detect exacerbations within their data. In addition, they did not

control for exacerbations occurring specifically during the current time window, the relevant etiologic time window where the presence of an exacerbation could precipitate an arrhythmia, thereby resulting in further insufficient control for this variable. The study results indicate that the two factors strongly associated with cardiac arrhythmias in patients taking respiratory medications are use of oral steroids and antibiotics. Since both these medications are cornerstone of the treatment of exacerbations, this is a further evidence of inadequate adjustment for exacerbations.

2.12.2 Observational Study #2

The second observational study published in September of 2008 by Lee et al titled "Risk for Death Associated with Medications for Recently Diagnosed Chronic Obstructive Pulmonary Disease was a nested-case control design in which risk set sampling was used.[184] This study showed that ipratropium use was associated with an increased risk of cardiovascular death (RR 1.34 [95% CI 1.22 to 1.47]) and to a lesser extent with all-cause mortality (RR 1.11 [95% CI 1.08 to 1.15]). The first methodological issue worthy of note is the fact that although the authors adjusted for inpatient and out-patient exacerbations, assessment of covariates was performed using the entire time window from the year before diagnosis date (cohort entry) until the index date. This is then another example of a study which did not consider the timing of exacerbations vis-à-vis the date of the index arrhythmia, and therefore is highly unlikely to have sufficiently controlled for exacerbations in the analysis.

The second methodological concern regarding the Lee study pertains to the inclusion of periods of hospital time in the analysis when it is not clear that data pertaining to medication use would be available during periods of hospitalisation within their databases. This could result in immeasurable time bias,[185] the term for the bias caused by a specific form of differential misclassification which can

occur in pharmacoepidemiology studies, given that COPD patients often are hospitalized just prior to dying, and inclusion of these hospitalizations will lead to an apparently lower use of drugs, while being likely associated with an increased risk of death. Since the time periods of underestimated exposure would be more likely to be associated with cases than non-cases, we would expect this bias would result in underestimated estimates of effect.

The third problem pertains to the fact that 180-day time windows were implemented to define bronchodilator exposure in COPD. In studies of acute effects such as cardiovascular death, the exposures which occur in the days leading up to the event are relevant in terms of inferring a causal association, as opposed to any exposure which would have occurred six months prior. The study therefore produced estimates of effect derived via a mix of exposure which could be categorized as both new use and past use which would very likely mask a true association from new or even current use of these medications.

The final issue which must be considered with regard to this study stems from the fact that although the title of the study infers that these are cases of recently diagnosed COPD, there is nothing in the cohort definition paragraph to indicate that this is an analysis of a new-user cohort[186]. Subjects aged 45 and older were eligible to enter with a COPD diagnosis within a specific 5-year calendar time period, but it is never stated that a backward time window was used to verify that this cohort entry diagnosis was in fact the first diagnosis for COPD per subject. Furthermore, assuming for a moment that the first COPD diagnosis per patient was indeed captured, this does not preclude the possibility of prevalent bronchodilator users to enter the cohort. We can only assume, therefore that there would be some mix of new and prevalent users in their cohort, thereby leaving their estimates of effect vulnerable to prevalent user bias.

2.12.3 Meta Analysis

In the systematic review and meta-analysis published also in September 2008, Singh et al conclude that inhaled anticholinergics are associated with a significantly increase risk of cardiovascular death, MI, or stroke among COPD patients.[187] While the confidence interval for the pooled estimate pertaining to all anticholinergics included randomized trials of tiotropium bromide just narrowly missed statistical significance (RR 1.43 [95% CI 0.95 to 2.16]), the pooled estimates derived for ipratropium obtained from both short-term and long-term trials (and by default, the combination of these strata) indicated a notably high and statistically significant risk at (RR 3.94 [95% CI 1.07 to 14.51]) and (RR 1.57 [95% CI 1.08 to 2.28]) respectively.

Although there are those who insist that randomized clinical trials are the gold standard for drug studies, it has been noted that therapeutic trials of COPD have suffered from methodological flaws,[188] and the trials included in this particular meta-analysis were no exception. In at least two out of the four short-term trials of ipratropium, for example, it is evident from the study protocol that prevalent ipratropium users were not excluded from study.[189;190] Given the that 43% of patients randomized in the Combivent™ Inhalation aerosol study trial[190] reported pre-study anticholinergic use (ranging from 46% to 41% depending on the trial treatment arm), interpretation of the study results is difficult at best.[188]

The meta-analysis category pertaining to long-term randomized controlled trials for ipratropium bromide, on the other hand, consisted of just one study which did not include prevalent users pre-randomization: the Lung Health Study. We agree that the published results of mortality and hospitalisations from the Lung Health Study results are intriguing, and as such, they have served to be the principle motivation for this thesis.

2.13 Our Question: General vs. specific objectives

Although several studies have examined the association between bronchodilators and arrhythmia, as outlined above, various methodological limitations lead to difficulty in their interpretation. The aim of this thesis is to evaluate the arrhythmia risk associated with the use of bronchodilators, the class of drugs which provide symptomatic benefit, in patients with COPD. We aim to answer this important research question and improve on the current status of scientific understanding by:

1. Commencing with a new-user cohort;
2. Sufficiently controlling for the confounding effects of time;
3. Focusing on the exposures which occur just before the outcome of interest;
4. Ensuring a comprehensive assessment of all available bronchodilators;
5. Appropriately identifying and controlling for the confounding effects of AECOPD;
6. Appropriately identifying and controlling for periods of hospitalisation which could result in immeasurable time bias;
7. Replicating our results in a second population to validate our results; and finally,
8. Gaining insight as to whether or not AECOPD is a time-dependent confounder which lies in the causal pathway between exposure and outcome.

Table 2-3 Description of the twelve most common arrhythmias including their epidemiology, risk factors, aetiology and prognosis. Adapted from *The American Heart Association Clinical Cardiac Consult*, 2007, J. V. (Ian) Nixon (ED) Lippincott Williams & Wilkins Philadelphia

Arrhythmia	Description	Epidemiology	Risk Factors	Aetiology	Prognosis
Atrial Premature Beats/Complexes (APCs)	APCs are early atrial systoles identified on the ECG by early P waves	Increase with aging quite prevalent among the elderly	Structural heart disease with abnormality of atrial physiology	• Aging • Stress • Hyperthyroidism • Myocardial infarction (MI) • Elevated atrial pressure and wall stress • Alcohol, tobacco and caffeine consumption • Digitalis toxicity	May be a harbinger for atrial fibrillation, and may trigger reentrant supraventricular tachyarrhythmias
Atrial Fibrillation (AF)	AF is the rapid, disorganized and asynchronous contraction of the atrial muscle • Characterized by absence of clearly defined atrial complexes on surface ECG • Ventricular rate is typically fast and irregularly irregular	A function of age and underlying heart disease	• Hypertension • Coronary Artery Disease (CAD) • Chronic heart failure (CHF) • Valvular heart disease (VHD) • Cardiomyopathy	• Hypertension • CAD • VHD • Cardiomyopathy	• Risk Ratio >12 of stroke and death for elderly patients with a risk factor for stroke
Atrial Flutter	A reentrant tachyarrhythmia resulting from a rapid electrical circuit in the atrium	Increases with age and underlying heart disease	• Prior cardiac surgery • Hypertension • Treatment with antiarrhythmic medications	Idiopathic Structural heart disease (including coronary and Valvular heart disease and cardiomyopathy) Following open heart surgeries Can occur for the first time inn patients using class IC antiarrhythmic drugs such as flecainide and propafenone	• Depends on age and underlying comorbidity • Normal prognosis with very low risk for stroke in the absence of comorbidity

Arrhythmia	Description	Epidemiology	Risk Factors	Aetiology	Prognosis
Atrioventricular Nodal Reentrant Tachycardia (AVNRT)	The most common paroxysmal regular supraventricular tachycardia Accounts for >50% of all cases referred for ECG	Common, more prevalent in women, can occur at any age but usually presents between the ages of 30-50 years		Pathological findings usually described in electrical terms. Usually begins with a premature atrial depolarization that blocks in the fast pathway The impulse then conducts through the slow pathway. IF the fast pathway recovers from depolarization, the impulse reenters the fast pathway and to the atria thus completing the reentry circuit (which can then repeat)	Good
Multifocal Atrial Tachycardia (MAT)	Characterized by a rate > 100 bpm and : • Discrete P waves of varying morphology from at least 3 foci • Irregular variation in PP, PR, and RR intervals reflecting absence of dominant pacemaker • Isoelectric baseline between P waves	More common among the elderly Occurs primarily in patients with severe exacerbations of lung disease Can occur in critically ill patients in any setting	• COPD • Recent surgery • Diabetes	Usually occurs during critical illness, especially in the setting of COPD. β-agonist and methyl xanthine therapy may be implicated	Dependant on underlying disease

Arrhythmia	Description	Epidemiology	Risk Factors	Aetiology	Prognosis
Premature Ventricular Contractions (PVCs)	Involve depolarization of the ventricle with inscription of QRS earlier than usual	Occurs more frequently after MI More prevalent among the elderly and patients with cardiomyopathy	Age Structural heart disease	• Reentry, automaticity and triggered mechanisms • Drug toxicity (digitalis, and agents which prolong the QT interval) • b-agonist use and caffeine which cause sympathetic stimulation • Slow heart rates during which ventricular beats may represent escape rhythms	Decreased survival among patients with ischemic heart disease Possibly decreased survival among patients with cardiomyopathy
Sick Sinus Syndrome (SSS)	Includes a number of arrhythmias involving impulse generation in the atria: 1. Sinus bradycardia 2. Sinus pauses 3. Bradycardia-tachycardia syndrome 4. Sinus node dysfunction	More prevalent among the elderly	• Age • Structural Heart Disease • Drugs which can induce sinus node dysfunction	• Aging • Structural heart disease • MI leading to damage to the sinoatrial node or atria	Dependant on underlying heart disease Prognosis is worse among patients with Atrioventricular block.
Supraventricular Tachycardia (SVT)	The general term for paroxysmal, regular supraventricular tachyarrhythmia	Common, but less so among the elderly	none	May be due to Atrioventricular nodal reentrant tachycardia (AVNRT) , AV reentrant tachycardia (AVRT) junctional tachycardia or atrial tachycardia	Good

Arrhythmia	Description	Epidemiology	Risk Factors	Aetiology	Prognosis
Torsade de Pointes Ventricular Tachycardia (TdP)	A polymorphic ventricular tachycardia which occurs in the setting of a long QT interval Two types of TdP: congenital and acquired.	Can affect all age groups, although presentation of the congenital form occurs more often among younger patients; presentation of the acquired form in older patients after exposure to	See etiology	**Congenital**: at least 6 genetic mutations have been identified as being associated with TdP **Acquired**: • Drug-induced • heart failure, ischemia, myocarditis • Electrolyte abnormality (hypokalaemia, hypomagnesaemia) • cerebrovascular disease (subarachnoid hemorrhage, ischemic stroke • Severe bradycardia • Thyroid disease	Good for the acquired form TdP which progresses to ventricular fibrillation is sometimes fatal

Arrhythmia	Description	Epidemiology	Risk Factors	Aetiology	Prognosis
Ventricular Fibrillation (VF)	VF is the rapid, disorganized asynchronous contraction of the ventricular heart muscle Characterized by the absence of a clearly defined QRS complex	Increases with age Associated with structural heart disease status	• Hyperlipidemia • Hypertension • Smoking • Prior MI • Abnormal left ventricular function • Increased age • Glucose intolerance • Non-sustained ventricular arrhythmias • Digitalis use	• CAD (with or without MI) • VHD • Myocardial scarring from any cause • Cardiomyopathy • Ischemia • Drug toxicity from antiarrhythmic drugs used in CAD and QT prolonging agents • Congenital • Wolff-Parkinson-White syndrome with • Rapid ventricular pre-excitation during AF • Myocarditis • Hypokalaemia and metabolic acidosis (electrolyte and acid-base abnormalities)	VT followed by VF is the most common cause of sudden, unexpected death. Prognosis is worse with patients with structural heart disease. Very rarely, CF will spontaneously terminate
Ventricular Tachycardia (VT)	VT is a wide ARS tachyarrhythmia originating in the ventricles due to reentry, triggered activity or automaticity	More common among the elderly (mostly due to concurrent CAD comorbidity) Prevalence is variable and depends on structural heart disease status.	• Coronary Artery Disease and associated factors (smoking, hyperlipidemia and hypertension) • Cardiomyopathy ECG abnormalities such as QT dispersion, T-wave alternans, ST-T wave changes, left ventricular hypertrophy, and low left ventricular ejection fraction	• Drug toxicity (digoxin or drugs which affect QT dispersion) • Ischemia • Myocardial scarring • Hypokalaemia • Bundle branch reentry Congenital heart disease	Among patients with VT and a structurally normal heart, prognosis is good. Cardiac arrest can often occur immediately following VT (or VF) VT followed by VF is the most common cause of sudden, unexpected death.

Arrhythmia	Description	Epidemiology	Risk Factors	Aetiology	Prognosis
Wolff-Parkinson-White (WPW)	WPW syndrome is defined by the combination of preexcitation on the electrocardiogram (ECG) (delta wave) and supraventricular tachycardia (either atrial fibrillation or reentrant tachycardia using the accessory pathway as part of the circuit).	Can occur at any age. More frequent among males The prevalence of ECG preexcitation has been reported to range from 0.1–3/1,000 population. The intermittent nature of preexcitation may have led to underestimation of the true prevalence of the disease. Accessory pathway-mediated tachycardia accounts for about 30–40% of paroxysmal supraventricular tachycardias seen in practice.	Conditions associated with WPW syndrome: ▪ hypertrophic cardiomyopathy ▪ mitral valve prolapse; ▪ congenital heart diseases. Not usually considered to be a genetic disorder. However, there have been case reports of autosomal-dominant inheritance without associated cardiac disorders.	Results from a developmental abnormality of the AV groove. During normal cardiogenesis, direct continuity between the atrial and ventricular myocardium is lost by growth of the annulus fibrosis. Defects in the annulus leave muscular connection(s) called accessory pathways or Kent bundles between the atrial and ventricular myocardium. By bypassing the AV node, these pathways can lead to preexcitation of the ventricles because atrial impulses are not delayed in the AV node. Right-sided accessory pathways are associated with Ebstein anomaly of the tricuspid valve.	If accessory pathways are ablated and the heart is structurally normal, prognosis is normal. Prognosis is excellent if accessory pathway has a long anterograde refractory period and cannot preexcite the ventricles rapidly during atrial fibrillation.

3 Chapter 3: Methodological issues and Introduction to Paper 1

3.1 Study overview

The purpose of this study was to examine the cardiac arrhythmia risk associated with exposure to bronchodilators among patients with COPD. We used the computerized databases of Saskatchewan Health to form a source population of subjects treated with bronchodilators within which a cohort was selected to examine this study question. In this chapter, we will present the methods used and discuss related methodological issues, which will include a detailed explanation of the sources of data, the cohort design, and the nested case-control approach which was used in this study.

3.2 Sources of Data: Saskatchewan Health Databases:

The Saskatchewan Health databases comprise multiple files covering different domains of health care. Each of these files contains a unique patient identifier which permits the linkage of these data files.

3.2.1 Health Insurance Registration File (HRIF)

The HRIF is the file containing demographic information for all registered residents who are eligible for Saskatchewan Health programs, which encompasses more than 95% percent of the population of approximately one-million[191] in the Province. Persons not covered by the plan are covered federally by the Government of Canada and include members of the Canadian Forces, the Royal Canadian Mounted Police, federal inmates, registered Indians and members of the Workers' Compensation Board and the Department of Veterans affairs. Since the inception of the Hospital Services Plan in 1947, each eligible Saskatchewan resident has been assigned a unique health services number, which has made it possible to perform electronic data filing and data linkage.[192] Demographic variables within this source population included study enrolment date (which is the later of September 1, 1987 or the actual coverage initiation with Saskatchewan Health), exit date (which is the earliest of death, coverage termination or end of study December 31, 2003), sex, and date of birth.

3.2.2 Hospital Inpatient Data

Data pertaining to all acute care inpatient separations (discharges or deaths), day surgeries, long-term care separations from the 132 general and rehabilitation hospitals (which include six tertiary and seven referral hospitals) in the province are collated and stored in the hospital data file. Date of admission, discharge, discharge type, type of admission (day surgery vs. inpatient stay) as well as diagnosis and procedure codes were available for use.

Prior to April 1, 1999 up to three diagnoses were reported and labelled primary, secondary, and other using the International Classification of Diseases version 9 (ICD-9)[193] coding convention. Beginning April 1, 1999 up to five diagnoses were reported with an accompanying "diagnosis type" code used to assess the diagnosis relevance as it denotes whether this diagnosis represented the most responsible diagnosis, a pre-admission comorbidity, a post-admission comorbidity, or a secondary diagnosis. For hospital services with discharge dates occurring after March 31, 2002, up to 25 diagnoses and 20 procedures were provided by Saskatchewan Health. This later subset of diagnosis and procedures were coded using the International statistical classification of diseases and related health problems, tenth revision (ICD-10-CA) coding convention, which represents an enhanced version of the ICD-10 developed by the Canadian Institute for health Information (CIHI) for morbidity classification in Canada.

3.2.3 Prescription Drug Data:

The prescription drug files contain data pertaining to all filled outpatient prescriptions which were prescribed by a Saskatchewan-licensed physician for medications listed on the province's formulary. Whereas the total utilization of prescription drugs not listed on the Formulary is unknown it was estimated to be very low given both the comprehensiveness of the Formulary and the fact that this list is under ongoing review[194]. Information available for each dispensed

prescription included the drug category, the dispensing date, the dosage form, the strength and the quantity dispensed. Cost data were also available but not used for analysis.

Due to administrative changes within Saskatchewan Health that saw reimbursement filed on a family unit basis (rather than on an individual patient basis) there were no drug data captured between July 1, 1987 and December 31, 1988, and therefore data pertaining to medication exposures during this18-month period were not available for study.

3.2.4 Physician Services Data:

The physician services file contains all visits to the fee-for-service clinicians paid by Saskatchewan Health. Data elements available for study were the date of service, diagnosis code, fee-for-service code, location of service and the amount paid. Diagnoses are reported using the ICD-9 coding convention throughout the study period.

Services and therefore visits delivered by physicians in salaried or contractual arrangements may or may not be captured (e.g., those on alternate payment contracts, some ER physicians, most psychiatrists, salaried Northern Medical Services physicians, etc). Data pertaining to claims for ICU physicians in Regina or salaried Saskatchewan Cancer Agency physicians were also not captured in these databases.

3.2.5 Oxygen file:

The Saskatchewan Health database reports each month that an invoice for oxygen therapy was submitted by a supplier. Under the home oxygen program, home oxygen and related equipment are covered benefits for patients who meet one of the three following medical criteria:

i) Patient is hypoxemic at rest - while at rest after being seated for 10 minutes, must have a PO2 </= 55 mm Hg or a pulse oximetry </= 87% for a minimum of 2 continuous minutes;

ii) Patient has cor pulmonale or polycythemia and is hypoxemic at rest - while at rest after being seated for 10 minutes must have a PO2 </= 59 mm Hg or a pulse oximetry </= 90% for a minimum of 2 continuous minutes;

iii) Patient is hypoxemic on exertion and has improved exercise tolerance with the use of oxygen.

Saskatchewan Health covers the cost of the basic systems, which are supplied by private medical oxygen supply firms under contract with Saskatchewan Health. This is first dollar coverage to a maximum amount. Patients therefore do not submit claims to the Department. The assigned oxygen supplier submits an invoice monthly for services provided and the database reports each month that an invoice was submitted by a supplier. Although there are no details on the type of service provided, service during a particular month is considered by Saskatchewan Health to be "a reasonable proxy for some oxygen use".[195] Data pertaining to home oxygen use was available from 1994 onwards.

3.2.6 Cause of Death file:

The cause of death file contains the vital statistics date of death as well as the underlying cause of death, whether or not an autopsy was performed, and whether or not the cause of death code took account of autopsy findings. The underlying cause of death is (a) the disease or injury which initiated the train of events leading directly to death, or (b) the circumstances of the accident or violence which produced the fatal injury. In addition, up to 13 multiple causes of death codes are recorded, which are defined as diseases, morbid conditions or injuries which either resulted in or contributed to death and/or the circumstances of the accident or violence which produced any such injuries.

These computerized databases of Saskatchewan Health were linked by the unique identification number (health services number) that allows the linkage of these database files. Drug use profiles were then produced, and a source population of subjects treated with bronchodilator medications was generated, from which a cohort was selected in order to investigate our research question. The details of these next steps are described in detail in the following section.

3.3 Identification of the study population

The objective of our research design was to assemble an inception cohort, that is a group of COPD patients identified for study at an early and uniform point in the course of their disease.[196] A new-user design is an inception cohort if all persons in the study are first-time users of study medications.[186] In order, therefore, to study the impact of bronchodilator therapy on arrhythmias among COPD patients, we began by first capturing a new-user cohort of COPD patients who began their treatment after January 1st 1990. The source population was a bronchodilator user database provided by Saskatchewan health which contained data pertaining to each covered Saskatchewan resident who had been dispensed at least one bronchodilator medication between September 1, 1980 and December 31, 1999. Subjects were at least 55 year of age on the date of their entry bronchodilator prescription. To confirm new-user status within the source population itself, subjects had been excluded if they had a history of use of these agents between September 1st 1975 and August 3, 1980.

From this source population bronchodilator database, the following bronchodilator medications were excluded as they are not used in the treatment for COPD:

1) Nasal ipratropium bromide (an anticholinergic), used to treat seasonal allergies;
2) Sublingual tablet isoproterenol (a β-agonist), used as a vasodilator to treat pulmonary hypertension;

3) Epinephrine (a β-agonist), an injectable drug used to treat life-threatening allergic reactions (anaphylaxis).

In order to ensure that the cohort would capture subjects whose treatment was more than occasional, subjects were included for study if they had been dispensed at least three prescriptions for a study bronchodilator (β2 agonist, inhaled anticholinergic, or theophylline) within a 1 year period, with their third qualifying bronchodilator dispensed on or after January 1, 1990. In addition, these three prescriptions had to be dispensed on at least two different dates within the year in order to indicate a reaffirmation of the decision to prescribe a bronchodilator, and some indication of continued exposure on the part of the subject. The date of the third prescription was taken as the date of cohort entry (**Figure 3-1**). Whereas some cohorts are defined by exposure to a specific drug of interest, and others by duration of disease, it should be noted that here, our zero time (t_0) is based on drug exposure which we use as a proxy for a specific point in a subjects progression of COPD disease, that being new users of bronchodilator medications.

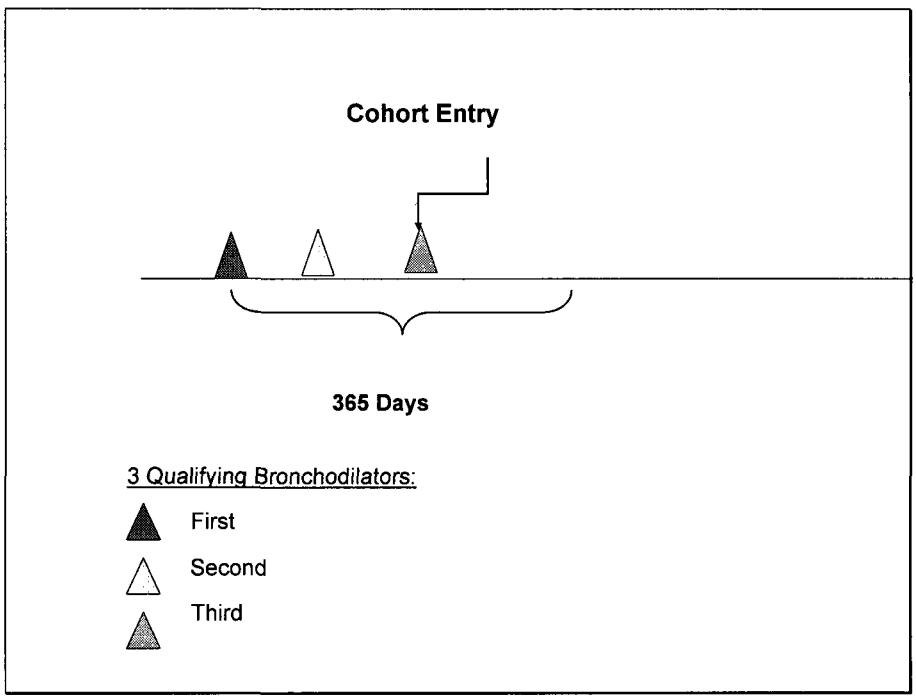


Figure 3-1 Bronchodilator exposure cohort entry criterion

It should be noted that it was necessary to establish the date of the third of the qualifying three bronchodilators as the date of cohort entry in order to avoid immortal time bias.[197;198] Immortal time can be defined as a time period during cohort follow-up during which, by design, subjects could not have incurred the outcome under study. Since we have imposed the requirement of three entry bronchodilators within a year as a proxy for active (as opposed to sporadic) treatment, by design we have imposed the condition that all cohort members survive both their first and second bronchodilators in order to have been included for study. In this particular study design, the time span between the first and third bronchodilator medications can also be considered as immortal time,[197;198] during which the true risk of exposure is under-represented.

Since it was necessary to confirm the incident nature of the treatment, subjects were excluded if they had been prescribed any study bronchodilators before the first of the sequence of 3 entry bronchodilators, during the 5 year time window before cohort entry. Bronchodilators are used in treatment of other airway diseases such as asthma. In an attempt to exclude subjects with asthma, we excluded subjects if they had been prescribed drugs more commonly prescribed for asthma such as inhaled or nasal corticosteroids, or any of the following respiratory agents: ketotifen, cromoglycate, nedocromil, montelukast or zafirkulast during the 5-year period before cohort entry.

3.4 New user cohort designs

As stated previously, this research is based on an inception cohort of newly prescribed bronchodilator users which excluded prevalent users. Since studies of drug effects outside the realm of clinical trials have shown that the inclusion of prevalent users can lead to various forms of bias,[64;186] this was an important and necessary design decision.

Firstly, since prevalent users are in effect "survivors" of an exposure, the inclusion of prevalent users can result in an underascertainment of events that happen early in treatment. When the hazard function is non-constant and there is more than one temporal pattern of drug usage, it has been shown that the odds ratio will estimate a weighted mean of incidence ratios with weights, dependent on the corresponding fractions of person-time.[199;200] If one can show that the duration-specific incidence ratios are sufficiently different, the odds ratio will therefore depend not only on the exposure itself but also on the pattern of use within a given study population.[199;200] In the case of arrhythmia, our primary hypothesis is that these are acute events triggered by the recent use of bronchodilator medications. It then follows that the inclusion of prevalent bronchodilator users could potentially bias our estimates of effect if we are correct in our assumption that the risk of an arrhythmic event indeed varies with time.

Secondly, the inclusion of prevalent users can often lead to the inability to control for disease risk factors that may be altered by the study drugs themselves. According to the Compendium of Pharmaceuticals and Specialties (CPS), certain bronchodilators are listed as being contraindicated, for example, in patients with coronary artery disease (CAD), since cardiac stimulation with bronchodilators could increase the risk of subsequent coronary events. Therefore since CAD is affected by bronchodilator use, the inclusion of prevalent users would render it difficult to control for CVD which includes CAD, which is a recognised risk factor for atrial fibrillation, a common arrhythmia among the elderly.[201]

Our cohort inclusion criteria required that subjects be prescribed at least three bronchodilators on at least two separate dates within a one-year period. This prescription-centered cohort definition was deemed necessary in order to ensure that we would be studying subjects who were beginning active therapy for COPD and not just those who were occasional users of these drugs. One factor that this study design will not account for, however is the early attrition of those patients

most susceptible to the event, or "depletion of susceptibles".[202] In as much as a first ever bronchodilator exposure might have resulted in an event which would have then precluded them from being prescribed a subsequent bronchodilator, these subjects (and, by definition, these events) would not have been included in our study. A separate analysis of a bronchodilator-user cohort where entry is the date of a first-ever prescription is underway and will be published under separate cover.

3.5 Nested case control design

The case control method within a cohort, known as the nested case-control design which was proposed by Mantel in 1973[203] and expanded upon by Liddell in 1977,[204] forms the cornerstone of the design and statistical analytical methodology of this study. The essence of such a method is to obtain a sample of control person-moments which are representative of the "person-time experience out of which the cases arise".[205] Put another way, controls are selected such that the exposure distribution among controls is equivalent to that among the person-time in the population from where the cases arise (with differences between the two accounted for by random error only).[206] This is a density case-control study design as the control selection is termed density sampling since it provides for estimation of relations among incidence rates, or "incidence densities". Furthermore, since density sampling is used, it has been shown by Miettinen (1976) that the odds ratios approximate the rate ratio without any consideration of a rare disease assumption.[206;207] The resulting estimates of effect, the odds ratios which are produced by the case-control method estimate the hazard ratios from the Cox proportional hazards model of a prospective cohort study.[208-210] Estimation of absolute risk functions as well as relative risk functions is possible from this design since we have knowledge of the sampling probabilities for cases and controls.[211]

Although a more conventional method of analyzing cohort data would be the standard survival analysis using a Cox proportional hazards model, this option would have posed several challenges in the face of our exposure/outcome pair under study. In the case of the essential Cox model,[212] exposure is classified at cohort entry and therefore pegged at that value throughout the study period. In this study, we are faced with a transient exposure, an acute outcome, and (in most cases) a long duration of follow-up. The probability that exposure as related to the event would be misclassified is therefore undoubtedly high. An alternative is the extended Cox model [213] which allows the flexibility to consider time-dependent exposures and covariates in the survival model. At the time that this research was proposed, however, this option was deemed to be computationally prohibitive, with a single model often taking weeks to run despite the availability of state of the art computer hardware and software. Indeed, the RAMQ cohort consisted of 76,661 subjects who each contributed (on average) 58 person-months, with each of these person months contributing to vectors of data corresponding to the time-dependent covariates under study. In total, therefore, the data matrix size involved would have been 76,666 observations * 750 variable vectors, for a total of approximately 57,500,000 cells.

While one theoretical drawback of the nested case-control design is a loss in precision for our estimate of effect, this cost is typically low in database studies such as this one which are typically very large.[206] Furthermore, it has been recently shown by Essebag et al, that the nested case-control approach is an effective alternative for cohort analysis when studying time-dependent exposures and that its superior computational efficiency may be particularly useful when studying rare outcomes in databases, where the ability to analyze larger sample sizes can improve the power of the study.[214]

The four main steps involved in a nested case control study are as follows:[215]

i) Defining the primary time axis for the cohort;

ii) Exhaustive identification of all cases, hereby defined as cohort subjects who experienced the adverse event under study;

iii) Formation of appropriate risk sets for each case;

iv) Random selection of controls from within each risk set.

The risk sets from the third step are derived by selecting all eligible control person moments for each case based on a predetermined set of matching factors. An eligible person moment is defined as all non-case person moments which are at risk of having the outcome under study at the exact moment in time that the case has occurred. It is worth noting that in risk set sampling, future cases are eligible to be controls for prior cases, and subjects may be selected into risk sets for multiple cases and therefore serve as controls for more than one case.[215]

3.6 Matching

Since risk sets contain all non-case person moments which are at risk of having the outcome under study at the exact moment in time that the case has occurred, each case is, by definition, matched on some axis of time to their set of eligible controls. Matching is therefore an inherent feature of the nested-case control design which must be executed by means of a computer matching algorithm. At the time that this matching is undertaken, there is an opportunity to include other candidate confounding variables in the list of matching variables.

In this study, we elected to match for the following four candidate confounding variables:

i) Age at index;

ii) Sex;

iii) Year of cohort entry; and

iv) Calendar index date.

3.6.1 Matching on Sex:

The manifestation of CVD differs by sex which is sufficient justification for its inclusion as a matching factor. In this research, the decision to include sex as a matching variable was predominantly motivated by the fact that many (if not most) cardiovascular clinical journals appear to make this a prerequisite for publication. While in an ideal world, such issues should not be the guiding forces behind epidemiologic methodology and design choices, in this case the determination was made that there was a clear cost-benefit advantage. Our chief goal is to obtain valid estimates of the risks associated with these transient bronchodilator exposures and these acute arrhythmic events. The practice of matching on sex should therefore be regarded as a reasonable methodological option as long as:

1) The research question at hand does not either include or readily lend itself to a question regarding the effect of sex on arrhythmia controlling for bronchodilator exposures; and
2) one is not attempting to match on a variable which is in the causal pathway between exposure and outcome , a situation which would result in what is termed "overmatching" in the literature.[216]

While it is true that by matching on sex that the effect of sex itself as a variable cannot be estimated, it however remains possible to estimate the parameters for interaction between sex and exposure,[217] and as far as our research interests were concerned, this was sufficient.

3.6.2 Matching on time axes of interest

There are three relevant time axes which come into play in our study, all of which had to be taken into consideration at the design stage:

i) **Calendar time** which may be associated with both our exposure and our outcome in terms of both temporal trends and seasonality, and may also be associated with exacerbations- a strong candidate confounding variable for our exposure-outcome pair;

ii) **Duration of disease**, and

iii) **Age**.

These time axes and their potential implications for influencing the validity of our estimates are discussed here.

3.6.2.1 Calendar Time and arrhythmia

Emerging evidence suggests that there has been an increase in the incidence and prevalence of atrial fibrillation over time which is not entirely explained by aging of the population.[218] Data from the Framingham heart study was only able to detect a statistically significant trend in the age-adjusted prevalence in men (and not women) aged 65-74 which rose from 3.2% to 9.1% between 1968 and 1989.[219] An other study which examined 4,618 adult residents of Olmsted County, Minnesota, who had ECG-confirmed first AF in the period 1980 to 2000, the age and sex-adjusted incidence increased significantly with a relative increase of 12.6% (95% CI, 2.1 to 23.1) over 21 years. Whereas it is theoretically possible that one source of this temporal trend could be due to some technological factor that effected a change in arrhythmia reporting and not the actual condition over calendar time, what remains is that there appears to be an association between arrhythmia and calendar time.

3.6.2.2 Calendar time and temporal trends in prescribing:

This study examines the risk of bronchodilator exposures which might have occurred over the thirteen year span between 1990 and 2003. With COPD guidelines that were often changing and many times seemingly in conflict with one another (as illustrated in section 2-7 in Chapter 2), treatment recommendations for the pharmaco-management of COPD changed substantially over this period. The first long-acting β-agonist was introduced to the market (albeit only as part of Saskatchewan's *Exception Drug Status Program)* in 1995. Furthermore, while clinical trials examining the efficacy of combining ipratropium bromide with a short-acting β-agonist for COPD began being

published in 1987[220-234] physicians were limited to prescribing each of these drugs separately for a prolonged period. Only in 1996 did the Saskatchewan Formulary list Combivent®, an inhalation aerosol whose valve actuations delivered a combination of 20mg ipratropium bromide and 120 mg salbutamol sulphate. A graph depicting the actual temporal trends in bronchodilator prescribing in the Province of Saskatchewan among patients with COPD during our study is given in **Figure** 3-2.

Temporal trends in prescribing imply that the probability of being exposed to a particular bronchodilator exposure may vary with calendar time. Since calendar time may also be associated with the risk of arrhythmia, calendar time may itself be a confounder of the exposure-outcome analysis, and it therefore must be accounted for in the design and/or analysis of observational studies of bronchodilator medications and arrhythmia outcomes.

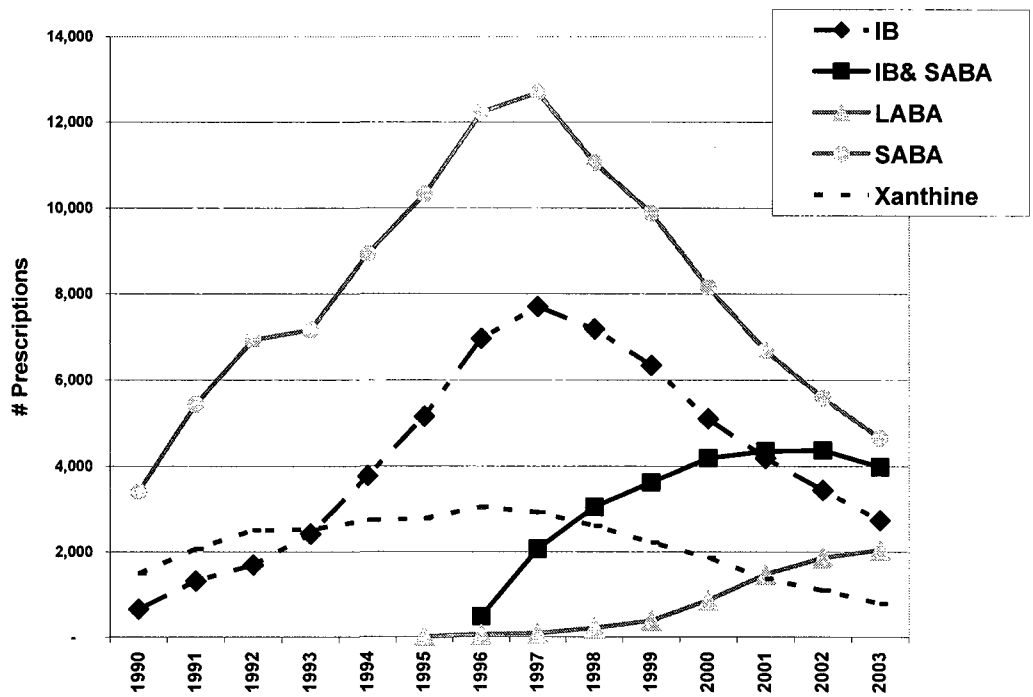


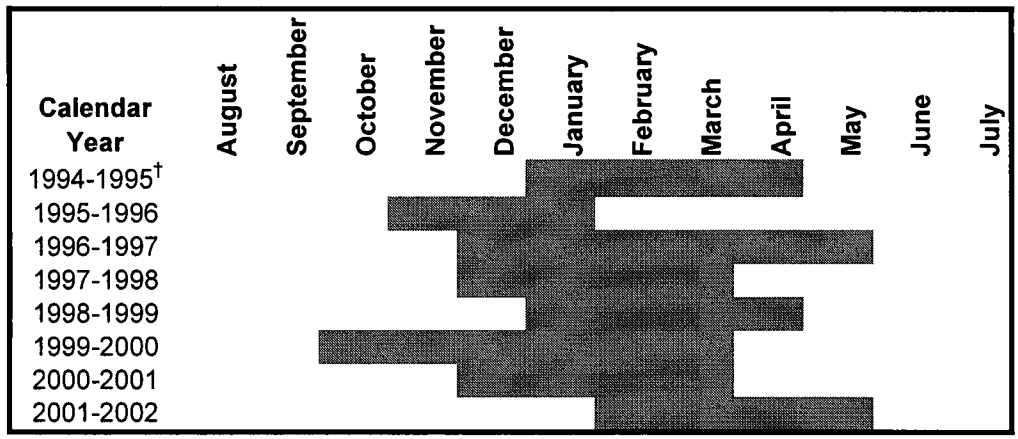
Figure 3-2 Temporal trends in bronchodilator prescribing in Saskatchewan among patients with COPD 1990-2003. Abbreviations: IB= ipratropium bromide, SABA= short-acting β-agonist, LABA= long-acting β-agonist.

It is for this reason that calendar year of cohort entry was a variable on which controls were matched to cases in the analysis. In this way, the probability of having been exposed to one agent over another over the course of a subject's COPD disease is equivalent with the probability faced by other subjects within each risk set.

3.6.2.3 Calendar Time and Seasonality of Exacerbations

In patients with moderate or severe COPD, the presence of a virus in upper airway secretions, such as those which occur when infected with the influenza virus is strongly associated with the development of COPD exacerbations. While other factors such as exposure to ambient particulate air pollution[235;236] are also hypothesized as a mechanism through which season can be associated with acute exacerbations, the influenza virus is generally seen as an important cause of excess mortality and morbidity in patients with COPD.[237] A recent study provides strong evidence of the causative role of viruses in triggering COPD exacerbations in the community. [238] In addition, influenza is thought to potentially accelerate COPD progression[239] and patients with COPD are at an increased risk for respiratory illness-related hospitalisation during influenza outbreaks irrespective of both age and degree of morbidity[240] .

Whereas at first glance, controlling for flu season may appear to be a relatively standard task, upon careful perusal of the actual data pertaining to flu outbreaks in Canada, one realises that the calendar months for each year fluctuate considerably for both total number of months and the specific month of onset[241-248] (Figure 3-3).



† the year 1994-1995 presents data pertaining to the extent of influenza-like illness reported for the province of Saskatchewan specifically. All other years present Laboratory-confirmed cases of influenza for the prairie region(which includes Manitoba, Saskatchewan and Alberta).

Figure 3-3 Month of onset of Laboratory-confirmed cases of Influenza in the Prairie Region 1994-2002

Within the paradigm of risk-set analysis, if one were to consider a case whose index event occurred in October 1999, for example, the consideration of control person-moments occurring in the months of May to September of that same calendar year would be an unreasonable comparison in that the case and control moments do not share the same potential for exacerbation. Since the control of exacerbations was deemed to be one of the fundamental priorities in this research, each case was matched to its group of risk-set control person-moments on the calendar index day of the case event. In this way, all factors associated with each index calendar date have been appropriately controlled for in the analysis.

3.6.2.4 Calendar Time and Seasonality of Arrhythmia

There exists a body of evidence which suggests that arrhythmia, our outcome under study, has a seasonal pattern as well. Season has been associated with atrial fibrillation in populations studied in Finland,[249] Israel,[250] Denmark,[251] Greece,[252]

Scotland,[253] Australia,[254] and Japan[255]. Seasonal patterns are apparently, however, not limited to atrial fibrillation alone. There is also documented evidence of seasonal variations in both ventricular arrhythmia clusters among defibrillator recipients in Switzerland[256] and of ventricular tachycardia registered in 24-hour Holter monitoring in Brazil[257]. Not all authors agree on the exact mechanism which is at work. Some argue that absolute temperatures can affect myocardial ischemia[249] or peripheral thyroid hormones[258]. Others hypothesize that season variation is attributed to ultraviolet radation[259] or other factors which fluctuate according to season such as changes in diet or physical activity,[259] seasonality of acute respiratory infections,[259] or changes in alcohol consumption[249]. Regardless of the cause, given the indication that there exist seasonal patterns of arrhythmia, it was important to control for this in the analysis. As was the case for the seasonal component of exacerbations, this was accomplished by matching each case to controls on the calendar index date.

3.6.2.5 Duration of COPD

As outlined earlier, our cohort inclusion and exclusion criteria were applied in order to assemble an inception cohort of COPD patients identified for study at an early and uniform point in the course of their disease. In as much as subjects newly treated with bronchodilators are likely to be on the lower end of the COPD severity spectrum, they are more likely to be treated with the first-line treatment strategies proposed by clinical guidelines of the day. Moreover, since COPD severity is associated with complications including hypercapnia and hypoxemia, both of which are associated with arrhythmia, duration of disease must also be a variable that is taken into account. We have controlled for duration of COPD in two ways. Firstly, as mentioned previously, we matched cases to controls on both year of cohort entry and by calendar index date. In addition to this, however, we also included a variable corresponding to the actual number of days each subject was observed in this study in the analysis in order to address any residual confounding by duration which may have remained.

3.6.2.6 Age

Age is a strong risk factor for many disease outcomes, is also frequently associated with drug exposures, and the relationship between age and bronchodilators and age and arrhythmia is no exception. Control of the confounding effects of age was first accomplished by matching cases to controls on age with a caliper of ±5 years. In order to control for any residual confounding which may remain within the ten-year band, age was also included as a continuous variable in the conditional logistic regression model.

3.7 Arrhythmia as outcome

According to the International Classification of Diseases version 9, rubric 427 corresponds to Cardiac dysrhythmias includes conditions which result in a variation from the normal rhythm or rate of the heart beat.[193] It excludes any arrhythmia which is a complication of abortion, ectopic or molar pregnancy, or labour or delivery, but seeing as our cohort consists of middle-aged and elderly persons, this is of no consequence to our study. In order to be included as a case, a subject had to either have:

i) Been hospitalized with a primary diagnosis code for arrhythmia at a point in time after cohort entry where the primary diagnosis for hospitalisations in Saskatchewan is meant to reflect the condition most responsible for intensity of treatment and length of stay;[192] or

ii) Died with an underlying cause of death code of arrhythmia.

3.7.1 Mapping from ICD-9-CM to ICD-10

Our study follow up window includes all hospital admissions from January 1st 1990 until December 31, 2003. On April 1 2002, Saskatchewan Health changed their hospital diagnosis coding system to the ICD-10-CM coding convention which consists of approximately 120,000 alphanumeric diagnosis codes and 2,033 categories (in contrast to the 13,000 alphanumeric diagnosis codes and 855 code categories within ICD-9-CM). As such, a computer conversion program[260] was employed in order to map each of the ICD-9 427 codes to ICD-10-CA. The

resulting list of codes corresponding to the arrhythmia diagnoses considered for case ascertainment are listed in

Table 3-1.

Table 3-1 Case definition arrhythmia diagnosis codes

ICD-9-CM		ICD-10	
427	**Cardiac dysrhythmias** Excludes: that complicating: Abortion (634-638 with .7, 639.8) ectopic or molar pregnancy (639.8) labor or delivery (668.1,669.4)	**I47**	**Paroxysmal tachycardia** *Excludes: complilcating:* abortion or ectopic or molar pregnancy (O00-O07 , O08.8) obstetric surgery and procedures (O75.4) tachycardia NOS (R00.0)
427.0	**Paroxysmal supraventricular tachycardia** Paroxysmal tachycardia: atrial [PAT] atrioventricular [AV] junctional nodal	**I47.1**	**Supraventricular tachycardia** Paroxysmal tachycardia: atrial atrioventricular [AV] junctional nodal
427.1	**Paroxysmal ventricular tachycardia** Ventricular tachycardia (paroxysmal)	**I47.2**	**Ventricular tachycardia**
427.2	**Paroxysmal tachycardia, unspecified** Bouveret-Hoffmann syndrome Paroxysmal tachycardia: NOS essential	**I47.9**	**Paroxysmal tachycardia, unspecified** Bouveret(-Hoffmann) syndrome
427.3 **427.31** **427.32**	**Atrial Fibrillation and flutter** Atrial fibrillation Atrial flutter	**I48**	**Atrial fibrillation and flutter**
427.4 **427.41** **427.42**	**Ventricular Fibrillation and flutter** Ventricular fibrillation Ventricular flutter	**I49.0**	**Ventricular fibrillation and flutter**
427.5	**Cardiac Arrest** Cardiorespiratory arrest	**I46**	**Cardiac arrest** *Excludes: cardiogenic shock (R57.0)* complicating: abortion or ectopic or molar pregnancy (O00-O07 , O08.8) obstetric surgery and procedures (O75.4)
		I46.0	**Cardiac arrest with successful resuscitation**
		I46.9	**Cardiac arrest, unspecified**
427.6	**Premature beats**	**I49**	**Other cardiac arrhythmias** *Excludes: bradycardia NOS (R00.1)* complicating: abortion or ectopic or molar pregnancy (O00-O07 , O08.8) obstetric surgery and procedures (O75.4) neonatal cardiac dysrhythmia (P29.1)
427.60	Premature beats, unspecified Ectopic beats Extrasystoles Extrasystolic arrhythmia Premature contractions or systoles NOS		
427.61	Supraventricular premature beats Atrial premature beats, contractions, or systoles	**I49.1**	**Atrial premature depolarization** Atrial premature beats
427.69	Other Ventricular premature beats, contractions, or systoles	**I49.2**	**Junctional premature depolarization**
		I49.3	**Ventricular premature depolarization**
		I49.4	**Other and unspecified premature depolarization** Ectopic beats Extrasystoles Extrasystolic arrhythmias Premature: beats NOS contractions
427.8	**Other specified cardiac dysrhythmias**		
427.81	Sinoatrial Node dysfunction Sinus bradycardia: persistent severe Sindrome: sick sinus tachycardia-bradycardia Excludes: sinus bradycardia NOS (427.89)	**I47.0** **I49.5**	**Re-entry ventricular arrhythmia** **Sick sinus syndrome** Tachycardia-bradycardia syndrome
427.89	**Other Rhythm Disorder** coronary sinus ectopic nodal Wandering (atrial) pacemaker Excludes: cartoid sinus syncope (337.0) reflex bradycardia (337.0) tachycardia NOS (785.0)	**I49.8**	**Other specified cardiac arrhythmias** Rhythm disorder: coronary sinus ectopic nodal
		R00	**Abnormalities of heart beat** *Excludes:* abnormalities originating in the perinatal period (P29.1) specified arrhythmias (I47-I49)
		R00.1	**Bradycardia, unspecified** Slow heart beat
427.9	**Cardiac dysrhythmia, unspecified** Arrhythmia (cardiac) NOS	**I49.9**	**Cardiac arrhythmia, unspecified** Arrhythmia (cardiac) NOS

It was necessary to perform several recursions mapping back and forth between the list of codes generated so as to ensure that the list of new codes would incorporate all case arrhythmias without over-including conditions which were not intended to be under study. As illustrated in Figure 3-4, consider the case of ICD9-CM code 427.9 "Cardiac dysrhythmia, unspecified". This condition maps to two unique ICD-10 codes: I49.9 "Cardiac arrhythmia, unspecified" and I51.8 "Other ill-defined heart diseases".

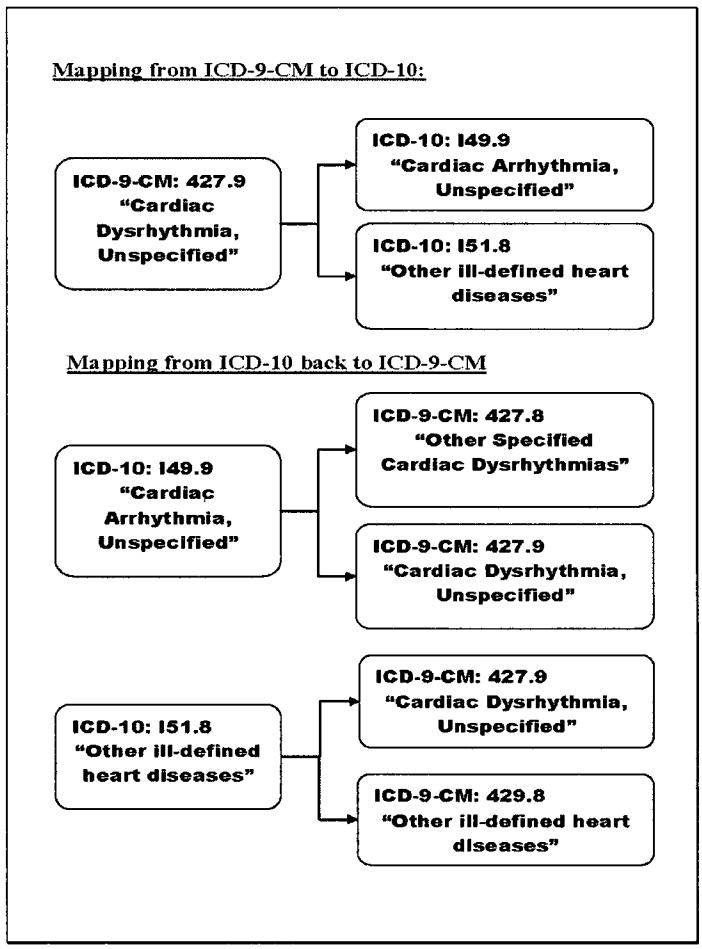


Figure 3-4 Diagnostic Coding from ICD-9-CM to ICD-10 mapping example

While I49.9 maps back to two ICD-9-CM codes currently under study, I51.8, which includes conditions such as acute or chronic carditis, and pancarditis, does not. As such this second ICD-10 code was therefore not considered for inclusion as part of case definition.

3.7.2 Validity of Arrhythmia as outcome

A number of studies have examined the validity of arrhythmia diagnosis codes from within administrative databases, a summary of which is provided in Table 3-2 . The published evidence suggest that the positive predictive values of arrhythmia coded as most responsible diagnosis (all arrhythmias as one inclusive category) range between 73%-86%,[261;262] atrial fibrillation (AF, not specified as to chronic or paroxysmal) range between 96%-98%,[263;264] incident chronic AF 64%,[263] selected specific arrhythmias combined at 48%,[261] and idiopathic ventricular arrhythmias at 21%[265] (Table 3-2). In addition, the sensitivity and specificity of arrhythmia where it was coded as the most responsible diagnosis code was estimated to be 60.7% and 97.8% respectively.[262]

Table 3-2 Summary of relevant Arrhythmia diagnosis code Validation Studies

First Author	Administrative Database	Outcome Definition	Gold Standard Used	Results				Notes
				Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)		
1. Curkendall[76;76]	Saskatchewan	Arrhythmia	Data abstracted from hospital records: Photocopies of the initial and 2 subsequent ECGs were requested.	—	—	**Any Arrhythmia**	**86**	Poster presented at 20th icpe, published in Pharmacoepidemiology and Drug Safety, 13: S1-S334 (2004)
						By Arrhythmia type (paroxysmal ventricular tachycardia, AF, VA, other)	**48**	
2. Austin[77]	Canadian Institute of Health Information (CIHI) hospital discharge abstracts from Ontario	Arrhythmia (ICD-9 427)	Fastrak II acute coronary syndromes database	**60.7**	**97.8**	**73.4**		**Where Arrhythmia was coded as the *Most Responsible* Diagnosis**
				83.2	**84.5**	**35.4**		Where Arrhythmia was coded as either the ***Most responsible or any Secondary*** diagnosis
3. Ruigómez[79]	UK GPRD	Paroxysmal Atrial Fibrillation	Questionnaire sent to the GPs requesting diagnosis confirmation, and classification as either paroxysmal or chronic AF	—	—	**98**		95% questionnaire response rate
4. Ruigómez[78]	UK GPRD	Chronic Atrial Fibrillation		—	—	**Any AF**	**95.9**	94% questionnaire response rate
						Incident Chronic AF	**64.4**	
						Break-down: remaining 35.6%		
						Paroxysmal AF	24.2	
						Had prior AF episode	7.3	
						No AF	4.1	
5. De Abajo[80]	UK GPRD	Ventricular Arrhythmias	Compared with clinical records obtained from GPs	—	—	**Idiopathic VA**	**21**	95% questionnaire response rate
						Break-down: remaining 79%		
						Dx not confirmed	22	
						Supraventricular Arrhythmias	16	
						Not referred	9	
						Past History of VA	14	
						MI/Angina	7	
						Right ventricular outflow tract tachycardia	2	
						Computer entry error	2	
						Finding in routine check-up	2	
						Arrhythmias developed in-hospital	2	
						Sarcoidosis	1	

3.7.3 Arrhythmia vs. Heart Block

Heart block is a different yet related heart condition which is a delay in the conduction of electrical current as it passes through the atrioventricular node, bundle of His, or both bundle branches, all of which are located between the atria and the ventricles. Although it is related to arrhythmia in that it also deals with the electrical system of the heart, we did not consider heart block as part of our outcome under study.

3.8 Exposure Definition

Exposure to the following four classes of bronchodilator medications were identified using the Prescription Drug Services data file: long-acting β-agonists (formoterol or salmeterol); short-acting β-agonists (fenoterol, isoproterenol, orciprenaline, metaproterenol, procaterol, salbutamol, or terbutaline); the short-acting anticholinergic (ipratropium bromide); and methyl xanthines (theophylline, aminophylline, and oxtriphylline). All bronchodilator prescriptions that were dispensed to the cases and controls were identified. It should be noted that neither tiotropium bromide (a long-acting anticholinergic), nor aformoterol (a long acting β -agonist) were listed on the Saskatchewan formulary during the study period and they therefore were not included for analysis.

3.8.1 Independent exposure and combination therapy exposure classification

In this study, our question of interest focused on the independent (as opposed to the exclusive) effects of bronchodilator use on our outcome under study, that is the effects of bronchodilator use conditioned on exposure to the other bronchodilator classes under study. There are, however, three scenarios during which a subject could be exposed to more than one bronchodilator class at a time, namely if they were prescribed:

i) A combination bronchodilator such as Combivent® which combines both an anticholinergic and a short-acting β-agonist in one canister;

ii) Multiple medications within a single prescription which included more than one class of bronchodilator; or

iii) Multiple prescriptions for different bronchodilator classes dispensed on different dates which resulted in overlapping time periods during which a subject would have been potentially exposed to more than a single class at that time.

In order to represent the independent effect of exposure, then, a subject who was exposed to two or more classes of bronchodilator within a specified time window was coded as being exposed to each of those classes. This method of defining exposure is in contrast with the alternative of analyzing exclusive exposure groups, in which exposure for a methyl xanthine, for example, would only be specifically coded as occurring in the case that it was the only bronchodilator class during that specified exposure time window. If a subject were prescribed more than one bronchodilator class during that time, exposure would be classified into some variable (or group of variables) representing combination therapy.

3.8.2 Exposure time-window definition

Since the essence of this study is to identify the risks of what can be regarded as transient exposures with the acute effect of an arrhythmia, it is necessary to hone in on exposures which occur within some etiologically relevant time context to each index event. Accordingly, we were particularly interested in the current use of bronchodilators at the time that each index event occurred. Furthermore, we wished to be able to distinguish between current use which was new and current use which had lasted for a longer period, was preceded by a period of past use, and could therefore not be considered as "new".

Current exposure to each class of bronchodilator was therefore considered as any prescription dispensed during the sixty days up to and including the index date.

Past use was defined as a dispensing during the 61-365 day time window before the index date. Thus, the referent category of being unexposed to a particular class of bronchodilators inferred that no dispensing of a drug within that particular class was issued during the entire 12 month period leading up to the index date. In order to assess the effect of new use to a particular class of bronchodilators, we considered currently exposed subjects who were not found to be past users of that specific class of bronchodilators. The hierarchical nature of exposure definition is illustrated in Figure 3-5.

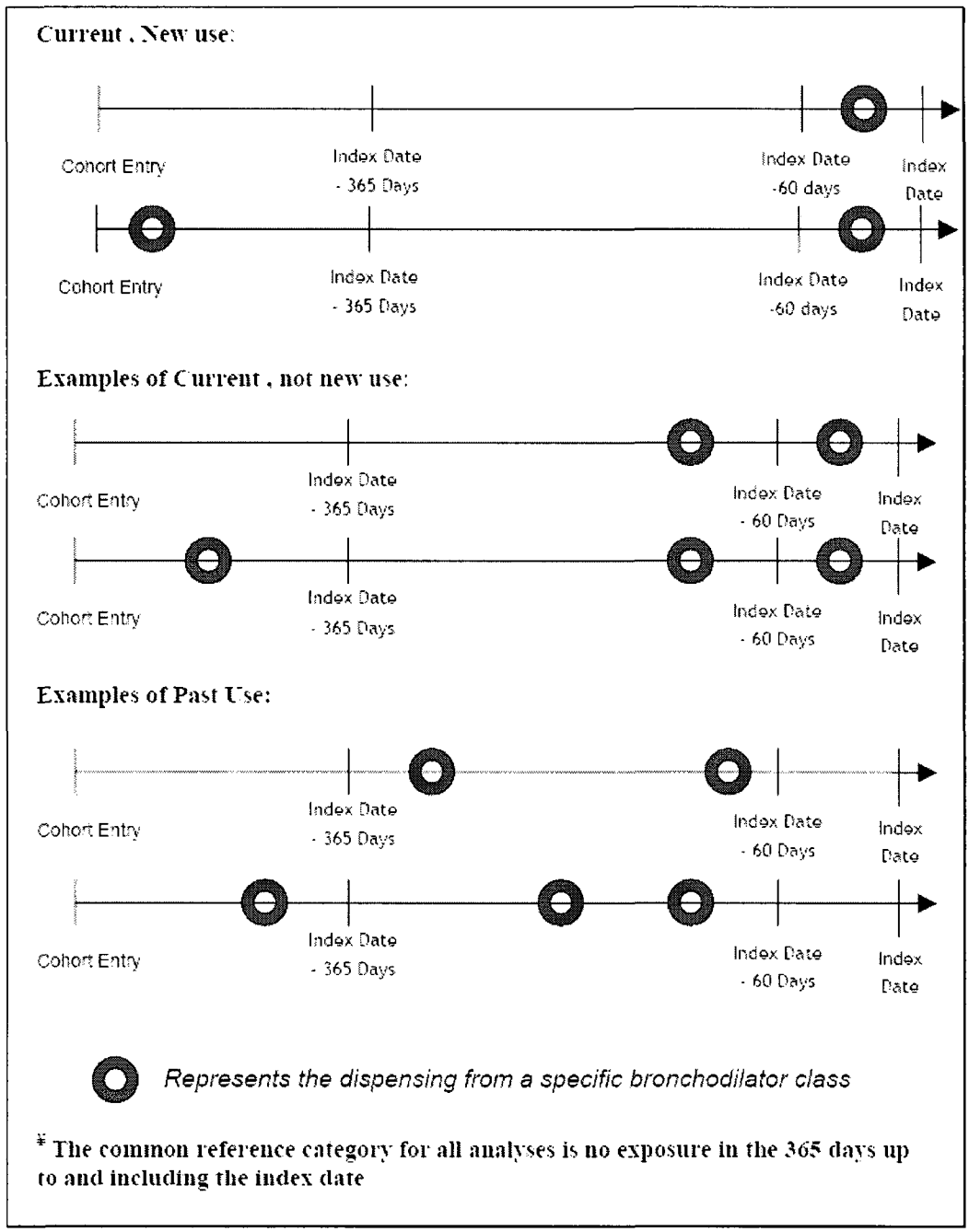


Figure 3-5 Graphical demonstration of the exposure category hierarchy employed in this study

3.9 *Exclusion of subjects hospitalised during the "current" time window*

Dispensings of medications during hospitalisations are not recorded by the Saskatchewan Health databases. Since exposures to bronchodilators during a hospitalisation (and potentially afterwards since it is possible that subjects could have been discharged with a hospital-dispensed canister) are unknown, it was decided that in order to avoid misclassification of exposure that these subjects be excluded from our analyses.

To examine this problem more carefully, we observed that over half of the 10,416 primary diagnosis COPD hospitalisations experienced by our Saskatchewan cohort at any time during their recorded time in the database (including time before their cohort entry date) were less than a week in length (figure 3-6).

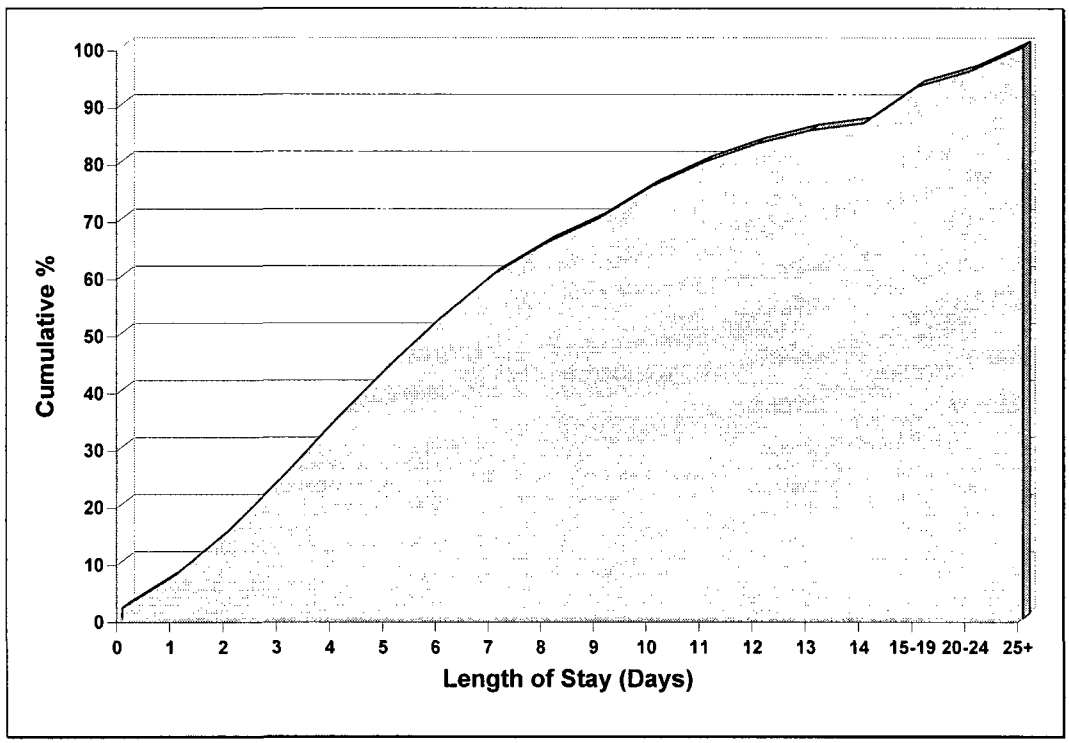


Figure 3-6 Length of stay distribution for primary diagnosis COPD hospitalisations

Upon inspection of the number of days between discharge from a primary diagnosis COPD hospitalisation and their next recorded bronchodilator dispensing, however, only 36% received their prescription on the day of or one day post-discharge (Figure 3-7).

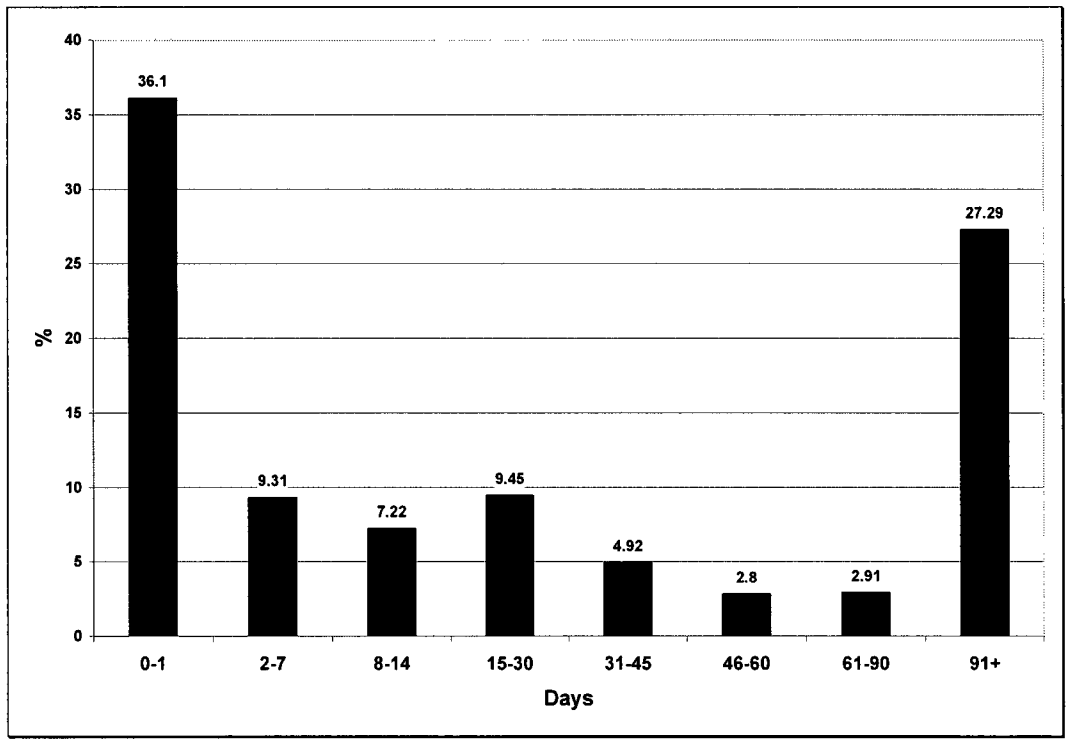


Figure 3-7 # Days until first bronchodilator dispensing post-discharge from a primary diagnosis COPD hospitalisation

These results suggest that not only is there is a black-out window regarding exposure information during a hospitalisation but that this window of uncertainty could extend for up to several months thereafter. It is for this reason, that patients who were hospitalised at any time during the current time window, that is the sixty days leading up to the index date, were eliminated from study. This assumption regarding inclusion/exclusion of subjects hospitalised during the "current" time window and misclassification of exposure was tested via sensitivity analyses, and reported upon both briefly in the manuscript in Chapter 4 (Paper 1), and more extensively in the sensitivity analysis section which follows.

3.10 Exacerbations

After case and exposure definition, the single most important variable in this analysis, whose definition had to be operationalised with the utmost of care pertains to COPD exacerbations. Although COPD exacerbations have been described in several ways by various authors, most published definitions include the mention of worsening of dyspnea, increase in sputum purulence, and increase in sputum volume.[266] What is currently understood, however, is that the frequency of exacerbations is not only a function of but also contributes to long term decline in lung function of patients with moderate to severe COPD.[267] A variety of operational definitions have been used in clinical studies, based on changes in patient symptoms or the requirement for antibiotic therapy, oral steroids or hospitalization.[268] In this study, we adhered to the operational definitions used by de Melo et al[269] who identified moderate exacerbations by prescriptions for a systemic antibiotic and an oral corticosteroid on the same day, and severe exacerbations as a hospitalization with a primary discharge diagnosis of COPD.

3.11 Statistical Analysis:

Univariate analyses were initially conducted in order to provide the descriptive statistics of the study population, after which multivariate analyses were performed.

When undertaking statistical analysis of a nested case-control study such as this, it is necessary to take into account the matching process- a fundamental feature of this particular design.[270] This necessity becomes even more important if the risk of arrhythmia were to change with COPD duration and bronchodilator exposures varied across calendar time.[215] We therefore used conditional logistic regression using both the PHREG and LOGISTIC Procedures (SAS/STAT software version 9.1) which uses the risk sets as the essential unit of analysis. It should be noted

that the conditional likelihood used in conditional logistic regression is identical to that of the partial likelihood used in Cox regression except that instead of including all available risk set subjects, the denominator includes only a selected number of sampled controls.[271]

Models were first run including only the twelve exposure covariates (current and new, current and not new and past use for our four classes under study) in order to obtain a measure of the estimate of effect of bronchodilator use adjusted for other bronchodilator use only. The risk factors for arrhythmia and potential confounder variables were then included in all models in order to obtain adjusted estimates.

Potential modification of bronchodilator use was tested by creating interaction terms between candidate effect modifier variables with our twelve exposure variables. Specifically, we tested whether sex, use of home oxygen therapy, moderate exacerbations, the use of medications possibly associated with arrhythmia, or comorbidity during the year leading up to the index date could modify the arrhythmic effect of bronchodilator agents.

Due to the likely significantly confounding nature of exacerbations, we opted to control for this variable by excluding cases and controls that experienced exacerbations during the sixty day time window leading up to the index date. Sensitivity analyses in which exacerbations were instead controlled for by means of statistical analysis were also performed, the results of which are offered in section 4.3.3.

3.12 Cohort Assembly Results:

Figure 3-8 presents the process of selection for the Saskatchewan cohort. After the inclusion and exclusion criteria were applied to the source population of 51,690 Saskatchewan subjects aged 55 and older who had been prescribed their first bronchodilator on or after January 1st, 1980, a total of 6,018 subjects were retained for study. These 6,018 subjects were then followed until the date of the study outcome, death, the date of emigration from the province, the date of end of coverage of the health insurance plan, or 31 December 2003, whichever occurred first.

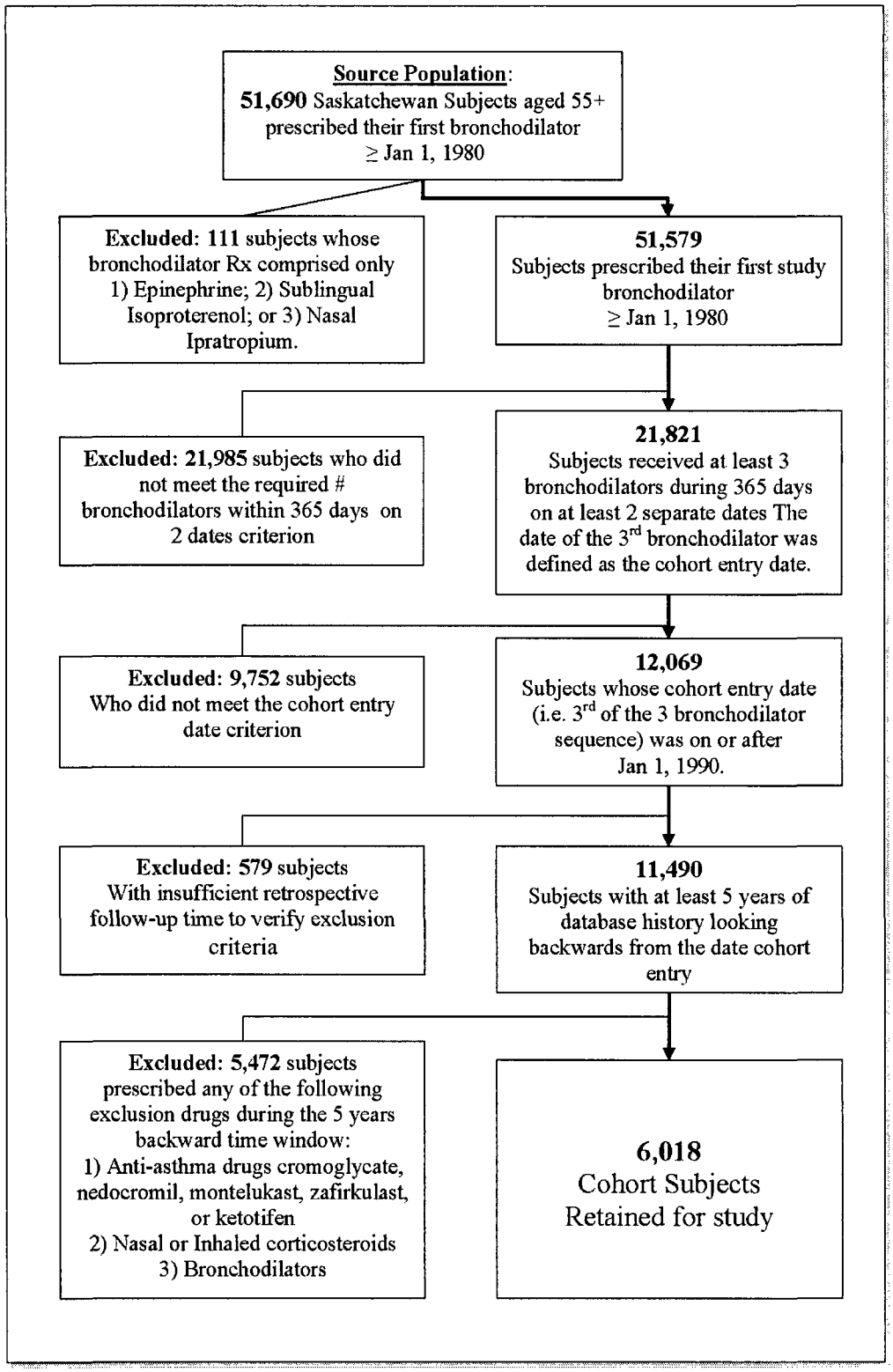


Figure 3-8 Saskatchewan Cohort Assembly Flow Chart

4 Chapter 4: The use of bronchodilators and the risk of arrhythmia in chronic obstructive pulmonary disorder (COPD): a nested case-control study

4.1 Preface to the manuscript:

This chapter contains the first manuscript in a series of three articles examining the arrhythmia risk of bronchodilator drug use in COPD and the associated methodological issues in measuring this association. The manuscript is the first of two cohort studies which were conducted in order to answer this specific research question. Specific details pertinent to how this cohort was derived are presented in Chapter 3.

This population-based new-user cohort study focuses on determining whether the risks of arrhythmia differ significantly by choice of bronchodilator agent, and whether or not the timing of exposure to these drugs is relevant to the question a hand. Particular care was given to the identification and handling of COPD exacerbations since they are associated with both bronchodilator use, and the risk of arrhythmia in the absence of bronchodilator exposure, thereby making them potentially powerful confounders which could violate the validity of our study results.

This article will be submitted for publication and should be referenced as follows:

Wilchesky, M., P. Ernst, J. M. Brophy, R. W. Platt, and Suissa S. 2008. The use of bronchodilators and the risk of arrhythmia in chronic obstructive pulmonary disease (COPD): a nested-case-control study. Unpublished manuscript. Montreal: Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, 2008.

4.2 The use of bronchodilators and the risk of arrhythmia in chronic obstructive pulmonary disease (COPD): a nested-case-control study

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Figures :1
Key Words : Bronchodilators, COPD, Arrhythmia, Pharmacoepidemiology
Running Title : Bronchodilator Use and Arrhythmia Risk in COPD

What is already known about this subject:

There is some evidence that bronchodilator use may increase the risk of cardiac arrhythmias in patients with COPD. Several clinical trials involving the short-acting anticholinergic ipratropium bromide have reported on arrhythmias but have produced conflicting results.

What this paper adds:

This time-matched nested case control study was able to compare the effects of new, current, past only, vs. non use of four different classes of bronchodilators within a new-user cohort of COPD patients. The discovery of an association between new use of ipratropium bromide and cardiac arrhythmias in this population provides further evidence following the published cardiovascular event reports from the Lung Health Study trial.

Summary

Aims: Bronchodilators are first line therapy for chronic obstructive pulmonary disease (COPD). There is some evidence that these agents may increase the risk of cardiac arrhythmias.

Methods: We identified a new-user COPD cohort of subjects 55 years of age or older using the computerized health databases of Saskatchewan Health (January 1990 to December 1999). The association between bronchodilator use and arrhythmias were analyzed using a time-matched, nested case–control approach comparing new users, current users, past users to non-users of the various bronchodilators.

Results: The cohort included 6,018 COPD subjects from which 469 cases of cardiac arrhythmia were identified. When the cohort was restricted by excluding subjects who had either been hospitalised or had a COPD exacerbation within 60 days of the index date, an elevated risk of cardiac arrhythmia associated with the new use of ipratropium bromide was (RR 3.65 [95% CI 1.72 to 7.74]), while for long-acting β– agonists, the association was not statistically significant (RR 1.73 [95% CI 0.21 to 14.33]). New use of methyl xanthines was also found to be associated with the risk of arrhythmia within this restricted cohort (RR 5.17 [95% CI 1.38 to 19.30]).

Conclusions: The new use of bronchodilators was found to increase the risk of cardiac arrhythmias in patients with COPD. These results require further confirmation in a larger cohort.

Introduction:

Bronchodilator medications are central to the symptomatic management of chronic obstructive pulmonary disease (COPD).[272-275] The choice of first line therapy for COPD usually includes a short-acting bronchodilator, whether it be a β2-agonist, an anticholinergic, or combination of these two bronchodilators, based on clinical response and tolerance of side effects.[12] Whereas the arrhythmogenic potential of β– agonists[165] and methyl xanthines[161;164] have been relatively well documented in the literature, an association between cardiac arrhythmias and anticholinergics is less well documented.

Several clinical trials involving the short-acting anticholinergic ipratropium bromide have reported on arrhythmias but have produced conflicting results. In 2002, a 10-center randomized trial involving 5,887 smokers, aged 35 to 60 with mild to moderate lung function impairment found that that 0.56% of subjects in the ipratropium bromide plus smoking cessation intervention arm experienced an arrhythmia as compared with 0.15% of subjects in either the smoking intervention plus placebo, or usual care groups.[182] Smaller trials, however, have not supported this result[276-278]

The objective of this study was to estimate the risk of cardiac arrhythmias associated with the use of long-acting β–agonists, short-acting β–agonists, ipratropium bromide, and methyl xanthines in a new user cohort of subjects with chronic obstructive pulmonary disease.

Methods:

Data Source

A new-user cohort of COPD patients was identified using the computerized databases of Saskatchewan Health. As documented elsewhere, these databases have been widely used and validated for use in epidemiologic studies.[279-282]

Study design

A population-based cohort of patients aged 55 and older with newly-treated COPD was defined as subjects with a minimum of three prescriptions for a bronchodilator, on two different dates, within any one year period. Bronchodilator medications being prescribed during this period and considered for inclusion of subjects included inhaled or oral β_2-agonists (both short and long-acting), methyl xanthines or ipratropium bromide. The date of entry into the cohort was therefore defined as the date of the third of this sequence of prescriptions for a bronchodilator between January 1, 1990, and December 31, 1999. Patients who had received any bronchodilator, anti-asthma drug (cromoglycate, nedocromil, montelukast, zafirkulast, or ketotifen), or nasal or orally inhaled corticosteroid in the 5 years prior to cohort entry were excluded in order to limit the analysis to patients with new-onset COPD who had more than occasional treatment and without a prior history of asthma. Lastly, subjects were excluded if they had less than 5 years of observation from the time of enrolment with Saskatchewan health such that sufficient time would be available to assess the inclusion and exclusion criteria. Subjects were followed until the date of their index event or the corresponding index date for the controls, December 31, 2003, or the end of coverage (including emigration from the province or death), whichever came first.

In order to study the effect of exposure to each of four classes of bronchodilators in the sixty days preceding the event while controlling for the potentially confounding effect of calendar time, we analyzed our population-based retrospective cohort using a time-matched, nested case–control method.[215]

Cases and Controls

The study end point was the first of either an arrhythmic death or a hospital admission with a primary discharge diagnosis of arrhythmia (ICD-9 codes 427x, ICD-10 codes I46x-I49x, R000 and R001) occurring any time after cohort entry. All cases of first arrhythmia during follow up were included in the analysis. The index date for case subjects was the date of their arrhythmic event.

For each case, 20 controls were randomly selected from all subjects in the cohort matched on age (±5 years), sex, calendar year of cohort entry, and who were alive and event-free on the calendar date of the case arrhythmia (the index date). Controls within each risk set were then assigned the case-patient's index date. Using this risk set sampling technique, our estimated exposure odds ratio is an unbiased estimate of the relative risk.[283;284]

Exposure Assessment

Exposure to the following four classes of bronchodilator medications was identified and compared for the purposes of this analysis: long-acting β-agonists (formoterol or salmeterol); short-acting β-agonists (fenoterol, isoproterenol, orciprenaline, metaproterenol, procaterol, salbutamol, or terbutaline); short-acting anticholinergics (ipratropium); and methyl xanthines (theophylline, aminophylline, and oxtriphylline). Tiotropium, a newer long-acting anti-cholinergic bronchodilator, was not available in Saskatchewan during the study period.

All bronchodilator prescriptions that were dispensed to the cases and controls were identified. Current exposure to each class of bronchodilator was considered as any prescription dispensed during the preceding sixty days up to and including the index date. Past use was defined as a dispensing during the 3–12 months before the index date. Likewise, the unexposed referent category to a particular bronchodilator class inferred no drug use during the entire 12 month period leading up to the index date. In order to assess the effect of new use to a particular class of bronchodilators, we considered currently exposed subjects who were not found to be past users of that specific class of bronchodilators.

Risk Factors and Confounders

We identified the use of drugs within 12 months of the index date that can introduce, aggravate, or protect against arrhythmia which include cardiotonic drugs such as antiarrhythmics and digoxin (digitalis), drugs that decrease potassium levels such as diuretics and corticosteroids; aspirin and non-steroidal anti-inflammatory drugs (NSAIDs); and drugs that are hypothesized to lengthen the Q-T interval such as macrolides, antidepressants, cisipride, and antipsychotics. Additionally, we identified other drugs used for the treatment of respiratory disease, specifically inhaled corticosteroids, oral corticosteroids, and other respiratory drugs (including cromoglycate, nedocromil, montelukast, zafirkulast, or ketotifen) used during the 12 months prior to index date.

Comorbid conditions of interest included congestive heart failure (CHF), enlarged heart, atherosclerosis, anemia, hypertension, congenital structural cardiovascular abnormalities and other cardiovascular diseases, cerebrovascular disease, diabetes, thyroid disease, hyperlipidemia and renal failure. In order to identify these conditions, both hospital and out-patient diagnoses identified within 12-months of the index date as well as medication use during this same time period for the treatment of these conditions were identified. Drugs used as markers for these diseases included ACE inhibitors, β–blockers (both selective and non selective), calcium-channel blockers, potassium-sparing diuretics, and other hypotensive agents, nitrates, diabetic and thyroid medications.

In addition, the use of home oxygen at any time (information only available starting in 1994), was used for adjustment. COPD duration (time from cohort entry until index date) and age (to resolve any residual confounding) were also included as covariates. Finally, a subject's previous history of arrhythmia, that is, a record of a hospitalization for arrhythmia prior to cohort entry, was identified and used for adjustment.

We defined exacerbations of COPD as per de Melo et al[269]who identified moderate exacerbations by prescriptions for a systemic antibiotic and an oral corticosteroid on the same day, and severe exacerbations as a hospitalization with a primary discharge diagnosis of COPD. Exacerbations which can cause respiratory failure[285;286] are themselves an independent risk factor for arrhythmia[287-289]. The occurrence of an exacerbation may also precipitate modification to a patient's prescribed bronchodilator medications. Due to the resulting confounding nature of this variable, we compared controlling for exacerbations by both including this variable in the regression model as a covariate, and by excluding cases and controls that experienced exacerbations during the sixty day time window leading up to the index date.

Data Analysis

Conditional logistic regression using SAS version 9.1 was used to estimate adjusted odds ratios (equivalent to adjusted rate ratios) for cardiac arrhythmias associated with the use of the four different classes of bronchodilators in our time-matched nested case–control data.

Since dispensing of medications during hospitalisations are not recorded by the Saskatchewan Health databases, bronchodilator exposures during a hospitalisation are unknown. In addition, since it's possible that subjects could have been discharged with a hospital-dispensed canister of medication, exposure information contained within our databases during the period immediately following a hospitalisation are also suspect. In order to assess the extent to which misclassification of exposure could have influenced our results, a restricted case-control sample was created by deleting subjects who had been hospitalised within 60 days of the index date.

Results

A total of 6,018 study subjects met the criteria required for entry to our COPD cohort. Of these, 413 were hospitalized with a primary diagnosis of arrhythmia after cohort entry, and 56 subjects within this cohort died with an arrhythmia diagnosis coded as the underlying cause of death, yielding a total of 469 case subjects. The overall rate of our outcome was 14.2 arrhythmias per 1,000 person-years. Table 4-1 provides a comparison of the various characteristics between cases and controls.

Case subjects were more likely to have had a previous history of arrhythmia, have established risk factors for arrhythmia such as CHF, enlarged heart, cerebrovascular disease and other cardiovascular diseases, and were more likely to have been using diuretics, ACE inhibitors, β–blockers, digitalis glycosides, calcium channel blockers and thyroid medications than were the controls. These differences (along with the other covariates listed in the methods section) were controlled for in the analysis.

Approximately half of the arrhythmia was reported as atrial fibrillation or flutter (Table 4-2).

Table 4-3 presents the crude and adjusted rate ratios of arrhythmia associated with each of the four bronchodilator classes during the 365 day period before the index date broken down by current use, past only use, and unexposed (referent).

Using this set of exposure categories current use of ipratropium bromide appears to be associated with arrhythmia (RR 1.46 [95% CI 1.12 to 1.90]) whereas past use of methyl xanthines appears to have a protective effect (RR 0.54 [CI 0.33 to 0.99]) when compared to those who were not exposed.

Furthermore, when current exposure is further broken down into "current and new" and "current and not new", (Table 4-4) we observe that after adjustment for

multiple risk factors and confounders, subjects newly exposed to ipratropium bromide were at higher risk for a cardiac arrhythmia than those subjects whose exposure to this bronchodilator class was current but not new (RR 2.39 [95% CI 1.42 to 4.05]) and (RR 1.33 [95% CI 1.00 to 1.76]). In addition, subjects newly exposed to long-acting β-agonists appear at high risk of arrhythmia, based on results accruing to four exposed cases (RR 4.55 [95% CI 1.43 to 14.45]). When limiting the outcome specifically to cases of atrial fibrillation and flutter, a persistent elevated risk associated with new short-acting β-agonists was observed (RR 2.34 [95% CI 1.08 to 5.08]) (not shown).

Table 4-5 presents results for the restricted case-control sample in which subjects who had either been hospitalised or had incurred a COPD exacerbation within 60 days of the index date were deleted. An elevated risk of cardiac arrhythmia associated with the new use of ipratropium bromide remained (RR 3.65 [95% CI 1.72 to 7.74] . Current (but not new) use as well as past use of ipratropium bromide were also associated with an elevated risk of arrhythmia (RR 1.60 [95% CI 1.13 to 2.25]) and (RR 1.60 [95% CI 1.09 to 2.23]) respectively. In contrast to the analyses from the full cohort, new use of methyl xanthines was also found to be associated with arrhythmia within this restricted cohort (RR 5.17 [95% CI 1.38 to 19.30]) based on three exposed cases. Given that restricting the cases and controls to subjects without recent exacerbation or hospitalisation left only one case newly exposed to long-acting β-agonists, the estimate is imprecise and we were unable to detect a statistically significant association.

When the analysis was further restricted to cases of atrial fibrillation and flutter, new use of methyl xanthines was found to be associated with an increased risk, RR 7.88 [95% CI 1.43 to 43.56] based on two exposed cases (Not shown). New exposure to ipratropium bromide showed a non-statistically significant risk of AF (RR 2.69 [95% CI 0.79 to 9.19]) based on four exposed cases.

The assumption pertaining to the duration of the exposure current time window was tested, where it was allowed to vary from between 45 to 90 days. New exposure to ipratropium bromide was found to be relatively impervious to the number of days used to assess current exposure. When the current tine window was defined to be 30 days in length, however, the risk rose almost two-fold (RR 6.33 [95% CI 2.21 to 18.15]). (Figure 4-1).

Two other sets of sensitivity analyses for which i) assumptions pertaining to the definition of a COPD exacerbation were sequentially relaxed; and ii) subjects experiencing exacerbations during the current time window were included, the variable exacerbation modeled as a covariate in the analysis. Neither of these analyses produced results pertaining to new use of ipratropium bromide different than those produced in the analyses reported above (data not shown).

Comment

Our results provide evidence that subjects newly dispensed ipratropium bromide are at increased risk of arrhythmias. These findings were robust, as sensitivity analyses, which tested several assumptions, produced very similar results. Our results raise concern regarding the risks of arrhythmia from new use of long-acting β-agonists and methyl xanthines, however since these results were based on very few exposed cases, they require confirmation in a larger data set.

In keeping with similar studies examining bronchodilator risks, we assumed in the previous analyses that the time window for current exposure was sixty (60) days.[290;291] However, some patients may actually take more frequent doses in order to obtain symptomatic relief, thereby depleting their bronchodilator supply earlier than expected. On the other hand, COPD patients have been found in general to have poor adherence to bronchodilator therapy [292-296] and therefore could potentially have a bronchodilator supply available to them beyond the assumed 60 day window. Seeing that duration of the current time window is proportional to the probability of misclassification of exposure, the fact that we

observe a high rate ratio at 30 days provides more support suggesting the risk of arrhythmia accruing to the new use of ipratropium bromide in COPD patients.

The fact that the majority of the arrhythmias were atrial fibrillation and flutter (AF) is consistent with the fact that is the most common sustained arrhythmia encountered in clinical practice,[297] is increasingly prevalent among the elderly,[201;298] and the findings of Bush et al who found that reduced lung function is an independent predictor for incident atrial fibrillation.[287].

These results enhance the results of a previous study,[183] which examined the risk of cardiac arrhythmias and current use of bronchodilators firstly, by focusing on more vulnerable sub-population of the more elderly patients with COPD. Secondly, we investigated the specific risk associated with being a new-user of these medications, the exposure category that we found to be the most relevant in investigating these acute events. Thirdly, we carefully matched on time in order to account for trends in the use of medications over time and seasonality of COPD exacerbations. Finally, as a conceptual advance, we hypothesize that exacerbations of COPD are potentially strong confounders of the bronchodilator-arrhythmia association, took great care in identifying exacerbations in the population so that they may be better controlled for in our analyses.

Our own study also has limitations. Firstly, since we did not have information regarding variables such as lung function, smoking status and body mass index, we expect that there may be residual bias from unmeasured confounding. In addition, as in all studies that rely on data from administrative databases, we measured exposure based on medication dispensing as opposed to the actual consumption of these drugs. Since COPD is a disease for which patients rely on their bronchodilator medications for relief, we do not expect misclassification of exposure to be an issue as compared with studies of asymptomatic conditions such as hypertension.

This study had insufficient power to detect an association with long-acting β–agonists, and was limited in terms of sample size to examine the risks associated with atrial fibrillation and flutter specifically, or any other of the specific arrhythmia diagnoses individually. Since long-acting β-agonists fall under the Saskatchewan Formulary *Exception Drug Status Program,* they are only dispensed after formal request by a respirologist, and are approved for use only in the most severe cases. By including this category of drugs in our statistical models (in addition to our other confounders and covariates), however, we believe we have been able to adequately adjust for severity of COPD.

Protopathic bias is said to occur when a drug is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnosed.[299] When the disease is later discovered, an association may be incorrectly inferred between that exposure and outcome. Chronic heart failure (CHF), a strong risk factor for cardiac arrhythmia, causes breathlessness and fatigue,[300] which could be mistaken under certain circumstances for either an exacerbation or increasing COPD severity. In this study, it is possible that the problem of protopathic bias may have occurred in situations where patients presented with symptoms of dyspnea, a diagnosis of CHF was missed, and the patient was prescribed a new bronchodilator medication.

In conclusion, we have found that new use of a short-acting anticholinergic increases the risk of cardiac arrhythmia. Our results also provide some preliminary evidence regarding the risks of arrhythmia from new use of long-acting β-agonists , and the risk of both arrhythmias in general and AF in particular from the new use of methyl xanthines. Although further studies using larger databases would be required in order to confirm these results, these finding reinforce the need for careful prescribing and observation of patients in the weeks following the initiation of bronchodilator medications in patients with COPD.

Table 4-1 Baseline characteristics of cases of arrhythmia and controls

	Cases	Controls
Subjects n	469	9,060
Age mean ± SD*	78.6 (8.4)	77.8 (8.0)
Male %*	55.2	55.5
Years of follow up from cohort entry to index date mean ± SD	3.86 (3.1)	3.90 (3.1)
Use of other COPD therapy during the 12 months prior to index date:		
Inhaled Corticosteroids	37.3	38.2
Oral Corticosteroids (OCS)	21.3	15.7
Other Respiratory Drugs	1.7	2.1
Home Oxygen Use during time on study	13.2	7.9
Any Previous History of Arrhythmia (prior to cohort entry)	49.2	27.4
Use of medications possibly associated with Arrhythmia during the 12 months prior to index date:		
Diuretic	66.3	47.7
Potassium-Sparing Diuretics	7.3	4.4
Macrolide antibiotics (not on same day as OCS)	11.1	12.7
Non-macrolide antibiotics (not on same day as OCS)	56.9	50.2
Ace inhibitors	39.2	26.4
Diabetic medications	10.0	9.8
ASA	16.0	10.0
Non-steroidal anti-inflammatory medications	27.7	20.9
Beta blockers (non selective)	4.9	2.6
Beta blockers (beta-1 selective)	9.0	5.3
Digitalis glycosides	34.3	13.9
Nitrates	30.1	15.1
Calcium-Channel blockers	32.4	17.4
Other Hypotensive Agents	9.6	7.1
Anti-Arrhythmic Medications	5.5	1.0
Antidepressants	13.2	14.7
Psychotherapeutic agents	6.0	6.0
Motility agents	10.2	7.4
Thyroid Medications	14.1	10.2
Hospital or out-patient diagnosis code indicating comorbidity during the 12 months prior to index date:		
CHF	37.3	16.4
Enlarged Heart	3.8	1.0
Hypertension	28.4	23.3
Cerebrovascular Disease	10.4	6.1
Atherosclerosis	3.2	1.0
Other Cardiovascular disease	52.9	28.3
Anaemia	11.1	5.9
Diabetes, Thyroid disease, or hyperlipidemia	21.8	18.6
Genito-Urinary disease	26.2	18.3
Any non- primary diagnosis COPD hospitalisation	14.7	9.2
Any other not otherwise specified hospitalisation	14.5	13.6

Table 4-2 Arrhythmia Case Distributions by Type

Arrhythmia Type:	non fatal		Fatal		All Arrhythmias	
Paroxysmal supraventricular tachycardia	16	4%	--	0%	16	3%
Paroxysmal ventricular tachycardia	15	4%	--	0%	15	3%
Paroxysmal tachycardia, unspecified	1	0%	--	0%	1	0%
Atrial fibrillation and flutter	207	50%	14	25%	221	47%
Ventricular fibrillation and flutter	3	1%	--	0%	3	1%
Cardiac arrest	37	9%	36	64%	73	16%
Premature beats	5	1%	--	0%	5	1%
Other specified cardiac dysrhythmias	95	23%	--	0%	95	20%
Cardiac dysrhythmia, unspecified	34	8%	6	11%	40	9%
Total	413	100%	56	100%	469	100%

Table 4-3 Rate ratio of arrhythmia associated with current (exposure between 0 to 60 days before index date) vs. past use (exposure during the 365 to 61 day period before index date) of bronchodilator agents as compared with no use during the year leading up to the index date

Hierarchical Independent Exposure	# (%) Cases Exposed	# (%) Controls Exposed	Crude RR	Adjusted RR (95% CI)
Ipratropium Bromide				
Current	138 (29.42)	2015 (22.24)	1.59 (1.24 - 2.02)	1.46 (1.12 - 1.90)
Past Only	62 (13.22)	970 (10.71)	1.48 (1.10 - 1.99)	1.29 (0.94 - 1.78)
Unexposed	269 (57.36)	6075 (67.05)	1.00 (Reference)	1.00 (Reference)
Short-Acting Beta Agonists				
Current	178 (37.95)	3187 (35.18)	0.98 (0.77 - 1.23)	0.91 (0.70 - 1.19)
Past Only	105 (22.39)	2056 (22.69)	1.01 (0.78 - 1.30)	0.92 (0.70 - 1.23)
Unexposed	186 (39.66)	3817 (42.13)	1.00 (Reference)	1.00 (Reference)
Methyl Xanthines				
Current	48 (10.23)	786 (8.68)	1.12 (0.82 - 1.54)	1.00 (0.72 - 1.40)
Past Only	19 (4.05)	560 (6.18)	0.63 (0.39 - 1.01)	0.54 (0.33 - 0.89)
Unexposed	402 (85.71)	7714 (85.14)	1.00 (Reference)	1.00 (Reference)
Long-Acting Beta Agonists				
Current	9 (1.92)	146 (1.61)	1.02 (0.51 - 2.07)	1.13 (0.53 - 2.43)
Past Only	7 (1.49)	51 (0.56)	2.36 (1.04 - 5.36)	1.81 (0.74 - 4.42)
Unexposed	453 (96.59)	8863 (97.83)	1.00 (Reference)	1.00 (Reference)

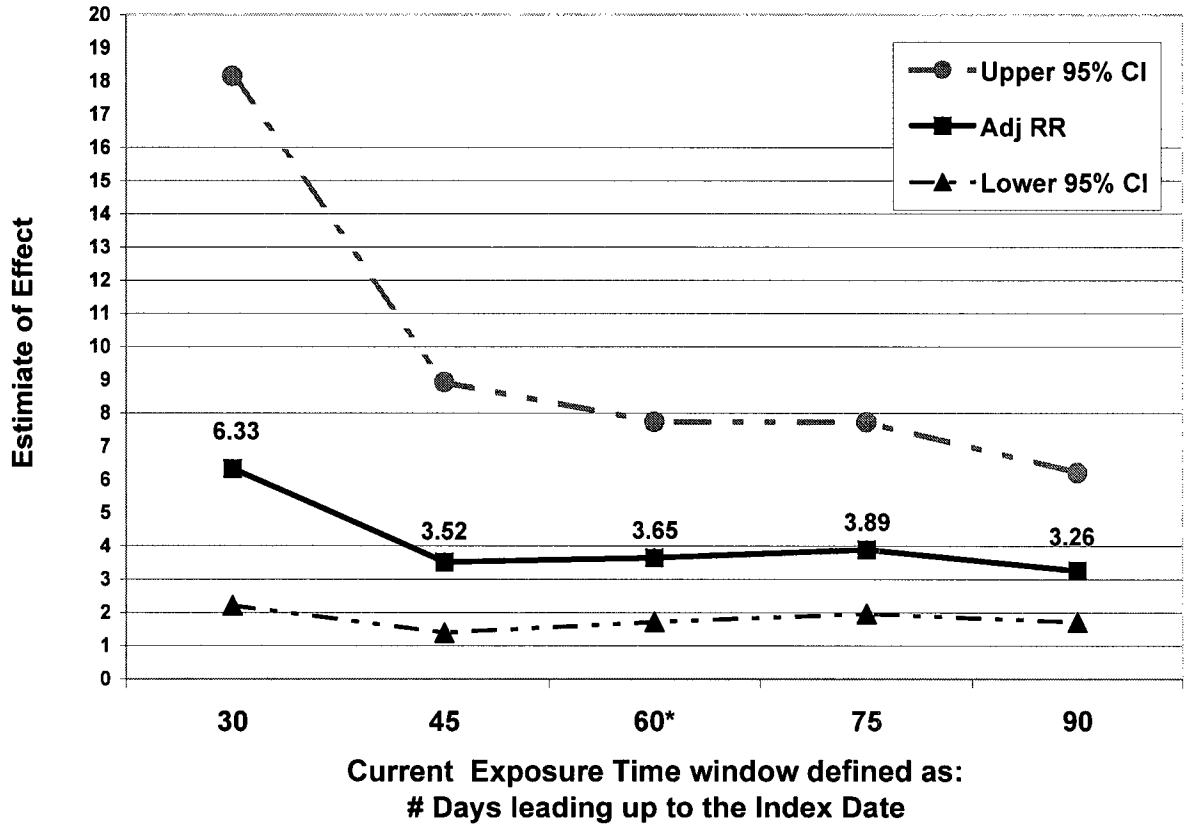
Table4-4 Rate ratio of arrhythmia differentiating between current and new use (exposure between 0 to 60 days before index date, with no past use during the previous 10 months) versus current and not new use (current users who are also past users) of bronchodilator agents

Hierarchical Independent Exposure	# (%) Cases Exposed	# (%) Controls Exposed	Crude RR	Adjusted RR (95% CI)
Ipratropium Bromide				
Current and New	24 (5.12)	206 (2.27)	2.54 (1.54 - 4.19)	2.39 (1.42 - 4.05)
Current, not New	114 (24.31)	1809 (19.97)	1.46 (1.13 - 1.89)	1.33 (1.00 - 1.76)
All Current	138 (29.42)	2015 (22.24)	1.59 (1.24 - 2.02)	1.46 (1.12 - 1.90)
Short-Acting β-Agonists				
Current and New	17 (3.62)	257 (2.84)	0.91 (0.52 - 1.63)	0.89 (0.48 - 1.63)
Current, not New	161 (34.33)	2930 (32.34)	0.99 (0.78 - 1.25)	0.92 (0.70 - 1.21)
All Current	178 (37.95)	3187 (35.18)	0.98 (0.77 - 1.23)	0.91 (0.70 - 1.19)
Methyl Xanthines				
Current and New	8 (1.71)	69 (0.76)	1.75 (0.81 - 3.75)	1.60 (0.70 - 3.69)
Current, not New	40 (8.53)	717 (7.91)	1.04 (0.74 - 1.46)	0.94 (0.66 - 1.34)
All Current	48 (10.23)	786 (8.68)	1.12 (0.82 - 1.54)	1.00 (0.72 - 1.40)
Long-Acting β-Agonists				
Current and New	4 (0.85)	21 (0.23)	3.07 (1.03 - 9.15)	4.55 (1.43 - 14.45)
Current, not New	5 (1.07)	125 (1.38)	0.68 (0.27 - 1.71)	0.72 (0.27 - 1.90)
All Current	9 (1.92)	146 (1.61)	1.02 (0.51 - 2.07)	1.13 (0.53 - 2.43)

Table 4-5 Rate ratio of arrhythmia associated bronchodilator use in the restricted cohort (after limiting the analysis to subjects who during the current period were neither hospitalised nor experienced an exacerbation)

	Cases # (%)	Controls # (%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Total	317	5,320		
Ipratropium Bromide				
Current and New	12 (3.79)	81 (1.52)	3.70 (1.83 - 7.51)	3.65 (1.72 - 7.74)
Current, not New	74 (23.34)	1008 (18.95)	1.64 (1.20 - 2.25)	1.60 (1.13 - 2.25)
Past Only	48 (15.14)	540 (10.15)	1.83 (1.29 - 2.59)	1.60 (1.09 - 2.33)
Unexposed	183 (57.73)	3691 (69.38)	1.00 (Reference)	1.00 (Reference)
Short-Acting Beta Agonists				
Current and New	6 (1.89)	116 (2.18)	0.56 (0.22 - 1.44)	0.61 (0.23 - 1.60)
Current, not New	101 (31.86)	1640 (30.83)	0.94 (0.70 - 1.26)	0.92 (0.65 - 1.28)
Past Only	77 (24.29)	1201 (22.58)	1.06 (0.78 - 1.44)	0.96 (0.69 - 1.35)
Unexposed	133 (41.96)	2363 (44.42)	1.00 (Reference)	1.00 (Reference)
Methyl Xanthines				
Current and New	3 (0.95)	17 (0.32)	2.00 (0.55 - 7.26)	5.17 (1.38 - 19.30)
Current, not New	24 (7.57)	406 (7.63)	0.95 (0.61 - 1.46)	0.88 (0.56 - 1.40)
Past Only	10 (3.15)	308 (5.79)	0.51 (0.26 - 0.97)	0.45 (0.22 - 0.89)
Unexposed	280 (88.33)	4589 (86.26)	1.00 (Reference)	1.00 (Reference)
Long-Acting Beta Agonists				
Current and New	1 (0.32)	13 (0.24)	0.93 (0.12 - 7.30)	1.73 (0.21 - 14.33)
Current, not New	3 (0.95)	67 (1.26)	0.62 (0.19 - 2.04)	0.63 (0.18 - 2.19)
Past Only	1 (0.32)	24 (0.45)	0.52 (0.07 - 3.95)	0.39 (0.05 - 3.17)
Unexposed	312 (98.42)	5216 (98.05)	1.00 (Reference)	1.00 (Reference)

Figure 4-1 Sensitivity Analysis for the duration definition of the current time window on the rate ratio of arrhythmia associated with current new use of ipratropium bromide



* It was assumed in this paper that the current time window was 60 days in length

4.3 *Additional analyses*

In the paper titled "The use of bronchodilators and the risk of arrhythmia in chronic obstructive pulmonary disease (COPD): a nested case-control study" we showed that new use of bronchodilators increased the risk of cardiac arrhythmias in patients with COPD. Due to journal submission guidelines which impose rather strict limitations regarding the number of tables included within an article, the accompanying tables of results corresponding to some sensitivity analyses were discussed but not shown.

In addition, one aspect of the analysis which was somewhat troubling was the observed instability of estimates which was possibly a result of random variation produced by the fixed number of cases to control selection process. As such, a second complete set of analyses generated from within the same database were produced where instead of sampling controls to cases, the entire risk set was used. The detailed sensitivity analyses results in addition to those pertaining to the full risk set analyses will be presented and discussed here.

4.3.1 Sensitivity Analyses pertaining to the definition of Acute Exacerbation (AECOPD):

In the preceding analysis, the operational definition for AECOPD was the observation of either a COPD primary diagnosis hospitalisation (corresponding to a severe exacerbation) or an oral corticosteroid and an antibiotic dispensed on the same calendar date (as per treatment guidelines for a moderate exacerbation). Short-term, high dose systemic (oral) corticosteroid therapy has been found to increase the rate of improvement in lung function and dyspnoea over the first 72 hours of treatment,[301] and was deemed to be commonplace treatment both in the community and tertiary care settings.[302] Although airway improvements achieved through treatment are expected to be modest, even small improvements are considered to be beneficial in patients with severe airway obstruction who cannot tolerate further respiratory deterioration.[51]

The antibiotic component of this definition is consistent with both evidence from clinical trials as well as the 1987 study by Anthonisen et al who investigated the potentially beneficial effects of antibiotic therapy in managing COPD exacerbations in which exacerbations were defined specifically in terms of signs indicative of an infectious aetiology (such as increased sputum production or purulence).[303;304] Approximately one third of exacerbations, however, are associated with the presence of a viral (and not bacterial) respiratory infection, and some members of the academic and clinical communities have debated as to whether or not some exacerbations can occur in a COPD patient without any infection at all.[305]

Ongoing dispute regarding whether the benefits associated with use of antibiotics in treating AECOPD, however, could result in some physicians not prescribing antibiotics if they are uncertain that the exacerbation has a bacterial aetiology. It should also be noted that oral corticosteroid exposure comes at a cost of some unwelcome side-effects such as fluid retention, hypertension, diabetes mellitus, adrenal suppression and osteoporosis. The risk of side-effects coupled with the fact that there also exists controversy regarding the appropriate systemic corticosteroid dosing regimen could potentially inhibit physicians from prescribing these drugs as well. Given these prevailing treatment issues, the fact that our initial AECOPD definition was strict in that it had the requirement of both drugs dispensed on the same date, this may have decreased our sensitivity in identifying cases of AECOPD among our cohort.

In order to address this issue, sensitivity analyses were performed in which the assumptions pertaining to the operational definition for moderate exacerbations were sequentially relaxed. It was reported in the manuscript that results pertaining to new use of ipratropium bromide were not appreciably different after application of these different AECOPD definitions. The full results of these sensitivity analyses are presented in Tables 4-6 and 4-7 below.

In Table 4-6, all definitions of AECOPD include a COPD primary diagnosis hospitalisation (i.e. severe exacerbation). After relaxing the definition of moderate exacerbation from both an oral corticosteroid (OCS) and an antibiotic (ABX) on the same day to:

- Only OCS; or
- Either OCS or ABX,

the rate ratios associated with being newly exposed to ipratropium bromide remained significant and ranged between 3.3 and 4.4, with overlapping confidence intervals depending on the definition being used. The statistically significant association between current but not new ipratropium use and arrhythmia did not persist in these sensitivity analyses.

We contend, however, that in order to handle immeasurable time bias[185] that it is necessary to exclude any subject who had been hospitalised during the curing time window, whether that subject was hospitalised for COPD or any other condition. Table 4-7 therefore provides a second set of exacerbation definition sensitivity analyses examining the outcome associated with relaxing the definition for moderate exacerbations after subjects who had been hospitalised during the current time window (for any reason) have been excluded from analysis.

The rate ratios associated with being newly exposed to ipratropium bromide once again remained relatively impervious to the operational definition for moderate exacerbations once all current hospitalisations had been excluded. As previously, the statistically significant association between current but not new ipratropium use and arrhythmia did not persist in these sensitivity analyses. Under the "Either OCS or ABX' definition for moderate exacerbation, there were no cases observed which had newly exposed to methyl xanthines, however the rate ratio associated

with the definition which only required a prescription for an OCS was essentially identical to the definition used during the main analysis. It should be noted that the corresponding number of exposed controls for the reported rate ratios of 5.17 and 5.99 were 15 and 17 respectively, with each scenario corresponding to only 3 exposed cases.

From this set of two sensitivity analyses, we can therefore conclude that the reported elevated risk associated with being newly exposed to ipratropium bromide was impervious to our exacerbation definition.

Table 4-6 Sensitivity Analysis: Altering the definition for current exacerbations as excluded from the analysis (before all current hospitalisations for any reason excluded)

Adjusted RR (95% CI) After Exclusion of subjects with a Current Exacerbation (During the 60 days from index date time window) Defined as:			
	A COPD Primary Dx Hospitalisation Or Oral Corticosteroid (OCS) and Antibiotic (Abx) Rx on the same date*	A COPD Primary Dx Hospitalisation Or Any OCS Rx	A COPD Primary Dx Hospitalisation Or Any OCS Rx or Any Abx Rx
Ipratropium Bromide			
Current & New	3.32 (1.89 - 5.83)	3.55 (1.98 - 6.39)	4.40 (2.07 - 9.33)
Current, not New	1.41 (1.05 - 1.90)	1.29 (0.94 - 1.77)	1.21 (0.83 - 1.76)
Past Only	1.37 (0.98 - 1.93)	1.35 (0.95 - 1.91)	1.31 (0.87 - 1.98)
Unexposed	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Short-Acting Beta Agonists			
Current & New	0.87 (0.44 - 1.72)	0.81 (0.39 - 1.69)	0.79 (0.33 - 1.90)
Current, not New	0.93 (0.70 - 1.24)	0.97 (0.72 - 1.31)	0.99 (0.69 - 1.42)
Past Only	0.88 (0.66 - 1.19)	0.91 (0.67 - 1.24)	0.93 (0.65 - 1.33)
Unexposed	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Methyl Xanthines			
Current & New	0.99 (0.28 - 3.55)	1.08 (0.30 - 3.93)	--[†]
Current, not New	0.90 (0.61 - 1.33)	0.97 (0.65 - 1.46)	0.71 (0.41 - 1.21)
Past Only	0.44 (0.25 - 0.79)	0.49 (0.28 - 0.88)	0.52 (0.26 - 1.01)
Unexposed	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Long-Acting Beta Agonists			
Current & New	3.05 (0.81 - 11.47)	3.00 (0.62 - 14.42)	1.66 (0.20 - 14.00)[‡]
Current, not New	0.92 (0.34 - 2.47)	0.99 (0.33 - 2.98)	0.64 (0.14 - 2.94)
Past Only	0.91 (0.25 - 3.29)	0.90 (0.19 - 4.18)	0.91 (0.19 - 4.41)
Unexposed	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

*Exacerbations were defined as either a COPD primary diagnosis hospitalisation (sever exacerbation) or a prescription for an oral corticosteroid and an antibiotic on the same date (moderate exacerbation) in the previous analyses

[†] There were no exposed cases available for study under this scenario

Table 4-7 Sensitivity Analysis: Altering the definition for current exacerbations as excluded from the analysis (after all current hospitalisations for any reason excluded):

Adjusted RR (95% CI) After Exclusion of subjects with a Current Exacerbation (During the 60 days from index date time window) Defined as:			
	Any Hospitalisation Or Oral Corticosteroid (OCS) and Antibiotic (Abx) Rx on the same date*	Any Hospitalisation Or Any OCS Rx	Any Hospitalisation Or Any OCS Rx or Any Abx Rx
Ipratropium Bromide			
Current & New	3.65 (1.72 - 7.74)	3.71 (1.71 - 8.05)	4.44 (1.72 - 11.43)
Current, not New	1.60 (1.13 - 2.25)	1.43 (0.99 - 2.06)	1.37 (0.90 - 2.09)
Past Only	1.60 (1.09 - 2.33)	1.62 (1.10 - 2.39)	1.57 (1.00 - 2.47)
Unexposed	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Short-Acting Beta Agonists			
Current & New	0.61 (0.23 - 1.60)	0.69 (0.26 - 1.84)	0.78 (0.26 - 2.33)
Current, not New	0.92 (0.65 - 1.28)	0.96 (0.67 - 1.36)	1.07 (0.71 - 1.62)
Past Only	0.96 (0.69 - 1.35)	0.96 (0.68 - 1.36)	0.98 (0.66 - 1.47)
Unexposed	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Methyl Xanthines			
Current & New	5.17 (1.38 - 19.30)	5.66 (1.46 - 21.91)	--†
Current, not New	0.88 (0.56 - 1.40)	0.96 (0.59 - 1.54)	0.62 (0.32 - 1.19)
Past Only	0.45 (0.22 - 0.89)	0.48 (0.24 - 0.96)	0.53 (0.24 - 1.18)
Unexposed	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Long-Acting Beta Agonists			
Current & New	1.73 (0.21 - 14.33)	2.10 (0.25 - 17.60)‡	3.02 (0.33 - 27.77)‡
Current, not New	0.63 (0.18 - 2.19)	0.52 (0.12 - 2.35)	--†
Past Only	0.39 (0.05 - 3.17)	--†	--†
Unexposed	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

*Exacerbations were defined as either a COPD primary diagnosis hospitalisation (sever exacerbation) or a prescription for an oral corticosteroid and an antibiotic on the same date (moderate exacerbation) in the previous analyses

‡ There was only one exposed case available for study under this scenario

† There were no exposed cases available for study under this scenario

4.3.2 The impact of excluding patients hospitalised during the current time window:

As discussed in the previous section, drugs dispensed in hospital are not captured by most administrative health databases, and the Saskatchewan Health databases are no exception. The resulting potential for misclassification of exposure during a hospitalisations can lead to immeasurable time bias[206]. To the extent that any residual supply of hospital-dispensed drugs would be available to subjects upon discharge, this extends the exposure misclassification time window by the expected duration of this residual supply. Since we expect, on average, that a bronchodilator prescription would last two months, at the limit then, hospitalised subjects could have up to two months supply upon discharge. This was the underlying rationale as to why we excluded any subject who was hospitalised at any dime during current time window.

We conducted sensitivity analyses in order to evaluate the impact of including versus excluding subjects who had undergone hospitalisation during the current use time window. One attempt was to limit the exclusions only to patients experiencing severe exacerbations, the notion being that this was the subset of subjects most likely to have been dispensed in-hospital COPD medications. In the previous manuscript we reported that none of these analyses produced results pertaining to new use of ipratropium bromide which were significantly different than those produced in the main analysis results. Table 4-8 presents three sets of results in which the occurrence of a current moderate exacerbations was modeled as a covariate and:

1) Hospitalised subjects were included;
2) Subjects hospitalised with a severe exacerbation defined as a COPD primary diagnosis during the current time window were excluded (i.e. subjects hospitalised for any other primary diagnosis not excluded);
3) Subjects hospitalised for any reason during the current time window were excluded.

Aside from the confidence interval width which increased in magnitude with each successive set of exclusions, the rate ratio associated with being newly exposed to ipratropium bromide was robust to this assumption. It is worth noting, that only in the third scenario does the risk associated with past use attain statistical significance which is of interest since this is the most restrictive case of the three and therefore had less sample size and therefore less power to detect an association.

Table 4-8 Sensitivity analysis: Exclusion of subjects who were hospitalised during the current period

	Adjusted RR (95% CI)		
	Before any Hospitalisation Exclusions	After current primary diagnosis COPD Hospitalisations Excluded	After All Current Hospitalisations Excluded
Ipratropium Bromide			
Current & New	2.39 (1.42 - 4.05)	2.93 (1.67 - 5.13)	3.41 (1.60 - 7.23)
Current, not New	1.33 (1.00 - 1.76)	1.39 (1.03 - 1.86)	1.57 (1.12 - 2.20)
Past Only	1.29 (0.94 - 1.78)	1.31 (0.94 - 1.84)	1.56 (1.07 - 2.27)
Unexposed	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Short-Acting Beta Agonists			
Current & New	0.89 (0.48 - 1.63)	0.80 (0.40 - 1.58)	0.58 (0.22 - 1.51)
Current, not New	0.92 (0.70 - 1.21)	0.94 (0.71 - 1.25)	0.94 (0.68 - 1.31)
Past Only	0.92 (0.69 - 1.22)	0.88 (0.66 - 1.19)	0.96 (0.69 - 1.35)
Unexposed	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Methyl Xanthines			
Current & New	1.60 (0.70 - 3.69)	0.89 (0.25 - 3.17)	3.70 (0.98 - 13.94)
Current, not New	0.94 (0.66 - 1.34)	0.94 (0.64 - 1.37)	0.94 (0.61 - 1.47)
Past Only	0.55 (0.33 - 0.90)	0.43 (0.24 - 0.76)	0.42 (0.21 - 0.84)
Unexposed	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Long-Acting Beta Agonists			
Current & New	4.55 (1.43 - 14.45)[§]	3.07 (0.82 - 11.48)[¥]	1.54 (0.19 - 12.56)[‡]
Current, not New	0.72 (0.27 - 1.90)	0.85 (0.32 - 2.27)	0.55 (0.16 - 1.93)
Past Only	1.83 (0.75 - 4.47)	1.64 (0.58 - 4.61)	0.84 (0.18 - 3.97)
Unexposed	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

Reported rate ratios arose from:

[‡] one exposed case

[¥] three exposed cases

[§] four exposed cases

4.3.3 Sensitivity Analyses pertaining to the analytical method used to control for exacerbations:

It was noted at the outset of this research that the identification and handling of exacerbations would likely prove to be a key challenge in this study. To this end, matching on calendar index date allowed (among other things) cases and controls to have equal opportunity to be exposed to the influenza virus, and thus be indirectly matched on exacerbation. Restriction and statistical modeling are both alternatively accepted methods to control of confounding in observational studies which should, in theory, produce similar results. Restriction is a simple and effective method which prevents the restricted factor from varying entirely, thereby eliminating its ability to confound the exposure-outcome estimate of effect.[206] Given that we feel somewhat hesitant regarding the validity of some of our estimates of effect based on the paucity of newly exposed cases, restriction which, by definition, further restricts sample size might be considered to be a suboptimal choice. Additionally, the creation of a homogenous (i.e. non-exacerbation within 60 days to index) dataset limits our ability to generalise our results to both stable and unstable COPD populations.[306] Control of confounding via restriction of course also eliminates the ability to test for effect modification by the restricted factor.

Multiple regression methods, our second option as a method to control confounding, however, are not without limitation as well. Regression models by definition impose structure on the data which may or may not fit the actual data under study. If the true shape of a the relationship between exacerbations and arrhythmia is different than that being imposed via regression, the regression model may not be effective in controlling for confounding and result in a biased estimate of effect.[306] In addition, when exposed and unexposed groups have markedly different distributions of exacerbation, the estimated association which is computed may be biased and/ or imprecise.[307]

It was reported in our previous manuscript, that in one last set of sensitivity analyses, instead of excluding subjects with moderate exacerbations during the current time window, these subjects were included for analysis with the variable exacerbation modeled as a covariate. After excluding subjects who had been discharged from hospital within 60 days of the index date, the results pertaining to new use of ipratropium bromide were once again quite similar (RR 2.33 [95% CI 1.01 to 5.36]) with the confidence interval overlapping all estimates produced in all other sensitivity analyses. Full reporting of all scenarios investigated where control for exacerbations was accomplished via the inclusion exacerbations as a covariate using multivariate regression are provided in Table 4-9.

Table 4-9 Sensitivity Analysis comparing three methods to control for confounding by exacerbations

Exposure Use Category		Riskset before exclusions: Modeling both moderate and severe Exacerbations occurring within the 60-day current time window	After excluding current Moderate Exacerbations, Modeling current Severe Exacerbations	After excluding current Severe Exacerbations, Modeling current Moderate Exacerbations	After excluding Both Severe and Moderate Current Exacerbations
Ipratropium Bromide	Current & New	2.39 (1.42 - 4.05)	3.11 (1.80 - 5.38)	2.93 (1.67 - 5.13)	3.32 (1.89 - 5.83)
	Current, not new	1.33 (1.00 - 1.76)	1.42 (1.06 - 1.90)	1.39 (1.03 - 1.86)	1.41 (1.05 - 1.90)
	Past Only	1.29 (0.94 - 1.78)	1.35 (0.97 - 1.87)	1.31 (0.94 - 1.84)	1.37 (0.98 - 1.93)
	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Short-Acting β-Agonists	Current & New	0.89 (0.48 - 1.63)	0.93 (0.50 - 1.76)	0.80 (0.40 - 1.58)	0.87 (0.44 - 1.72)
	Current, not new	0.92 (0.70 - 1.21)	0.96 (0.73 - 1.27)	0.94 (0.71 - 1.25)	0.93 (0.70 - 1.24)
	Past Only	0.92 (0.69 - 1.22)	0.95 (0.71 - 1.27)	0.88 (0.66 - 1.19)	0.88 (0.66 - 1.19)
	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Methyl Xanthines	Current & New	1.60 (0.70 - 3.69)	1.39 (0.49 - 3.96)	0.89 (0.25 - 3.17)	0.99 (0.28 - 3.55)
	Current, not new	0.94 (0.66 - 1.34)	0.87 (0.59 - 1.27)	0.94 (0.64 - 1.37)	0.90 (0.61 - 1.33)
	Past Only	0.55 (0.33 - 0.90)	0.56 (0.34 - 0.94)	0.43 (0.24 - 0.76)	0.44 (0.25 - 0.79)
	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Long-Acting β-Agonists	Current & New	4.55 (1.43 - 14.45)	4.81 (1.47 - 15.77)	3.07 (0.82 - 11.48)	3.05 (0.81 - 11.47)
	Current, not new	0.72 (0.27 - 1.90)	0.86 (0.32 - 2.28)	0.85 (0.32 - 2.27)	0.92 (0.34 - 2.47)
	Past Only	1.83 (0.75 - 4.47)	1.39 (0.49 - 3.92)	1.64 (0.58 - 4.61)	0.91 (0.25 - 3.29)
	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

Note: The definition of a severe exacerbation is the occurrence of a primary diagnosis COPD hospitalisation.

4.3.4 Sampling Error and resulting instability of estimates of effect using 1:10 instead of 1:20 matching

In studies of rare outcomes where the number of cases within a cohort is limited, one method by which we may increase statistical power is by increasing the control-to case ratio. [308] When the expected relative risk is close to unity, sample size tables provided by Breslow and Day indicate that the gain in power associated with every additional control up to four controls per case is significant, but that this gain becomes negligible beyond this ratio.[215] In circumstances where the exposure is rare, the relative risk is appreciably different than unity, or when several exposures are being assessed concurrently, the number of required controls per case could be as many as ten or higher.[214;271;309]

In previous incarnations of these analyses, we had originally intended to create our nested case-control risk sets using a 1:10 case to control matching ratio. In order to perform the randomized selection of controls for each case from within the set of all eligible controls within the risk set, a random number was assigned to each control. This was accomplished by means of a computerised random generator, where the random number seed (a value determined by the investigator) determines the starting value for the random number generator. In the interest of experimentation, however, we noticed that our point estimates and confidence intervals were markedly unstable depending on which random seed was entered to the program.

In order to investigate this phenomenon, we undertook to experiment with eleven random seeds; thereby producing eleven distinct 1:10 matched nested case-control datasets from which to compare results. It should be noted, that at the time this experiment was undertaken, we were using an analytical model in which:

- The case definition included only primary diagnoses arrhythmia hospitalisations (i.e. it did not include fatal cases of arrhythmia); and
- Only cases of exacerbation within 60 days to the index date were excluded from the analysis (i.e. subjects hospitalised within the current time window were still included).

In addition, the results represent a slightly different covariate structure than that selected for our final models presented in the manuscript. Although one is unable, therefore, to directly compare these results to those from within the original manuscript, the point of presenting these data is to demonstrate the degree to which the random process of control selection can impact the results.

In Figure 4-2, the point estimates and confidence intervals associated with new use of ipratropium bromide produced from the 11 generated datasets are shown. We contrast these results to those associated with using the entire risk set where no sampling was performed, and all eligible controls contributed to the analysis. We observe that the estimates associated with seeds #2, #7, and #11 produce point estimates of 1.7 and confidence intervals which contained one. In these three circumstances, more exposed controls were selected with these risk sets containing more than 2.5% exposed controls as compared with 5.1% of our cases which were exposed. In the full risk set analysis, however, we observe that the point estimate is greater than 2 and statistically significant.

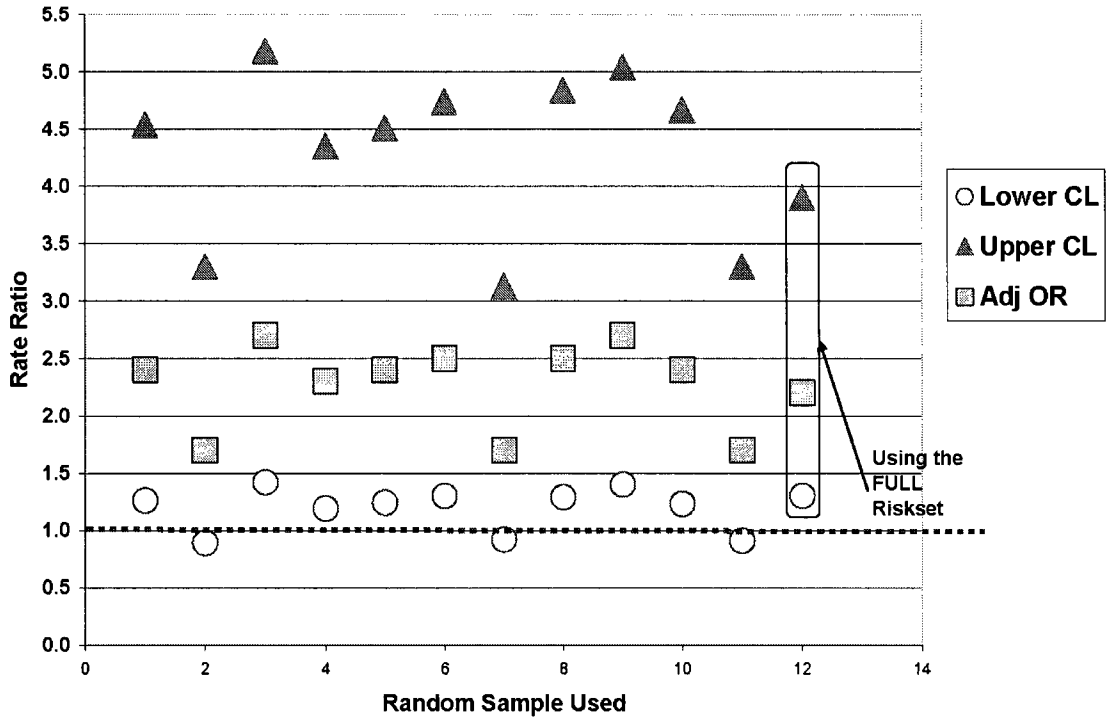


Figure 4-2 Random variation in point estimates and confidence bounds for new exposure to short-acting ipratropium bromide using 1:10 matching

Similarly, Figure 4-3 presents the same sensitivity analysis for point estimates and confidence intervals associated with new use of long-acting β-agonists. Although in this case, all point estimates remain statistically significant, we observe our rate ratios ranging between 4.7 and 11.3 depending on the random sample of ten controls generated. The corresponding widths of the 95% confidence intervals ranged from 17.2 to 52.32. In the full risk set analysis of this scenario (where only subjects with an exacerbation within 60 days of the index date were excluded) we observe a significant point estimate with a much tighter confidence interval (RR 4.4 [95% CI 1.53 to 12.47]). It should be noted, however, that we do not put much emphasis on these results owing to the fact that they are derived from having observed only four exposed cases.

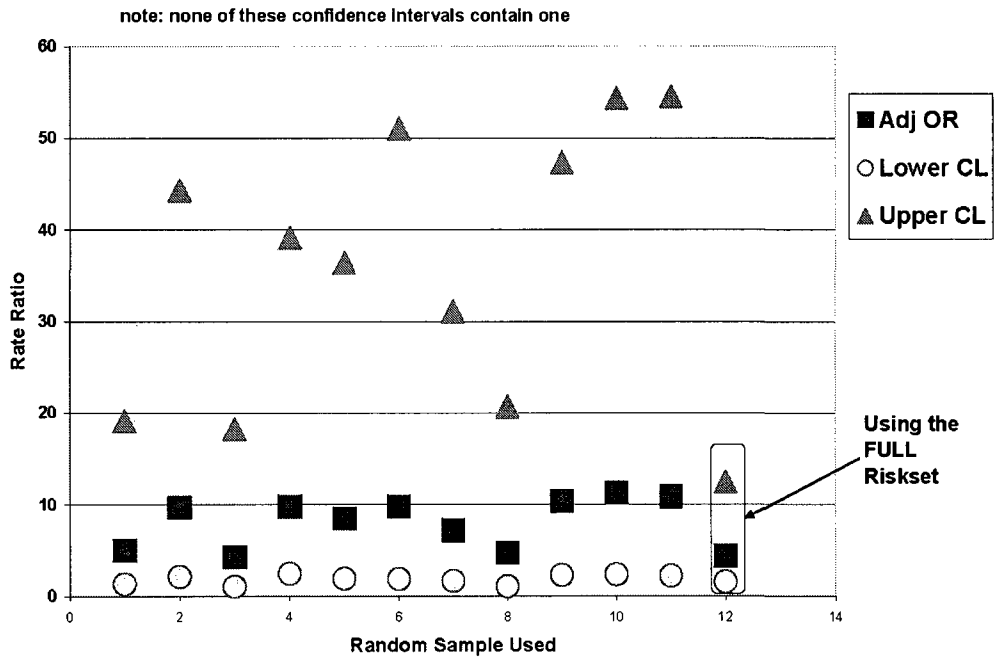


Figure 4-3 Random variation in point estimates and confidence bounds for new exposure to long-acting β-agonists using 1:10 matching

4.3.5 Reanalysis of the Saskatchewan cohort using a full risk set

The nested case-control approach has been shown to produce unbiased estimates of the rate ratios which would be obtained from a full Cox regression analysis.[271]

In addition to producing valid estimates of effect, it has been shown that the penalty incurred in precision is rather minimal. Given the computational intensity required when analyzing time-varying exposures within a full Cox model, the nested case control approach is an appealing option for the conduct of many epidemiologic studies, including those examining drug risks.

The key to the similarity between these two statistical approaches lies in the fact that the conditional likelihood used in conditional logistic regression is equivalent to the partial likelihood used in Cox regression with the exception that the denominator of the conditional likelihood includes only a selected number of sampled controls as opposed to the pool of all subjects available in the risk set. If then, one were to perform the conditional likelihood risk set sampling approach but use the entire pool of all subjects available in the risk set, there would be no difference between these two approaches and the estimated rate ratios and associated standard errors would be mathematically equivalent.

This next section presents a re-analysis of the Saskatchewan COPD cohort data in which all controls within each risk set was included for analysis, and thus should be regarded as a full Cox analysis.

Table 4-10 Full risk set- Characteristics of cases and controls

	Cases	Controls
Subjects *n*	469	31,232
Age mean ± SD*	78.6 (8.4)	76.2 (7.1)
Male %*	55.2	55.5
Years of follow up from cohort entry to index date mean ± SD	3.9 (3.1)	3.3 (1.0)
Use of other COPD therapy during the 12 months prior to index date:		
Inhaled Corticosteroids	37.3	38.6
Oral Corticosteroids	21.3	16.2
Other Respiratory Drugs	1.7	1.9
Any Previous History of Arrhythmia (prior to cohort entry)	49.2	27.1
Home Oxygen Use (dichotomous) during time on study	13.2	7.1
Use of medications possibly associated with Arrhythmia during the 12 months prior to index date:		
Anti-Arrhythmic Medications	5.5	1.4
Digitalis glycosides	34.3	13.3
Nitrates	30.1	14.4
Diuretics	66.3	45.0
Ace inhibitors	39.2	25.4
Beta blockers (non selective)	4.9	2.9
Beta blockers (beta-1 selective)	9.0	5.2
Calcium-Channel blockers	32.4	18.3
Other Hypotensive Agents	9.6	6.7
Net macrolide antibiotics	11.1	12.8
Net non-macrolide antibiotics	56.9	51.1
Motility agents	10.2	7.2
ASA	16.0	9.6
Non-steroidal anti-inflammatory medications	27.7	21.9
Antidepressants	13.2	13.7
Other Psychotherapeutic agents	6.0	5.0
Diabetic medications	10.0	9.6
Thyroid Medications	14.1	9.6
Hospital or out-patient diagnosis code indicating comorbidity during the 12 months prior to index date:		
CHF	37.3	16.4
Enlarged Heart	3.8	1.0
Hypertension	28.4	25.8
Cerebrovascular Disease	10.4	5.8
Atherosclerosis	3.2	1.1
Other Cardiovascular disease	52.5	29.3
Anaemia	11.1	6.2
Diabetes, Thyroid or Hyperlipidemia	21.8	19.5
Genitourinary Disease	26.2	19.4
Any non- primary diagnosis COPD hospitalisation	14.7	9.3
Any other not otherwise specified hospitalisation	14.5	13.8

Table 4-10 provides a comparison of the various characteristics between cases and controls. Using the same case series as previously, the full risk set analysis yielded a total of 31,232 control subjects for an average of 67 controls per case. As in the previous nested case-control approach, case subjects were more likely to have had a previous history of arrhythmia, have established risk factors for

arrhythmia such as CHF, enlarged heart, cerebrovascular disease and other cardiovascular diseases, and were more likely to have been using anti-arrhythmia medications, diuretics, ACE inhibitors, β–blockers, digitalis glycosides, calcium channel blockers and thyroid medications than were the controls. As previously, these differences were among the list of covariates controlled for in the analysis.

In the previous analyses, several models for estimating the arrhythmia risk associated with bronchodilator use in this population were explored based on the criteria used for the operational definition of exacerbations as well as the inclusion or exclusion of subjects:

- Experiencing a moderate exacerbation;
- Who were hospitalized with a primary diagnosis for COPD; or
- Who were hospitalized for any reason.

Table 4-11 provides the results accruing to the following seven modeling options for the risk of incurring any arrhythmia primary diagnosis hospitalisation or death after cohort entry:

1. All risk set subjects included, exacerbations and hospitalisations controlled for in the analysis;
2. Excluding subjects experiencing moderate exacerbations in the current time window (the sixty day period leading up to the event), hospitalisations controlled for in the analysis;
3. Excluding subjects who were hospitalized with a primary diagnosis code for COPD during the current time window, moderate exacerbations controlled for in the analysis;
4. Excluding subjects who were hospitalized for any reason during the current time window, moderate exacerbations controlled for in the analysis;
5. Excluding subjects experiencing either moderate exacerbations or who were hospitalized with a primary diagnosis code for COPD during the current time window, the event of being hospitalized for other reasons during the current period controlled for in the analysis;
6. Excluding both subjects with a primary diagnosis code for COPD as well as subjects who had been prescribed either an oral corticosteroid or an antibiotic during the current time window. This should be regarded as a relaxation of the definition of exacerbation

which in all other models required that both drugs be prescribed on the same day. Non-COPD hospitalisations occurring during the current time period were controlled for in the analysis; and finally,

7. The "restricted cohort" model, where any subject who had experienced either a moderate exacerbation or had been hospitalized for any reason during the current period were excluded from the analysis.

As demonstrated by these analyses, new use of ipratropium bromide was consistently associated with an increase risk of arrhythmia, with rate ratios ranging from 2.4 to 4.01. Current users of ipratropium bromide were also found to be at increased risk albeit to a lesser degree with rate ratios ranging from 1.15-1.51 (all but models #1 and #6 statistically significant), and past users of ipratropium was found to be associated with a statistically significant 50% increase the risk of arrhythmia for both models where subjects who had been hospitalized for any reason during the current period were excluded (models #4 and #7).

New use of long-acting β-agonists was associated with a statistically significant four-fold higher risk of arrhythmia in the first two models where hospitalisations (either COPD or not) were modeled as a covariate. The rate ratio for new use in all other models was variable and non statistically significant. We found no elevated risks for those treated with short-acting β-agonists or methyl xanthines, although past use of methyl xanthines demonstrated a protective effect with rate ratios ranging from 0.45 to 0.60.

Table 4-11 Summary table for the full risk set analyses, All Arrhythmias, by model definition

	Exposure Use Category	1. Before Riskset Exclusions: Modeling all Current Exacerbations	2. Excluding Current Moderate Exacerbations; Modeling Current Severe Exacerbations (primary diagnosis COPD hospitalization)	3. Modeling Current Moderate Exacerbations; Excluding Current Severe Exacerbations	4. Modeling Current Moderate Exacerbations; Excluding subjects with ANY hospitalization within 60-day current window	5. Excluding Current Moderate Exacerbations; Excluding Current Severe Exacerbations	6. Excluding ANY Current : • Antibiotic Rx or • OCS Rx; • Severe Exacerbations	7. *"The Restricted Dataset"* Excluding Current Moderate Exacerbations and Excluding subjects with ANY hospitalization within 60-day current window
Ipratropium Bromide	Current & New	2.14 (1.29 - 3.54)	2.84 (1.68 - 4.81)	2.66 (1.56 - 4.55)	2.60 (1.31 - 5.16)	3.07 (1.79 - 5.26)	4.01 (2.03 - 7.91)	3.03 (1.51 - 6.07)
	Current, not new	1.30 (0.99 - 1.70)	1.37 (1.03 - 1.81)	1.38 (1.04 - 1.82)	1.51 (1.09 - 2.09)	1.38 (1.03 - 1.83)	1.15 (0.81 - 1.64)	1.51 (1.09 - 2.10)
	Past Only	1.21 (0.89 - 1.64)	1.25 (0.91 - 1.72)	1.24 (0.90 - 1.72)	1.51 (1.06 - 2.17)	1.30 (0.94 - 1.80)	1.18 (0.80 - 1.74)	1.55 (1.08 - 2.22)
	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Short-Acting β-Agonists	Current & New	0.86 (0.47 - 1.55)	0.85 (0.46 - 1.59)	0.76 (0.39 - 1.47)	0.60 (0.24 - 1.52)	0.78 (0.40 - 1.51)	0.75 (0.33 - 1.73)	0.57 (0.22 - 1.46)
	Current, not new	0.96 (0.74 - 1.24)	0.99 (0.76 - 1.30)	0.96 (0.73 - 1.26)	0.95 (0.69 - 1.30)	0.95 (0.73 - 1.25)	0.97 (0.70 - 1.35)	0.94 (0.69 - 1.30)
	Past Only	0.92 (0.70 - 1.20)	0.95 (0.72 - 1.26)	0.89 (0.67 - 1.18)	0.96 (0.70 - 1.32)	0.90 (0.68 - 1.20)	0.94 (0.68 - 1.31)	0.98 (0.71 - 1.34)
	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Methyl Xanthines	Current & New	1.77 (0.82 - 3.83)	1.34 (0.51 - 3.53)	0.89 (0.26 - 3.02)	2.53 (0.75 - 8.48)	0.90 (0.26 - 3.06)	--	2.69 (0.79 - 9.13)
	Current, not new	0.96 (0.68 - 1.36)	0.90 (0.62 - 1.31)	0.95 (0.66 - 1.37)	0.90 (0.58 - 1.38)	0.91 (0.63 - 1.33)	0.75 (0.45 - 1.25)	0.85 (0.54 - 1.33)
	Past Only	0.60 (0.37 - 0.98)	0.61 (0.37 - 1.01)	0.47 (0.27 - 0.82)	0.45 (0.23 - 0.87)	0.48 (0.28 - 0.84)	0.56 (0.29 - 1.05)	0.46 (0.24 - 0.90)
	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Long-Acting β-Agonists	Current & New	4.40 (1.47 - 13.18)	4.38 (1.42 - 13.47)	3.02 (0.86 - 10.65)	1.50 (0.19 - 11.72)	2.92 (0.82 - 10.37)	2.10 (0.26 - 16.81)	1.51 (0.19 - 11.96)
	Current, not new	0.71 (0.28 - 1.80)	0.81 (0.32 - 2.09)	0.84 (0.33 - 2.15)	0.54 (0.16 - 1.81)	0.86 (0.33 - 2.22)	0.55 (0.13 - 2.43)	0.59 (0.18 - 1.96)
	Past Only	1.98 (0.85 - 4.62)	1.67 (0.63 - 4.45)	1.84 (0.69 - 4.95)	0.86 (0.19 - 3.82)	1.12 (0.33 - 3.82)	1.16 (0.26 - 5.25)	0.43 (0.05 - 3.31)
	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

Similarly, Table 4-12 provides the results accruing to the same seven models for the risk of atrial fibrillation primary diagnosis hospitalisation or death after cohort entry. While power considerations did not allow us to find any association between atrial fibrillation and the use of short-acting β-agonists, long-acting β-agonists or methyl xanthines, new use of ipratropium bromide was associated with a higher risk in four of the seven models evaluated.

Table 4-12 Summary table for the full risk set analyses, Cases of Atrial Fibrillation only, by model definition

Exposure Use Category		1. Before Riskset Exclusions: Modeling all Current Exacerbations	2. Excluding Current Moderate Exacerbations; Modeling Current Severe Exacerbations (primary diagnosis COPD hospitalization)	3. Modeling Current Moderate Exacerbations; Excluding Current Severe Exacerbations	4. Modeling Current Moderate Exacerbations; Excluding subjects with ANY hospitalization within 60-day current window	5. Excluding Current Moderate Exacerbations; Excluding Current Severe Exacerbations	6. Excluding ANY Current : • Antibiotic Rx or • OCS Rx; • Severe Exacerbations	7. *"The Restricted Dataset"* Excluding Current Moderate Exacerbations and Excluding subjects with ANY hospitalization within 60-day current window
Ipratropium Bromide	Current & New	2.10 (0.99 - 4.46)	2.62 (1.20 - 5.71)	2.45 (1.09 - 5.49)	1.77 (0.57 - 5.49)	2.72 (1.20 - 6.18)	3.83 (1.40 - 10.46)	2.00 (0.64 - 6.30)
	Current, not new	1.08 (0.71 - 1.63)	1.16 (0.76 - 1.77)	1.12 (0.73 - 1.73)	1.36 (0.84 - 2.21)	1.14 (0.74 - 1.77)	1.07 (0.63 - 1.79)	1.38 (0.85 - 2.25)
	Past Only	1.16 (0.75 - 1.79)	1.20 (0.77 - 1.87)	1.22 (0.77 - 1.92)	1.49 (0.91 - 2.44)	1.24 (0.79 - 1.96)	1.26 (0.73 - 2.16)	1.47 (0.89 - 2.42)
	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Short-Acting β-Agonists	Current & New	0.87 (0.36 - 2.07)	0.87 (0.35 - 2.16)	0.81 (0.31 - 2.10)	0.48 (0.11 - 2.22)	0.79 (0.30 - 2.08)	0.67 (0.19 - 2.41)	0.46 (0.10 - 2.14)
	Current, not new	0.95 (0.64 - 1.41)	0.97 (0.65 - 1.46)	0.94 (0.62 - 1.41)	1.02 (0.64 - 1.63)	0.92 (0.61 - 1.39)	0.92 (0.57 - 1.49)	0.99 (0.62 - 1.58)
	Past Only	1.22 (0.83 - 1.79)	1.19 (0.81 - 1.76)	1.16 (0.78 - 1.72)	1.38 (0.89 - 2.14)	1.14 (0.77 - 1.69)	1.12 (0.71 - 1.78)	1.38 (0.89 - 2.14)
	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Methyl Xanthines	Current & New	2.65 (0.97 - 7.27)	2.43 (0.76 - 7.74)	1.26 (0.27 - 5.98)	4.37 (0.96 - 19.98)	1.25 (0.26 - 6.08)	--	4.46 (0.97 - 20.42)
	Current, not new	1.23 (0.76 - 2.00)	1.27 (0.77 - 2.08)	1.29 (0.78 - 2.12)	1.22 (0.68 - 2.17)	1.31 (0.80 - 2.16)	1.28 (0.69 - 2.36)	1.24 (0.69 - 2.21)
	Past Only	0.74 (0.38 - 1.45)	0.77 (0.39 - 1.51)	0.53 (0.24 - 1.17)	0.44 (0.16 - 1.23)	0.53 (0.24 - 1.16)	0.53 (0.20 - 1.37)	0.44 (0.16 - 1.24)
	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Long-Acting β-Agonists	Current & New	2.29 (0.27 - 19.37)	2.07 (0.23 - 18.25)	2.02 (0.23 - 17.87)	2.78 (0.31 - 25.21)	1.84 (0.21 - 16.43)	3.57 (0.38 - 33.19)	2.68 (0.29 - 24.36)
	Current, not new	0.70 (0.16 - 3.03)	0.72 (0.16 - 3.16)	0.86 (0.19 - 3.76)	0.44 (0.06 - 3.45)	0.84 (0.19 - 3.68)	0.66 (0.08 - 5.20)	0.44 (0.06 - 3.39)
	Past Only	1.62 (0.36 - 7.23)	1.88 (0.40 - 8.70)	1.05 (0.13 - 8.39)	--	0.98 (0.12 - 7.97)	2.05 (0.24 - 17.40)	--
	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

4.3.6 Sensitivity analysis pertaining to the duration definition of the current time window

In the 1:20 matched analysis, it was demonstrated that new exposure to ipratropium bromide had been found to be relatively impervious to the number of days used to assess current exposure when the duration of the current time window was allowed to vary between 45 to 90 days. When the current tine window was defined to be 30 days in length, however, the risk rose almost two-fold (RR 6.33 [95% CI 2.21 to 18.15]). (Figure 4-1).

We undertook to reassess this phenomenon within the context of the full cohort analysis and found that the effect associated with a very precise time window was not sustained. As presented in Table 4-13, the rate ratio associated with new exposure to ipratropium bromide ranged between 2.2 and 3.2. It is worth noting that the small excess risk observed for both current but not new, and past only exposure to ipratropium was also impervious to our current time window duration definition, as was the persistent protective effect observed for past use of methyl xanthenes. One possible reason for this observed protective effect associated with past use but not current use of methyl xanthines might be reverse protopathic bias,[310] a phenomenon which will be discussed in greater detail in our second manuscript.

Table 4-13 Sensitivity Analysis for the duration definition of the current time window on the rate ratio of arrhythmia associated with use of bronchodilator medications

Exposure Use Category		Current Exposure Time Window defined as # days preceding the index date:				
		30 days	45 days	60 days*	75 days	90 days
Ipratropium Bromide	Current & New	3.06 (1.17 - 8.03)	2.20 (0.91 - 5.31)	3.03 (1.51 - 6.07)	3.20 (1.72 - 5.97)	2.60 (1.42 - 4.76)
	Current, not new	1.69 (1.18 - 2.41)	1.57 (1.12 - 2.20)	1.51 (1.09 - 2.10)	1.44 (1.04 - 2.01)	1.41 (1.02 - 1.95)
	Past Only	1.46 (1.05 - 2.02)	1.56 (1.11 - 2.20)	1.55 (1.08 - 2.22)	1.62 (1.11 - 2.35)	1.76 (1.20 - 2.57)
	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Short-Acting β-Agonists	Current & New	1.03 (0.33 - 3.22)	0.88 (0.32 - 2.46)	0.57 (0.22 - 1.46)	0.53 (0.23 - 1.22)	0.62 (0.30 - 1.28)
	Current, not new	0.91 (0.64 - 1.29)	0.94 (0.68 - 1.31)	0.94 (0.69 - 1.30)	0.94 (0.69 - 1.28)	0.96 (0.70 - 1.31)
	Past Only	0.96 (0.72 - 1.30)	0.95 (0.69 - 1.29)	0.98 (0.71 - 1.34)	1.02 (0.73 - 1.41)	0.99 (0.71 - 1.40)
	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Methyl Xanthines	Current & New	5.19 (1.11 - 24.28)	2.31 (0.53 - 10.17)	2.69 (0.79 - 9.13)	1.59 (0.48 - 5.31)	1.23 (0.38 - 4.04)
	Current, not new	0.88 (0.55 - 1.42)	0.94 (0.61 - 1.46)	0.85 (0.54 - 1.33)	0.87 (0.56 - 1.34)	0.90 (0.58 - 1.38)
	Past Only	0.52 (0.30 - 0.91)	0.42 (0.22 - 0.82)	0.46 (0.24 - 0.90)	0.45 (0.23 - 0.90)	0.42 (0.20 - 0.87)
	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Long-Acting β-Agonists	Current & New	2.56 (0.30 - 22.08)	1.85 (0.23 - 14.98)	1.51 (0.19 - 11.96)	2.23 (0.50 - 9.96)	1.95 (0.44 - 8.60)
	Current, not new	0.28 (0.04 - 2.14)	0.43 (0.10 - 1.82)	0.59 (0.18 - 1.96)	0.40 (0.09 - 1.70)	0.38 (0.09 - 1.62)
	Past Only	0.70 (0.21 - 2.39)	0.68 (0.15 - 3.00)	0.43 (0.05 - 3.31)	0.46 (0.06 - 3.60)	0.58 (0.08 - 4.48)
	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

4.3.7 Testing for effect modification

Age, sex, previous history of arrhythmia, severity, duration of COPD, CHF, and other cardiovascular disease are all important determinants of arrhythmia and as such, may modify the association between bronchodilators and arrhythmia. To test for effect modification, we included the relevant set of interaction terms (one for each level of exposure for each bronchodilator), one variable set at a time, in subsequent models. All subgroup analyses were carried out using a two-sided test of $\alpha = 0.05$. None of our bronchodilator use exposure categories were modified by either age, CHF, Home oxygen use (a marker for COPD severity), or previous history of arrhythmia before cohort entry. Tests for interaction with sex, COPD duration, and the presence of non-CHF cardiovascular disease did indicate the possibility of an interaction, but given the lack of a consistent pattern and the paucity of data pertaining to exposed cases and controls upon stratification, we expect that these observations were indicative of type-I error.

4.4 Discussion

In this study, we assessed the arrhythmia risk associated with the use of bronchodilators from within in a bronchodilator new-user cohort from Saskatchewan. Our research revealed an elevated risk of cardiac arrhythmia associated with the new use of ipratropium bromide, a finding which was robust to sensitivity analyses and was reaffirmed by a full Cox model reanalysis.

Given the importance of exacerbations, the potential threat this variable poses to the validity of our results, and the fact that their lack of sufficient control is seen as being a major limitation of previous observational studies, careful attention was given to exploring various operational definitions and methods for their control in the analysis. In the end, however, we demonstrated that the cleanest analysis was one which limits the study to stable COPD in which subjects who experience an exacerbation during the current time period were excluded.

Other strengths of this study lie in the fact that in this analysis, we identified and controlled for periods of hospitalisation in order to avoid immeasurable time bias. Given that arrhythmia is an acute event, we also focused on the exposures which occurred during the etiological time window, i.e. during the short period of time leading up to each arrhythmia event. In addition, we had access to data pertaining to home oxygen use, a variable which is strongly associated with COPD severity and yet not commonly available in most database studies.

One limitation of this study stems from the small size of our Saskatchewan cohort out of which 469 cases arose. Given the importance of breaking down exposure into hierarchical use categories which distinguished between current which was new, versus current which was not new, the number of exposed cases for some of our bronchodilator classes were small. As a result some of our estimates were somewhat unstable, and we had insufficient power to detect an effect in some cases.

An additional limitation of this study was the inability to study the risks associated with an association with long-acting β-agonists use owing to the fact that their use is strictly regulated by Saskatchewan Health via the *Exception Drug Status Program* which sees these agents being approved for use only in the most severe COPD cases. On the other hand, inclusion of long-acting β-agonists use in our statistical models has strengthened our ability to adjust for COPD severity.

Given the limitations of this study, we sought to perform a confirmatory re-analysis in a larger population. The next chapter provides the results of the analyses conducted within a second bronchodilator new-user cohort.

5 Chapter 5: Bronchodilator use and the risk of arrhythmia in chronic obstructive pulmonary disease (COPD): Re-assessment in a large Quebec cohort

5.1 Introduction

Hills nine Criteria of Causation, as originally presented by Austin Bradford Hill (1897-1991), outlined what he deemed to be the minimal conditions needed to establish a causal relationship between an exposure and an outcome.[311] Although to some extent being displaced by the emerging field of modern causal inference, Hill's Criteria formed the basis of modern epidemiological research for decades. Consistency was one of these criteria which stated that an association is consistent when results are replicated in studies in different settings using different methods. That is, if a relationship is causal, we would expect to find it consistently in different studies and in different populations. [311]

As stated in the July 1977 issue of Epidemiology,[312]

> *Science places a premium on the replication of results. The ability to reproduce research findings is an essential defense against error. In its narrowest form, replication involves faithfully reproducing previous numeric results using the original experimental protocol. Its objective is to eliminate investigator error, inadvertent or intentional as an explanation for research results. More broadly, replication involves the systematic variation of experimental conditions to determine whether earlier results can be observed under new conditions.*

This is not to suggest that successful replication is a necessary condition for determining causality. Indeed, when it was suggested that pharmacoepidemiologic studies with relative risks of 2.0 or less not be published until replicated in a different environment,[313] the recommendation was justly dismissed as being unwarranted and unreasonable.[314] What is certain, however, is that replication of a study protocol within a second population can increase confidence in the validity of results, and it was in this spirit that we set out to reassess the arrhythmic risks from bronchodilator use in COPD from within a second cohort assembled from the larger population of Quebec.

5.2 Methodological issues and introduction to Paper 2

5.2.1 Sources of the Québec Data:

Established in 1969, the Régie de l'assurance maladie du Québec (RAMQ) is the government agency which administers the provinces public health and public prescription drug insurance plans. All healthcare services (with the exception of hospitalisations) are recorded in multiple files covering different domains of health care. Each of these files contains a unique patient identifier which permits the linkage of these data files.

5.2.1.1 Medicare Beneficiary File (Fichier des bénéficiaires)

The Medicare Beneficiary File contains demographic information pertaining to all Québec residents covered by the provincial health plan (approximately 97.7% of Québecers in 1991). Demographic variables included age, sex, and date of death (where applicable).

5.2.1.2 Prescription Drug Data:

The prescription drug files contain data pertaining to all filled outpatient prescriptions which were prescribed by a Québec -licensed physician and filled at community pharmacies for medications listed on the *liste de médicaments*, the province's formulary. Prior to January 1, 1997, the RAMQ prescription drug insurance plan covered residents who were either 65 years and older, or welfare recipients and their children. After this date, the drug plan was modified to give access to employed residents and their spouses/children who did not have access to alternate private drug insurance coverage. Information available for each dispensed prescription included the dispensing date, drug identification number (DIN), drug class (AHF) and drug common denomination (denocom) codes, the dosage form, the strength and the quantity dispensed. These data have been shown to be valid and comprehensive.[315]

5.2.1.3 Physician claims Data:

The physician claims database contains data pertaining to all fee-for-service physician claims for medical services rendered. Data elements available for study were the date of service, diagnosis code (ICD-9), fee-for-service code, and the location of service.

Validation of the RAMQ medical services claims data have found diagnosis codes to be highly specific but variable in terms of their sensitivity for many conditions.[316]

5.2.1.4 Hospital Inpatient Data

Data pertaining to all Québec hospital discharges have been maintained by *Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière* (Med-Écho) since the year 1980. Date of admission, discharge, discharge type, type of admission (day surgery vs. inpatient stay), type of establishment, as well as diagnosis and procedure codes were available for use. One primary and up to an additional 15 diagnoses are reported as well as up to 15 procedure codes (with corresponding procedure dates), and the medical diagnoses recorded in these data have been shown to be both comprehensive and valid.[317]

5.2.1.5 Cause of Death file:

The fichier des événements démographiques du Québec administered by the Institut de la statistique du Québec (ISQ) contains the vital statistics date of death as well as the medical code corresponding to the underlying cause of death, as well as the establishment where the death took place (if any).

The RAMQ, Med-Écho, and ISQ computerized databases were linked by the anonymised unique identification number (health services number) that allows the linkage of these database files. As in the last study, drug use profiles were then produced, and a source population of subjects newly treated with bronchodilator medications was generated, from which a cohort was selected in order to investigate our research question. The details pertaining to cohort assembly are described next.

5.2.2 Identification of the Québec study population

As in our previous study, we set out to assemble a bronchodilator new-user cohort who began their treatment after January 1st 1990. The source population was a respiratory medications database consisting of 352,696 Québec residents who had been dispensed at

least one respiratory medication between January 1, 1988 and December 31, 2001. The list of respiratory medications included bronchodilators as well as corticosteroids, sodium cromoglycate, nedocromil, ketotifen, and one of two formulary listed leukotrine antagonists montelukast or zafirkulast.

Whereas in the Saskatchewan study we had access to information pertaining to a population aged 55 and older, in Québec the age at which the entire population is captured is 65 and older. Our aim was to replicate the Saskatchewan study as closely as possible, but we faced a tradeoff between similarity of average age of cohort entry, and replicating the Saskatchewan study criterion which imposed a 5-year backward time window from date of cohort entry as a catchment period during which cohort members were prohibited from having been dispensed exclusionary drugs. Had we imposed a 5-year window within the Québec population, this would have raised the earliest age of cohort entry to 70 years. The compromise which was reached was to instead impose a 2-year backward time window from cohort entry, thereby allowing the earliest age of cohort entry to be 67 which corresponded to two years after their first potential database entry.

Figure 5-1 presents the process of selection for the Québec cohort. With the one exception noted above, the remaining Saskatchewan cohort inclusion and exclusion criteria were applied to the Québec population, resulting in a cohort of 76,661 subjects retained for study. These 76,661 subjects were then followed until the date of the study outcome, death, or 31 December 2003 whichever occurred first.

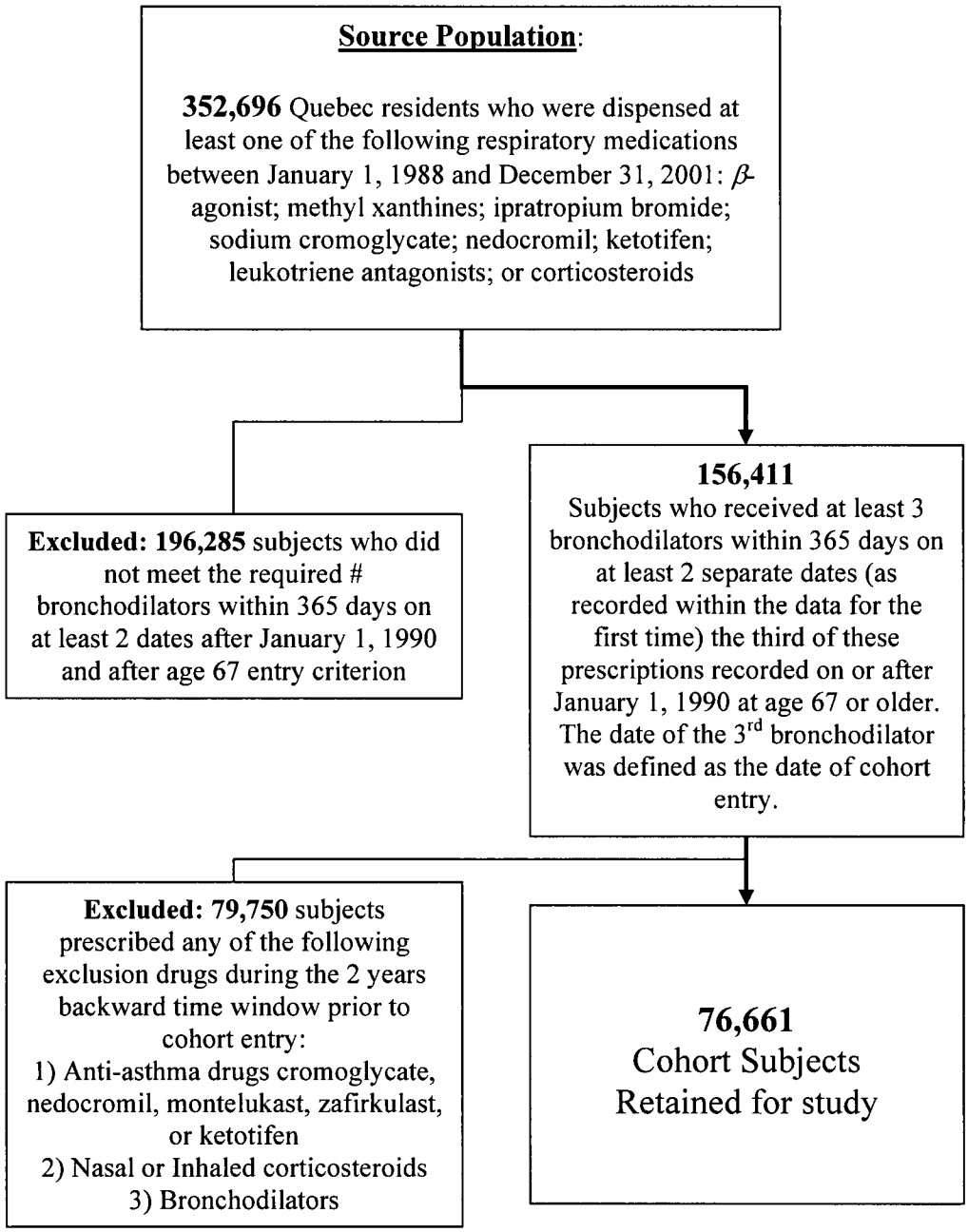


Figure 5-1 Québec Cohort Assembly Results

5.2.3 Temporal trends in prescribing, the Québec experience

In chapter 3, fluctuating temporal trends in prescribing were presented and offered as one of the many reasons why matching on calendar time is necessary in our study. As shown in Figure 5-1, the change in the share of total bronchodilator prescribing by bronchodilator class by year was equally remarkable in the province of Québec. As was

the case in Saskatchewan, RAMQ listed the first long-acting β-agonist (LABA) as well as Combivent® (the inhalation aerosol which delivered both ipratropium bromide plus salbutamol) in 1996, the latter which increasingly gained favor over prescriptions for either agent alone. Whereas short-acting β-agonists (SABA) were the bronchodilator of choice in 1990 in Saskatchewan, methyl xanthines (XAN) were the favored bronchodilator at the beginning of the study period in Québec, but their share of total bronchodilator prescriptions fell dramatically over the period.

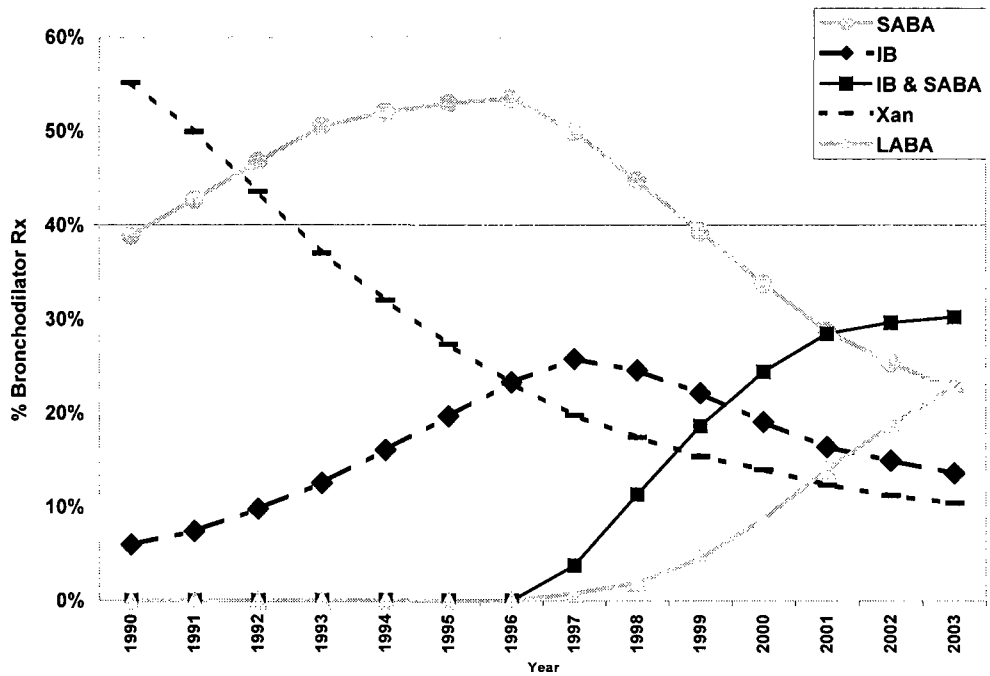


Figure 5-2 Temporal Trends in bronchodilator prescribing within the Québec COPD cohort 1990-2003

5.2.4 Long-acting β-agonists and changes to the Québec formulary:

In addition to sample size advantages, one of the underlying reasons for conducting this replication study within the framework of the databases from Québec healthcare system was the opportunity to study the arrhythmia risk associated with long-acting β-agonist (LABA) use. As shown in Figure 5-3, salmeterol was the first of these agents to be introduced in January 1997 followed by formoterol in July of the same year. Shortly after the first of the LABA plus inhaled corticosteroid formulations (salmeterol plus fluticasone) was listed in January 2000, it was evident that combination therapy was rapidly gaining favor among prescribers, and by 2002, LABA combination therapy

secured more than a 50% of the total share of LABA prescriptions within our COPD cohort. The experience on a population-level was similar, and concern was raised, for example, when it was noted that these drugs were increasingly being used as *initial maintenance therapy* for asthma when their originally intended use was second-line asthma therapy in patients whose symptoms were not optimally controlled with a moderate dose of ICS alone.[318]

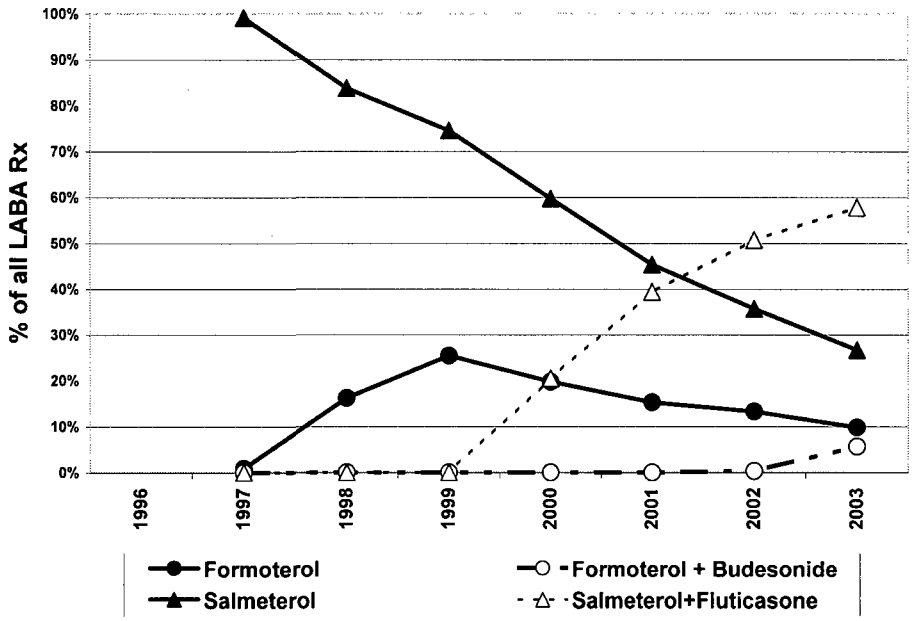


Figure 5-3 Temporal Trends in long-acting β-agonist (LABA) prescribing within the Québec COPD cohort 1990-2003

In order to curb the rising costs associated with these drugs, in October 2003, the RAMQ limited access to LABA combination therapy by modifying their status to that of an exception drug. For patients with COPD, this meant that reimbursement for new prescriptions of these medications would have to be pre-approved on the basis of fulfilling one of the following two criteria:[319]

1) Having moderate or severe COPD for whom control of symptoms was not attained despite use of a short-acting β-agonists or a long-acting β-agonists in conjunction with an anticholinergic;
2) Having moderate or severe COPD who despite regular use of a long-acting bronchodilator experienced an exacerbation during the last year.

Any COPD patient who had previously obtained reimbursement for one of the LABA combination drugs during the year prior to October 1st 2003, however, was exempt from this new rule, and was covered for the purposes of continuing their treatment.

The follow-up period for this study ended on December 31st 2003 which was exactly three months after this formulary modification. We do not expect this issue to impact on our results in any meaningful way for two reasons. First, by the time the modification was implemented most (if not all) of our cases will have already occurred. Secondly, while this could impact the choice of LABA formulation, any physician who intended to initiate LABA therapy after this date could have done so either by prescribing LABA monotherapy, or by prescribing both the LABA and the inhaled corticosteroid as two separate inhalers, both of which would have been covered by the plan in the usual amount.

5.3 Preface to the manuscript:

What follows is the second manuscript, and the second of two cohort studies which were conducted in order to assess the arrhythmia risk of bronchodilator drug use in COPD. This article will be submitted for publication and should be referenced as follows:

Wilchesky, M., P. Ernst, J. M. Brophy, R. W. Platt, and Suissa S. 2008. Bronchodilator use and the risk of arrhythmia in chronic obstructive pulmonary disease (COPD): Re-assessment in a large Quebec cohort. Unpublished manuscript. Montreal: Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, 2008.

5.4 Bronchodilator use and the risk of arrhythmia in chronic obstructive pulmonary disease (COPD): Re-assessment in a large Quebec cohort

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Word Count: 3,504

Tables: 5

Key Words: Bronchodilators, COPD, Arrhythmia, Pharmacoepidemiology

Running Title: Bronchodilator Use and Arrhythmia Risk in COPD

Abstract

Rationale: There is limited information on the risks of arrhythmias in the general population of patients treated with bronchodilator drugs.

Objectives: To determine the risks associated with long-acting β- agonists, short-acting beta agonists, ipratropium bromide, and methyl xanthines on the risk of cardiac arrhythmias in a large cohort of patients with chronic obstructive pulmonary disease.

Methods: We identified people 67 years of age or older without previous asthma who were currently taking bronchodilators using the computerized health databases of Quebec (January 1990 to December 2002). Data on bronchodilator use and arrhythmia outcome were analyzed using a time-matched, nested case–control approach, comparing new users, current users, past users with non-users of ipratropium bromide, short and long-acting β-agonists and methyl xanthines in the sixty days preceding arrhythmia hospitalisation or arrhythmic death.

Measurements and Main Results: Of 76,661 COPD subjects, 621 experienced a fatal arrhythmia, and a further 4,686 were hospitalized with a primary diagnosis code for arrhythmia. New use of short-acting β-agonists and methyl xanthines were found to independently increase cardiac arrhythmias (RR 1.34 [95% CI 1.12 to 1.61]) and (RR 1.31 [CI 1.00 to 1.72]) respectively. After exclusion of subjects who had either recently been hospitalised or had a COPD exacerbation, arrhythmia risk was associated with new use ipratropium bromide, and both short and long-acting β-agonists (RR 1.43 [95% CI 1.08 to 1.88]), (RR 1.28 [CI 1.02 to 1.61]) and (RR 1.54 [CI 1.00 to 2.36]) respectively. Results were robust to limiting arrhythmias to atrial fibrillation and flutter.

Conclusions New use of ipratropium bromide and both short and long-acting β-agonists were found to increase the risk of cardiac arrhythmia, particularly atrial fibrillation and flutter, in patients with COPD.

At a glance Commentary:

Scientific Knowledge on the Subject: There is some evidence that bronchodilator use may increase the risk of cardiac arrhythmias in patients with COPD. Several clinical trials involving the short-acting anticholinergic ipratropium bromide have reported on arrhythmias but have produced conflicting results. One observational study which included both asthma and COPD patients age 10-74 found no association between bronchodilator use and arrhythmia, while another which studied COPD subjects aged 55 and older showed an increase risk of arrhythmia associated with the new use of ipratropium bromide.

What this study adds to the field: This time-matched confirmatory replication nested case-control analysis confirms that new use of bronchodilators, in particular ipratropium bromide and both short and long-acting β-agonists, is associated with a higher risk of arrhythmia within this COPD population.

Introduction:

Bronchodilator medications are central to the symptomatic management of COPD.[272-275] Whereas the arrhythmogenic effects of beta agonists[165] and methyl xanthines[161;164] have been relatively well documented in the literature, the Lung Health Study (the first large-scale clinical intervention trial in respiratory medicine[180]) also detected a small increase in risk associated with ipratropium bromide.[182] Confirmation of this finding through observational study, however, either did not find an association,[183] or was conducted within a population which was limited in its ability to include long-acting agents, and too small to yield well powered results.[320] We therefore undertook the present study of the risk of cardiac arrhythmias within the larger population of COPD subjects in the Province of Quebec which afforded us both a large sample size as well as the ability to study the risks associated with the two long-acting β-agonists salmeterol and formoterol.

Methods:

Data Sources

Three administrative databases of the Province of Quebec were used in this research: the Régie de l'assurance-maladie du Québec (RAMQ), Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière (Med-Écho), and the fichier des événements démographiques du l'Institut de la Statistique du Québec (ISQ). The RAMQ physician claims database documents physician services for all provincial beneficiaries including date, diagnosis and, when applicable, procedure codes. The Quebec drug plan covers all residents of Quebec aged ≥65 years, welfare recipients, and individuals without private insurance. The pharmaceutical database consists of information from pharmacists' claims for dispensed medications reimbursed by the Plan, but not medications received in hospitals. The Med-Écho administrative database captures acute care inpatient abstracts of clinical and demographic data elements including admission and discharge information, most responsible diagnosis and up to 15 non-primary diagnostic codes. Finally, the ISQ death certificate database contains diagnostic codes corresponding to an underlying cause as well as secondary causes of death. As documented elsewhere, these databases have been widely used and validated for use in epidemiologic study.[316;321-325]

Study population

A population-based cohort of patients aged 67 and older with newly-treated COPD was defined as follows: To be included, it was required that subjects had a minimum of three prescriptions for a bronchodilator, on at least two different dates, within any one period after January 1, 1990. Bronchodilator medications being prescribed during this period and considered for analysis included inhaled or oral β-agonist (both short and long-acting), methyl xanthines or ipratropium bromide. The date of entry into the cohort was defined as the date of the third of this sequence of prescriptions for a bronchodilator between January 1, 1990, and December 31, 2002. In order to assure that we were capturing a new-user cohort[186] of COPD patients, subjects were excluded if they had received any bronchodilator, anti-asthma drug (cromoglycate, nedocromil, montelukast, zafirkulast, or ketotifen), or nasal or inhaled corticosteroids in the 2 years prior to cohort entry. Subjects were excluded if they had less than 2 years of history since their enrolment with the RAMQ. Subjects retained for study were then followed from their date of cohort entry until the date of their index event, December 31, 2003, or the date of their death from any cause, whichever came first.

Study design

In order to study the effect of exposure to each of our four classes of bronchodilators in the sixty days in the period preceding the event while simultaneously controlling for the potentially confounding effect of calendar time, we analyzed our population-based retrospective cohort using a time-matched, nested case–control method.[215]

Cases and Controls

The study end point was the earlier event corresponding to either death with an underlying cause of death of arrhythmia, or a hospital admission with a primary discharge diagnosis of arrhythmia (ICD-9 codes 427x, ICD-10 codes I46x-I49x, R000 and R001) occurring any time after cohort entry. All cases of first arrhythmia during cohort time which were identified were included for the analysis. The index date for case subjects was the date of their arrhythmic event.

For each case, 10 controls were randomly selected from all subjects in the cohort matched on age (±5 years), sex, and who were alive and event-free on the calendar date of the case arrhythmia (the index date). Controls within each risk set were then assigned their corresponding case-patient's index date.

Exposure Assessment

Exposure to the following four classes of bronchodilator medications were identified and compared for the purposes of this analysis: long-acting β- agonists (formoterol or salmeterol); short-acting β agonists (fenoterol, isoproterenol, orciprenaline, pirbuterol, procaterol, salbutamol, or terbutaline); the short-acting anticholinergic ipratropium bromide; and methyl xanthines (theophylline, aminophylline, and oxtriphylline). Tiotropium bromide, a long-acting anticholinergic was only available to Quebec patients from October 2003, and was therefore unavailable for study.

All bronchodilator prescriptions that were dispensed to the cases and controls during follow-up were identified and classified hierarchically in terms of the timing of their use. Using a single common reference category of no use during the past 365 days from the index date, the three categories of exposure identified were:

1) Past use, as exposure during the 61-365 day time window before the index date ;
2) Current but not new use, as exposure during the 60 days leading up to the index date, where there was also past use; and
3) Current new use, as exposure during the 60 days leading up to the index date preceded by a 10-month period of no use.

Risk Factors and Confounders

Variables that were identified as being known or potential risk factors for arrhythmia and known or potential confounders of the association between bronchodilators and arrhythmia were identified and used for adjustment of the crude estimates of effect. As such, we identified the use of drugs within 12 months of the index date that can introduce, aggravate, or protect against arrhythmia. This includes cardiotonic drugs such

as antiarrhythmics and digoxin (digitalis), drugs that decrease potassium levels such as diuretics and corticosteroids; aspirin and non-steroidal anti-inflammatory drugs (NSAIDs); and drugs that are hypothesized to lengthen the Q-T interval thereby predisposing to Torsade de Pointes such as macrolides, antidepressants, cisipride, and antipsychotics. Additionally, variables pertaining to inhaled corticosteroids, oral corticosteroids, and other respiratory drug (including cromoglycate, nedocromil, montelukast, zafirkulast, or ketotifen) use during the 12 months prior to index date were identified.

Comorbid conditions of interest identified include congestive heart failure (CHF), cardiomegaly, atherosclerosis, anaemia, hypertension, congenital structural cardiovascular abnormalities and other cardiovascular diseases, cerebrovascular disease, diabetes, thyroid disease, hyperlipidemia and renal failure. In order to identify these conditions, both hospital and out-patient diagnoses identified within 12-months of the index date as well as medication use during this same time period for the treatment of these conditions were identified. Drugs used as markers for these diseases included ACE inhibitors, beta blockers, calcium-channel blockers, potassium-sparing diuretics, and other hypotensive agents, nitrates, diabetic and thyroid medications.

Hospitalizations for conditions not previously specified as being risk factors or co-morbid conditions including hospitalisations without a primary diagnosis of COPD were identified within the 12-months to index date window and used for adjustment. Finally, a subject's previous history of arrhythmia, that is, record of a hospitalization for arrhythmia prior to cohort entry, was identified and used for adjustment.

We identified exacerbations of COPD using the operational definitions suggested by de Melo et al[269]who identified moderate exacerbations by prescriptions for a systemic antibiotic and an oral corticosteroid on the same day, and severe exacerbations as a hospitalization with a primary discharge diagnosis of COPD. Since the occurrence of an exacerbation could result in a change in a COPD patient's bronchodilator medications and is as well an independent risk factor for arrhythmia [287-289] we expect these episodes to

be potential confounders for the association between arrhythmia and bronchodilator use. In order to restrict our study to a population of patients with stable COPD[326] and to deal with the confounding nature of this variable, we compared two methods to control for exacerbations: modeling these events as a covariate in the analysis, and excluding cases and controls that experienced exacerbations during the sixty day time window leading up to the index date.

Data Analysis

Conditional logistic regression using SAS version 9.1 was used to estimate adjusted odds ratios. Since we use the risk set sampling technique, we expect our estimated exposure odds ratio to be an unbiased estimate of the hazard rate ratio[211;327] for cardiac arrhythmias associated with the use of the four different classes of bronchodilators in our time-matched nested case–control data.

Medications dispensed during hospitalisations are not recorded by the RAMQ databases, and therefore bronchodilator exposures during periods of hospitalisation are unknown. In order to assess the extent to which misclassification of exposure could have influenced our results, a restricted cohort was created by deleting subjects who had been hospitalised within 60 days of the index date.

Results

A total of 76,661 study subjects met the criteria required for entry to our COPD cohort. Of these, 621 experienced a fatal arrhythmia, and a further 4,686 were hospitalized with a primary diagnosis code for arrhythmia after cohort entry, giving rise to a total of 5,307 cases within our cohort. As shown in **Table 1**, slightly more than half of the arrhythmia cases were atrial fibrillation and flutter. The overall rate of our outcome was 11.3 arrhythmias per 1,000 person-years.

Table 2 provides a comparison of the various characteristics between cases and controls. As we had anticipated, case subjects were more likely to have had a previous history of arrhythmia, have established risk factors for arrhythmia such as CHF, enlarged heart,

diabetes, cerebrovascular disease and other cardiovascular diseases, and were more likely to have been using diuretics, ACE inhibitors, beta blockers, digitalis glycosides, calcium channel blockers, nitrates, and thyroid medications than were the controls. These differences (along with the other covariates listed in the methods section) were controlled for in the analysis.

Table 3 presents the crude and adjusted hazard rate ratios of arrhythmia associated with the use each of the four bronchodilator classes during the 365 day period before the index date (the etiologically relevant time-period). After adjustment for multiple risk factors and confounders, subjects current and newly exposed (exposed within the prior 60 days but not in the period of 61-365 days prior to the index event) to short-acting β-agonists and methyl xanthines were found to be at an increased risk for a cardiac arrhythmia when compared to those who were not exposed (RR 1.34 [95% CI 1.12 to 1.61]) and (RR 1.31 [CI 1.00 to 1.72]) respectively.

After excluding subjects who had been either hospitalised or had experienced a moderate exacerbation during the current time window (restricted cohort), those found to be at higher risk for cardiac arrhythmias were new users of ipratropium bromide, and both short and long-acting β-agonists (RR 1.43 [95% CI 1.08 to 1.88]), (RR 1.21 [CI 1.02 to 1.61]) and (RR 1.54 [CI 1.00 to 2.36]) respectively (Table 4).

Since atrial fibrillation and flutter was the arrhythmia which produced approximately half our cases were, we further focused the analysis to cases of this type of arrhythmia only, and observed that within the restricted cohort, this subset of cases, being new users of ipratropium bromide and long-acting β-agonists was associated with an increased risk of arrhythmia (RR 1.61 [CI 1.13 to 2.30]) and (RR 1.89 [CI 1.13 to 3.16]) respectively (Table 5).

We had insufficient power to assess the risks associated with new use of bronchodilators and fatal arrhythmias (Table 5).

In one final sensitivity analysis, we changed the duration of the exposure current time window such that it was equivalent to 45 days instead of 60. Using this shorter duration for new current exposure, ipratropium bromide and both long and short-acting β-agonists were found to be associated with a higher risk of arrhythmia (RR 1.56 [CI 1.14 to 2.13]), (RR 1.40 [CI 1.08 to 1.82), and (RR 1.87 [CI 1.16 to 3.03]) respectively (Table 5). Finally, among subjects in the restricted cohort who had a previous history of arrhythmia prior to cohort entry, current new use of ipratropium bromide was the only bronchodilator associated with an elevated risk (RR 2.29 [CI 1.20 to 4.38]) (not shown).

Comment

The findings of this large population-based time-matched nested-case control study provide confirmatory evidence that bronchodilator-induced arrhythmias are events associated with being newly exposed these agents. New use of ipratropium bromide and both short and long-acting β-agonists were found to increase the risk of cardiac arrhythmia in patients with COPD. New use of ipratropium bromide and long-acting β-agonists were specifically associated with a higher risk of atrial fibrillation. The finding that only ipratropium bromide was associated with an elevated risk among patients with a previous history of arrhythmia may be due to systematic channelling of patients towards this class of drug seeing as anticholinergics are poorly absorbed after inhalation, and have long been believed to not be associated with cardiovascular effects [112]

One strength of this study resides in the fact that special care was taken to identify and exclude subjects who had experienced an exacerbation during the current time window. Not only does this focus the analysis on a homogenous stable COPD population, but through restriction, it effectively eliminates the potential for confounding by this variable. An other strength of this study resides in the minimisation of misclassification of exposure and consequent immeasurable time bias[206] by means of eliminating subjects who had been hospitalised during the current time window.

These results are in line with the findings of a previous smaller study using another Canadian database, which indicated that new use of ipratropium bromide was associated

with an elevated risk of cardiac arrhythmias.[320] In that study, we were unable to assess the risks associated with long-acting β-agonists as these medications were under restricted access and thus used much less frequently. In contrast to our findings in our previous study, we did not detect an elevated arrhythmia risk associated with the new use of methyl xanthines from within the restricted cohort.

These results also extend the findings of a previous study [183], which examined the risk of cardiac arrhythmias and current use of respiratory drugs in a population aged 10-74 comprised of both asthma and COPD patients where no association between cardiac arrhythmias and current use of bronchodilators was identified. We focused our study on the older and more vulnerable sub-population of patients with COPD and then examined the specific risk associated with recent initiation of these medications. We felt that this group of current new users to be the most etiologically relevant in investigating these acute events. Since we carefully matched on time using risk-set sampling in our individually-matched case-control study, we were able to account for trends in the use of medications over time and seasonality of COPD exacerbations. Finally, in contrast to the previous authors, we carefully controlled for exacerbations of COPD within the current time window instead of during the year leading up to the index date, since it is more likely that more recent exacerbations would be associated with an index arrhythmic event.

Our own study has limitations which are worth mentioning. As with any observational study, the potential for residual bias arising from unmeasured confounders remains. Our databases did not include information pertaining to lung function or smoking status (either primary or secondary), and to the extent that either of these variable could be strong confounders of our bronchodilator use-arrhythmia association, our estimates of effect may by biased. Both lung function and smoking are associated with arrhythmia and severity of COPD. Arrhythmias are prevalent in advanced COPD[328] and atrial and ventricular arrhythmias are common in severe yet stable COPD[329]. Current smoking has also been shown to be predictive of sudden cardiac death[330;331] and smoking cessation has

been demonstrated as being important in reducing arrhythmic death among patients with advanced ischemic heart disease.[332]

The absence of data pertaining to lung function, and smoking status may therefore have resulted in inadequate adjustment for severity of illness. We did, however attempts to adjust for disease severity with the information available to us. We began by assembling a new-user cohort of COPD patients and matched cases to controls based on both year of cohort entry and the index date, and adjusted for duration of time on study. As such, we expect cases and controls to also be matched on some expected or average disease severity based on time since first bronchodilator use. In addition, disease severity was accounted for by means of exclusion of both subjects who had recently experienced an exacerbation or had been recently hospitalised, and by adjusting for the use of other COPD therapies (oral and inhaled steroids, as well as other respiratory drugs) during the 12 month period leading up to the index date.

In order for severity of illness itself to qualify as an unmeasured confounder, however, severity would have to be associated with the bronchodilator use in the population, associated with arrhythmia conditional on the exposure (i.e., among the unexposed), and severity would have to not in fall along the causal pathway between the exposure and the outcome. While we concur that this study could have benefitted from better control of severity of illness, it is questionable as to whether or not severity per se would have been strongly associated with the use of bronchodilators during the period under study. The 1990s and early 2000s were a time of conflict and controversy regarding therapeutic recommendations suggested by COPD practice guidelines.[86;333;334] The first published Canadian therapeutic guidelines in 1992 promoted inhaled short-acting bronchodilators due to the rapid response and minimal systemic side effects as compared with oral agents with a slight preference given to inhaled anticholinergic agents for stable disease.[79] A few years later, however, both the American and British thoracic societies published recommendations indicating a preference towards first line therapy with inhaled short-acting β-agonists over anticholinergics . In the year 2000 there was still no clear agreement among the various COPD guidelines whether an anticholinergic, a β-agonist,

or a combination of the two was preferred as first-line therapy.[334] Furthermore, long-acting β-agonists salmeterol and formoterol only became available for use in Quebec in 1997 and 1998 respectively (in combination with corticosteroids from the year 2000), and the first mention of these drugs within any Canadian published guidelines was during the last year of follow-up in 2003 where they were recommended for use in patients whose symptoms persist despite reasonable short-acting bronchodilator therapy.[335] Seeing as there was lack of consensus concerning their use during the study period some question regarding the strength of an association between clinical severity and bronchodilator use remain.

As in all pharmacoepidemiology studies which makes use of administrative databases, exposure classification is based on recorded dispensing of medications as opposed to the actual drug administration. Since COPD is a symptomatic disease for which patients rely on their bronchodilator medications for relief, we do not expect misclassification of exposure to be an issue as compared with studies of asymptomatic conditions.

Protopathic bias is said to occur when a drug is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnosed.[299] When the disease is later discovered, an association may be incorrectly inferred between that exposure and outcome. Chronic heart failure (CHF), a strong risk factor for cardiac arrhythmia, causes breathlessness and fatigue,[300] which could be mistaken under certain circumstances for either an exacerbation or increasing COPD severity. In this study, it is possible that the problem of protopathic bias may have occurred in situations where patients presented with symptoms of dyspnea, a diagnosis of CHF was missed, and the patient was prescribed a new bronchodilator medication.

An interesting finding in this study was a protective effect associated with past use but not current use of ipratropium bromide. If a patient on ipratropium bromide were to describe past symptoms indicative of an arrhythmia (such as palpitations, light headedness, loosing consciousness, or chest pain), then the medical decision to switch their bronchodilator from this to another class would provide an example of reverse

protopathic bias.[310] It is the opposite of protopathic bias because in this case, it is the discontinuation of a prescription due to an early manifestation of a disease that has either not yet been diagnosed or has been avoided by virtue of the medication switch. As such, if cases were more likely than controls to stop a treatment prior to the current time window due to early symptoms, we would observe what appears to be a protective effect associated with past use only exposure, when in fact, the actual mechanism is the avoidance (or delay) of the full-blown disease by virtue of prescription discontinuation.

In conclusion, we have found that initiation of treatment with ipratropium bromide and both short and long-acting β-agonists was found to increase the risk of cardiac arrhythmia in patients with COPD. New use of ipratropium bromide and long-acting β-agonists were specifically associated with a higher risk of atrial fibrillation and flutter. While this association might possibly be explained by worsening COPD, the clinical implication is that patients should be warned and/or monitored for the onset of arrhythmia when instituting any new bronchodilator therapy. Future research should examine the risk of arrhythmias associated tiotropium bromide, the newer long acting anticholinergic.

Table 5-1 Distribution of arrhythmia cases, by type

Arrhythmia Type:	Fatal		Non-Fatal		ALL	
	#	%	#	%	#	%
Paroxysmal supraventricular tachycardia	1	0%	240	5%	241	5%
Paroxysmal ventricular tachycardia	-	0%	154	3%	154	3%
Paroxysmal tachycardia, unspecified	-	0%	8	0%	8	0%
Atrial fibrillation and flutter	228	37%	2,715	58%	2,943	55%
Ventricular fibrillation and flutter	30	5%	50	1%	80	2%
Cardiac arrest	190	31%	150	3%	340	6%
Premature beats	-	0%	33	1%	33	1%
Other specified cardiac dysrhythmias	31	5%	1,175	25%	1,206	23%
Cardiac dysrhythmia, unspecified	141	23%	161	3%	302	6%
All	**621**	100%	**4,686**	100%	**5,307**	100%

Table 5-2 Baseline characteristics of cases of arrhythmia and controls

	Cases	Controls
Subjects *n*	5,307	53,070
Age mean ± SD*	75.7 (5.8)	75.3 (5.5)
Male %*	53.5	53.5
Years of follow up from cohort entry to index date mean ± SD	4.8 (3.5)	4.8 (3.5)
Use of other COPD therapy during the 12 months prior to index date:		
Inhaled Corticosteroids	33.5	28.5
Oral Corticosteroids	13.2	8.7
Other Respiratory Drugs	13.5	10.4
Any Previous History of Arrhythmia (prior to cohort entry)	32.6	15.2
Use of medications possibly associated with Arrhythmia during the 12 months prior to index date:		
Anti-Arrhythmic Medications	15.6	4.1
Digitalis glycosides	32.2	12.8
Nitrates	41.2	24.2
Diuretic	56.4	38.8
Ace inhibitors	36.4	22.4
Beta blockers (non selective)	10.1	6.2
Beta blockers (beta-1 selective)	14.4	8.7
Calcium-Channel blockers	35.7	27.0
Other Hypotensive Agents	22.9	16.2
Net macrolide antibiotics	10.7	9.3
Net non-macrolide antibiotics	50.2	43.5
Cisapride	4.0	3.0
ASA	42.5	31.8
Non-steroidal anti-inflammatory medications	22.9	22.7
Antidepressants	13.9	12.1
Benzodiazepines	54.0	46.4
Other Psychotherapeutic agents	9.0	8.5
Narcotics	38.3	33.3
Antilipemic medications	12.2	11.1
Diabetic medications	15.5	11.4
Thyroid Medications	14.6	12.2
Hospital or out-patient diagnosis code indicating comorbidity during the 12 months prior to index date:		
CHF	29.9	10.2
Enlarged Heart	1.6	0.5
Hypertension	34.2	27.4
Cerebrovascular Disease	10.8	6.5
Atherosclerosis	6.5	4.1
Other Cardiovascular disease	57.5	31.7
Anaemia	12.7	7.5
Diabetes	16.3	10.8
Thyroid disease	8.7	5.6
hyperlipidemia	5.3	3.5
Renal Failure	2.2	0.9
Any non- primary diagnosis COPD hospitalisation	24.1	12.8
Any other not otherwise specified hospitalisation	8.2	6.9

Table 5-3 Rate ratios of arrhythmia comparing "Current& new use" (exposure between 0 to 60 days before the index date, with no preceding exposure in the previous 10 month period), "Current, not new use" (exposure between 0 to 60 days before the index date preceded by exposure in the previous 10 month period), and "Past use" (no current exposure, exposure during the 365 to 61 day period before the index date) as compared with no use to each bronchodilator agent during the year leading up to the arrhythmia.

Exposure Use Category	Cases (%)	Controls (%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Total	5,307	53,070		
Ipratropium Bromide				
Current & New	191 (3.60)	1008 (1.90)	1.59 (1.31 - 1.92)	1.09 (0.89 - 1.33)
Current, not new	1070 (20.16)	8685 (16.37)	1.24 (1.14 - 1.35)	0.94 (0.86 - 1.04)
Past Only	419 (7.90)	4224 (7.96)	1.03 (0.92 - 1.16)	0.79 (0.70 - 0.90)
Never	3627 (68.34)	39153 (73.78)	1.00 (Reference)	1.00 (Reference)
Short-Acting β-Agonists				
Current & New	247 (4.65)	1443 (2.72)	1.64 (1.38 - 1.94)	1.34 (1.12 - 1.61)
Current, not new	1957 (36.88)	17233 (32.47)	1.21 (1.12 - 1.31)	1.06 (0.97 - 1.15)
Past Only	1070 (20.16)	10715 (20.19)	1.16 (1.07 - 1.26)	1.00 (0.91 - 1.09)
Never	2033 (38.31)	23679 (44.62)	1.00 (Reference)	1.00 (Reference)
Methyl Xanthines				
Current & New	70 (1.32)	504 (0.95)	1.29 (0.99 - 1.66)	1.31 (1.00 - 1.72)
Current, not new	850 (16.02)	8324 (15.68)	0.99 (0.91 - 1.08)	1.11 (1.02 - 1.22)
Past Only	487 (9.18)	5137 (9.68)	0.97 (0.88 - 1.08)	0.99 (0.89 - 1.11)
Never	3900 (73.49)	39105 (73.69)	1.00 (Reference)	1.00 (Reference)
Long-Acting β-Agonists				
Current & New	47 (0.89)	279 (0.53)	1.40 (1.02 - 1.93)	1.20 (0.86 - 1.68)
Current, not new	186 (3.50)	1607 (3.03)	1.07 (0.91 - 1.26)	1.02 (0.85 - 1.21)
Past Only	79 (1.49)	817 (1.54)	0.94 (0.74 - 1.19)	0.78 (0.61 - 1.01)
Never	4995 (94.12)	50367 (94.91)	1.00 (Reference)	1.00 (Reference)

Table 5-4 Rate ratios of arrhythmia associated with use in the *Restricted Cohort* (analysis limited to subjects who during the current period were neither hospitalised nor experienced an exacerbation)

Exposure Use Category	Cases (%)	Controls (%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Total	4,049	36,850		
Ipratropium Bromide				
Current & New	88 (2.17)	440 (1.19)	1.60 (1.23 - 2.08)	1.43 (1.08 - 1.88)
Current, not new	718 (17.73)	5511 (14.96)	1.17 (1.05 - 1.30)	0.97 (0.87 - 1.08)
Past Only	316 (7.80)	2832 (7.69)	1.05 (0.92 - 1.19)	0.83 (0.72 - 0.95)
Never	2927 (72.29)	28067 (76.17)	1.00 (Reference)	1.00 (Reference)
Short-Acting β-Agonists				
Current & New	130 (3.21)	797 (2.16)	1.40 (1.13 - 1.75)	1.28 (1.02 - 1.61)
Current, not new	1404 (34.68)	11441 (31.05)	1.17 (1.07 - 1.28)	1.08 (0.98 - 1.19)
Past Only	835 (20.62)	7519 (20.40)	1.13 (1.03 - 1.24)	1.01 (0.91 - 1.12)
Never	1680 (41.49)	17093 (46.39)	1.00 (Reference)	1.00 (Reference)
Methyl Xanthines				
Current & New	43 (1.06)	305 (0.83)	1.23 (0.89 - 1.70)	1.25 (0.89 - 1.76)
Current, not new	654 (16.15)	5762 (15.64)	1.01 (0.92 - 1.12)	1.14 (1.03 - 1.26)
Past Only	356 (8.79)	3564 (9.67)	0.92 (0.82 - 1.04)	0.95 (0.84 - 1.08)
Never	2996 (73.99)	27219 (73.86)	1.00 (Reference)	1.00 (Reference)
Long-Acting β-Agonists				
Current & New	29 (0.72)	141 (0.38)	1.68 (1.12 - 2.52)	1.54 (1.00 - 2.36)
Current, not new	132 (3.26)	1045 (2.84)	1.08 (0.89 - 1.31)	1.06 (0.86 - 1.30)
Past Only	55 (1.36)	545 (1.48)	0.91 (0.68 - 1.21)	0.83 (0.61 - 1.12)
Never	3833 (94.67)	35119 (95.30)	1.00 (Reference)	1.00 (Reference)

Table 5-5 Sensitivity Analyses

	Cases (%)	Controls (%)	Crude RR	Adjusted RR
1. Atrial Fibrillation and Flutter				
Total	2,279	20,728		
Ipratropium Bromide	55 (2.41)	261 (1.26)	1.63 (1.16 - 2.28)	**1.61 (1.13 - 2.30)**
Short-Acting β-Agonists	80 (3.51)	475 (2.29)	1.47 (1.11 - 1.95)	1.28 (0.95 - 1.73)
Methyl Xanthines	25 (1.10)	181 (0.87)	1.23 (0.80 - 1.88)	1.23 (0.79 - 1.93)
Long-Acting β-Agonists	21 (0.92)	82 (0.40)	2.10 (1.29 - 3.42)	**1.89 (1.13 - 3.16)**
2. Fatal Arrhythmia				
Total	316	2,856		
Ipratropium Bromide	7 (2.22)	31 (1.09)	2.06 (0.76 - 5.54)	1.70 (0.57 - 5.09)
Short-Acting β-Agonists	10 (3.16)	67 (2.35)	1.06 (0.48 - 2.37)	1.18 (0.49 - 2.84)
Methyl Xanthines	2 (0.63)	18 (0.63)	0.93 (0.21 - 4.05)	1.30 (0.28 - 5.99)
Long-Acting β-Agonists	2 (0.63)	6 (0.21)	2.47 (0.48 - 12.64)	3.02 (0.49 - 18.44)
3. All arrhythmias, 30 day "current" time window				
Total	4,049	36,850		
Ipratropium Bromide	47 (1.16)	204 (0.55)	1.49 (1.04 - 2.14)	1.29 (0.88 - 1.88)
Short-Acting β-Agonists	82 (2.03)	358 (0.97)	2.03 (1.54 - 2.67)	**1.98 (1.48 - 2.65)**
Methyl Xanthines	22 (0.54)	136 (0.37)	1.33 (0.84 - 2.10)	1.42 (0.88 - 2.30)
Long-Acting β-Agonists	20 (0.49)	70 (0.19)	2.30 (1.39 - 3.81)	**2.08 (1.22 - 3.56)**

5.5 Additional Analyses

5.5.1 Full reporting of all seven modeling options

Similar to the results presented for the Saskatchewan cohort full riskset analyses, Tables 5-6 and 5-7 present results of the following seven modeling options for the risk of incurring the outcome event associated with treatment initiation with our four bronchodilator classes within the Québec data:

1. All riskset subjects included, exacerbations and hospitalisations controlled for in the analysis;
2. Excluding subjects experiencing moderate exacerbations in the current time window (the sixty day period leading up to the event), hospitalisations controlled for in the analysis;
3. Excluding subjects who were hospitalized with a primary diagnosis code for COPD during the current time window, moderate exacerbations controlled for in the analysis;
4. Excluding subjects who were hospitalized for any reason during the current time window, moderate exacerbations controlled for in the analysis;
5. Excluding subjects experiencing either moderate exacerbations or who were hospitalized with a primary diagnosis code for COPD during the current time window, the event of being hospitalized for other reasons during the current period controlled for in the analysis;
6. Excluding both subjects with a primary diagnosis code for COPD as well as subjects who had been prescribed either an oral corticosteroid or an antibiotic during the current time window. This should be regarded as a relaxation of the definition of exacerbation which in all other models required that both drugs be prescribed on the same day. Non-COPD hospitalisations occurring during the current time period were controlled for in the analysis; and finally,
7. The "restricted cohort" model, where any subject who had experienced either a moderate exacerbation or had been hospitalized for any reason during the current period were excluded from the analysis.

Table 5-6 Rate Ratios for the risk of arrhythmia associated with initiating treatment with bronchodilators- Summary table by model definition

Bronchodilator Class	1. Before Riskset Exclusions: Modeling all Current Exacerbations	2. Excluding Current Moderate Exacerbations; Modeling Current Severe Exacerbations (primary diagnosis COPD hospitalization)	3. Modeling Current Moderate Exacerbations; Excluding Current Severe Exacerbations	4. Modeling Current Moderate Exacerbations; Excluding subjects with ANY hospitalization within 60-day current window	5. Excluding Current Moderate Exacerbations; Excluding Current Severe Exacerbations	6. Excluding ANY Current : • Antibiotic Rx or • OCS Rx; • Severe Exacerbations	7. *"The Restricted Dataset"* Excluding Current Moderate Exacerbations and Excluding subjects with ANY hospitalization within 60-day current window
Ipratropium Bromide	1.09 (0.89 - 1.33)	1.18 (0.94 - 1.48)	1.23 (0.97 - 1.57)	1.37 (1.05 - 1.80)	1.26 (0.97 - 1.62)	1.36 (1.00 - 1.85)	1.43 (1.08 - 1.88)
Short-Acting β-Agonists	1.34 (1.12 - 1.61)	1.31 (1.08 - 1.58)	1.26 (1.03 - 1.55)	1.29 (1.03 - 1.61)	1.26 (1.03 - 1.56)	1.17 (0.91 - 1.51)	1.28 (1.02 - 1.61)
Methyl Xanthines	1.31 (1.00 - 1.72)	1.27 (0.93 - 1.71)	1.28 (0.93 - 1.75)	1.19 (0.85 - 1.68)	1.32 (0.96 - 1.81)	1.37 (0.92 - 2.05)	1.25 (0.89 - 1.76)
Long-Acting β-Agonists	1.20 (0.86 - 1.68)	1.29 (0.88 - 1.89)	1.37 (0.93 - 2.03)	1.48 (0.98 - 2.22)	1.43 (0.94 - 2.16)	1.64 (1.03 - 2.62)	1.54 (1.00 - 2.36)

As demonstrated by these analyses (Table 5-6), the modeling decision regarding exclusion of subjects who had a moderate exacerbation and had been hospitalized within the 60-day current time window had an impact on our results. The risks associated with treatment initiation with a short-acting β-agonist were reasonably consistent across all seven models with respect to producing a statistically significant increased risk of arrhythmia, with rate ratios ranging from 1.2 to 1.3. The risks associated with being initiated with ipratropium bromide and long-acting β-agonists, however, were not as consistent. The process of excluding recently hospitalized subjects resulted in a sufficient increase in the proportion of unexposed controls (or, conversely, a decrease in the proportion of exposed controls) to these two bronchodilator classes such that statistically significant rate ratios for the risk of arrhythmia were observed post exclusion. As such, differences in estimates pre and post exclusion are an illustration of the impact of immeasurable time bias.

Similarly, Table 5-7 provides the results accruing to the same seven models for the risk of atrial fibrillation primary diagnosis hospitalisation or death after cohort entry associated with initiation with each bronchodilator class. The risks associated with treatment initiation with a long-acting β-agonist were reasonably consistent across all seven models with respect to producing a statistically significant increased risk of arrhythmia, with rate ratios ranging from 1.4 to 2.0. The rate ratios associated with treatment initiation with ipratropium bromide ranged from 1.2 to 1.6, but were statistically significant mostly in models where immeasurable time bias was accounted for.

Table 5-7 Rate Ratios for the risk of atrial fibrillation and flutter associated with initiating treatment with bronchodilators- Summary table by model definition

Bronchodilator Class	1. Before Riskset Exclusions: Modeling all Current Exacerbations	2. Excluding Current Moderate Exacerbations; Modeling Current Severe Exacerbations (primary diagnosis COPD hospitalization)	3. Modeling Current Moderate Exacerbations; Excluding Current Severe Exacerbations	4. Modeling Current Moderate Exacerbations; Excluding subjects with ANY hospitalization within 60-day current window	5. Excluding Current Moderate Exacerbations; Excluding Current Severe Exacerbations	6. Excluding ANY Current : • Antibiotic Rx or • OCS Rx; • Severe Exacerbations	7. *"The Restricted Dataset"* Excluding Current Moderate Exacerbations and Excluding subjects with ANY hospitalization within 60-day current window
Ipratropium Bromide	1.22 (0.94 - 1.59)	1.36 (1.02 - 1.82)	1.34 (0.97 - 1.84)	1.48 (1.06 - 2.09)	1.41 (1.01 - 1.96)	1.45 (0.97 - 2.16)	1.61 (1.13 - 2.30)
Short-Acting β-Agonists	1.39 (1.09 - 1.75)	1.32 (1.02 - 1.69)	1.28 (0.98 - 1.67)	1.31 (0.98 - 1.75)	1.27 (0.97 - 1.68)	1.18 (0.84 - 1.65)	1.28 (0.95 - 1.73)
Methyl Xanthines	1.14 (0.78 - 1.65)	1.09 (0.72 - 1.66)	1.08 (0.70 - 1.67)	1.15 (0.73 - 1.81)	1.18 (0.76 - 1.82)	1.02 (0.56 - 1.84)	1.23 (0.79 - 1.93)
Long-Acting β-Agonists	1.44 (0.95 - 2.19)	1.51 (0.94 - 2.42)	1.76 (1.09 - 2.85)	1.81 (1.10 - 2.96)	1.83 (1.11 - 3.01)	1.96 (1.09 - 3.51)	1.89 (1.13 - 3.16)

5.5.2 Testing for effect modification

As was the case in the previous study, age, sex, previous history of arrhythmia, duration of COPD, CHF, and other cardiovascular disease are all important determinants of arrhythmia and as such, may modify the association between bronchodilators and arrhythmia. To test for effect modification, we included the relevant set of interaction terms (one for each level of exposure for each bronchodilator), one variable set at a time, in subsequent models. All subgroup analyses were carried out using a two-sided test of $\alpha = 0.05$.

As was the case in our Saskatchewan cohort, none of our bronchodilator use exposure categories were modified by either age, CHF, or previous history of arrhythmia before cohort entry. Within the Quebec data, there was no interaction observed with sex, however tests for interaction with age, COPD duration, and the presence of non-CHF cardiovascular disease did indicate the possibility of an interaction. The individually statistically significant effects, however, were different than those detected within the Saskatchewan data, and once again there was a lack of a consistent pattern, very small numbers of exposed cases and controls upon stratification, and relatively high p-values (within the 0.02-0.04 range) particularly given the fact that we were in a multiple testing situation. We therefore maintain that the observed individual statistically significant interaction terms are most likely to be indicative of type-I error.

5.5.3 The Combivent Effect:

Combivent Inhalation Aerosol is a combination of ipratropium bromide (as the monohydrate) and albuterol sulfate.[336] As outlined in the section on combination bronchodilator therapy in Chapter 2, the rationale behind a therapy regimen which combines both ipratropium and SABA would be to take advantage of both the rapid onset of action of the adrenergic agents and the prolonged action of the anticholinergic,[125] in order to achieve in maximum reversibility of airflow obstruction[126]. In addition, since combinations of anticholinergics and β_2-agonists

at sub maximal doses will produce an additive effect,[127-129] it is possible to prescribe each component bronchodilator using a reduced dose thereby avoiding unintended side-effects.[125]

As illustrated in Table 5-8, this effect appears to have been realized as the combination of both agents prescribed at reduced doses resulted in a lower risk of arrhythmia (RR=1.43) than the risk associated with being initiated with either IB or SABA alone (RR=1.90 and 1.46 respectively). In this analysis we are observing a mix of effects of prescribing Combivent and prescribing the two agents separately as Combivent per se wasn't listed on the RAMQ formulary pre May1996. Upon verification, however, over 90% of all exposures to both agents classified as "New & Current" occurred after 1997 and were indeed prescriptions for this combined formulation.

Table 5-8 Comparison of rate ratios associated with treatment initiation with ipratropium bromide, by study cohort

Result for "restricted cohort" as reported in Manuscript #2				
variable	**# Cases Exposed (%)**	**# Controls Exposed (%)**	**Crude RR**	**Adj RR**
New Use of Ipratropium	88 (2.17)	440 (1.19)	1.60 (1.23 - 2.08)	1.43 (1.08 - 1.88)
New Use of SABA	130 (3.21)	797 (2.16)	1.40 (1.13 - 1.75)	1.28 (1.02 - 1.61)
After teasing out the effect of both of these agents combined:				
variable	**# Cases Exposed (%)**	**#Controls Exposed (%)**	**Crude RR**	**Adj RR**
New use of Both agents	42 (1.04)	249 (0.68)	1.74 (1.24 - 2.42)	1.43 (1.00 - 2.04)
New Use of Ipratropium without new use of SABA	46 (1.14)	191 (0.52)	2.18 (1.57 - 3.03)	**1.90** (1.33 - 2.70)
New Use of SABA without new use of Ipratropium	88 (2.17)	548 (1.49)	1.62 (1.28 - 2.05)	1.46 (1.14 - 1.88)

Further investigation of this apparent negative interaction revealed that the p-value for the statistical test for interaction between initiation with SABA and initiation with IB was p=0.018 within this cohort.

5.6 Discussion

The findings of this confirmatory re-analysis of our study question within the larger Québec cohort provides additional evidence in support of the notion that bronchodilator-induced arrhythmias are events associated with being newly exposed these agents. Treatment initiation with new use of ipratropium bromide and both short and long-acting β-agonists were found to increase the risk of cardiac arrhythmia in patients with COPD. New use of ipratropium bromide and long-acting β-agonists were specifically associated with a higher risk of atrial fibrillation.

While our finding pertaining to an elevated arrhythmia risk associated with treatment initiation with ipratropium was confirmed by the Quebec study, the estimates of effect themselves appear to be quite different. One reason for this may be due to the fact that we have presented the risks associated with the independent effects of treatment initiation conditioned on other exposures such as treatment initiation (as well as other current and past use) of other bronchodilator classes. Due to statistical power limitations within the Saskatchewan cohort, we initially did not investigate the effects pertaining to bronchodilator combinations within these data. Upon observing the negative interaction between ipratropium bromide and short-acting β-agonists within this cohort, however, we revisited the Saskatchewan data and found that after removing the effect of concurrent treatment initiation with a short-acting β-agonist the estimates were in fact more similar and no longer lay outside the confidence bounds of the second estimate (Table 5-9).

With regard to the reported negative interaction (between treatment initiation with ipratropium bromide and short-acting β-agonists) itself; it is of course possible

(albeit with a probability of approximately 2%) that the observed effect was by chance alone. It should be noted that this should not be regarded as a multiple-testing situation as no other bronchodilator combinations were investigated. Given the clinically plausible explanation that the combination of these two agents is produced using lower doses of each individual drug thereby limiting the therapeutic range for cardiac toxicity, we feel that this might be an important result. We therefore recommend that this negative interaction be investigated in both additional populations as well as for other possible cardiovascular outcomes of interest.

Table 5-9 Comparison of Québec and Saskatchewan cohort estimates of effect for treatment initiation with Ipratropium bromide both with and without concurrent treatment initiation with a short-acting β-agonist, and the risk of cardiac arrhythmia within the "restricted cohort"

Independent (conditioned) effect (before teasing out the effect of both of these agents combined)			
	# Cases Exposed (%)	**# Controls Exposed (%)**	**Adj RR**
Québec	88 (2.17)	440 (1.19)	1.43 (1.08 - 1.88)
Saskatchewan	12 (3.97)	277 (1.53)	3.03 (1.51 – 6.07)
Effect of Ipratropium treatment initiation without SABA			
	# Cases Exposed (%)	**# Controls Exposed (%)**	**Adj RR**
Québec	46 (1.14)	191 (0.52)	1.90 (1.33 - 2.70)
Saskatchewan	7 (2.21)	149 (0.82)	2.47 (1.10 - 5.57)

In both cohort studies, careful attention was given to the identification and handling of COPD exacerbations given the potential threat this variable posed to the validity of our results. In addition, we focused our attention to results emanating from the restricted cohort in which we eliminated immeasurable time bias and as well restricted the cohort to subjects who those who had stable COPD during the time of the index event. A question which is yet to be answered, however, is whether or not within the context of a longitudinal analysis it would

be valid to model exacerbations using standard techniques, or whether or not they are time-dependent confounders which lie in the causal pathway between exposure and outcome. In our next chapter, we therefore explore this possibility using marginal structural models, a novel class of causal models designed to adjust for time-dependent confounding in observational studies of time-varying treatments.[337]

6 Chapter 6: Using Marginal Structural Models to assess time-varying confounding status in longitudinal analyses: an example of bronchodilator use and the risk of serious arrhythmia in COPD

6.1 Preface to the manuscript

The proportional hazards model as developed by Sir David Cox in 1972 was a methodological breakthrough for the analysis for censored time-to-event data.[338] This model, as originally conceived, was a fixed covariates model which did not particularly suit situations where data are collected longitudinally and where we often observe covariates which change values over time. The extension of the proportional hazards model for time-dependent covariates[339] in which the fixed covariates constraint was relaxed, is now used quite extensively in medical research[340].

COPD is a chronic disease characterized by progressive, partially reversible airway obstruction and lung hyperinflation, systemic manifestations and increasing frequency and severity of exacerbations.[341] Clinical practice guidelines recommend that bronchodilator therapy should be escalated in accordance with the increasing severity of symptoms and disability.[341] As such, implementation of an intention-to-treat approach in long-term observational follow-up studies of outcomes in COPD would be highly inappropriate given patterns of bronchodilator discontinuation and switching seen within this patient population over the course of their disease. Indeed given the systemic nature of the disease itself, variables which measure comorbidity are also subject to notable changes over time which makes these data best suited for analysis using models with the flexibility for handling time-dependent covariates.

One of the often overlooked complexities of longitudinal data is that in certain situations, time-dependent covariates can be time-dependent confounders if they simultaneously meet the criteria of being a confounder and as well an intermediate variable on the causal pathway from exposure to disease.[342] While controlling for time-dependent confounders may still yield an unbiased estimate for the direct effect of exposure on disease, estimates of the total effect of exposure on disease using standard techniques have been shown to be biased.[342]

In the presence of time-dependent confounding, it is therefore necessary to turn to one of the two techniques which have been developed which can validly estimate the causal effect of a time-dependent exposure, namely g-estimation of structural nested models and marginal structural models.

Unfortunately, we often do not know a priori if a variable (or indeed, if a set of variables) would satisfy the conditions necessary to classify them as time-dependant confounders. We may postulate a mechanism by which this might be true, for example, by using directed acyclic graphs (DAGs) in which the relationships between measured and unmeasured variables are graphically encoded. This exercise, however, yields information about how the scenario of time-dependent confounding might be true, and not the degree to which time-dependent confounding would threaten the validity of estimates produced in the absence of the aforementioned specialised techniques.

It would be useful in the research of respiratory diseases to have knowledge concerning the potential time-dependent confounding status of many of the covariates which come into play. In this context, the purpose of our third manuscript was to investigate the time-dependent confounder status pertaining to several key variables in our study of bronchodilator use and risk of serious arrhythmia in COPD.

This article will be submitted for publication and should be referenced as follows:

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6.2 *Using Marginal Structural Models to assess time-varying confounding status in longitudinal analyses: an example of bronchodilator use and the risk of serious arrhythmia in COPD*

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Running Title: Marginal Structural Models to assess time-varying confounding status

Introduction:

In epidemiology, we attempt to describe and quantify causal pathways by means of controlling for possible mediating variables. Epidemiologists often "adjust" for an intermediary variable on a causal pathway to block the pathway and thereby separate a direct effect from indirect effects. Although that practice has been debated, recent work has clarified the conditions under which such conditioning is permissible. Further methodological complications arise, however when one or more model covariates satisfy the conditions of a time-dependent confounder in that:

1) the covariate is a risk factor for the outcome;
2) the covariate predicts future exposure; and
3) Past exposure predicts the covariate.

The method typically used to estimate the effect of a time-varying exposure (such as a bronchodilator) on an outcome (such as arrhythmia) is a model of the hazard of failure at a given time as a function of past exposure history using a time-dependent Cox proportional hazards model. When time-dependent confounders are present in such an analysis, regardless of whether or not past covariate history is adjusted for, the resulting estimates of effect may be biased. [343]

Marginal structural models (MSMs) are a novel class of causal models for the estimation, from observational data, of the causal effect of a time-dependent exposure in the presence of time-dependent covariates that may be simultaneously confounders and intermediate variables.[337] In these analyses, a model is fitted to the observed data using inverse probability weighting (IPW) where the contribution from each uncensored subject is re-weighted (approximately) by the inverse of the joint probability of having his/her treatment and censoring histories as a function of his/her covariate history.[337] The re-weighting is said to create a "pseudo population" consisting of all study subjects and their counterfactuals, in which confounders are no longer associated with treatment. Two key advantages of MSMs in pharmacoepidemiology, therefore, are that they address both confounding by indication[344-346] and time-dependent confounding[337;347;348] since

we can directly contrast the outcomes of subjects who are treated versus those who were not treated.

In some observational studies, the mechanisms of all or most model variables are well understood, making verification of time-dependent confounder status relatively straightforward. In other cases, however, either one is uncertain whether or not all three of the above conditions are satisfied, or whether or not all three arms are strong enough such that modeling the variable in question in the usual way would be a problem. In the case of a study analyzing the effect of bronchodilator use on the risk of serious arrhythmia resulting in hospitalization or sudden death, there are a number of candidate variables, such as COPD exacerbation or minor arrhythmia which could possibly satisfy the definition of a time-dependent confounder.

An exacerbation, for example, could potentially be a time-dependent confounder for the effect of ipratropium bromide on serious arrhythmia, because it is a risk factor for the outcome,[287-289] and depending on the time period under study and the associated clinical guidelines in play,[79] exacerbations could also potentially be a predictor of subsequent initiation of ipratropium bromide therapy. It is also possible, that past ipratropium bromide history is an independent predictor of subsequent exacerbation given the fact that at least one study has shown that regimes which included ipratropium bromide prevented exacerbations more effectively than a β-agonist alone.[111] If exacerbations are, in fact, time dependent confounders, then all standard methods such as Cox or Poisson regression that predict the outcome rate at each time using a summary of ipratropium bromide history up to that time may produce biased estimates of the causal effect of ipratropium bromide whether or not one adjusts for past exacerbation in the analysis.

Figure 6-1 is a simple directed acyclic graph (DAG),[349] which represents a hypothetical COPD cohort study with T=2 months of person-time in which we

are trying to estimate the effects of time-dependent treatment with ipratropium bromide $IB_{(t1)}$ and $IB_{(t2)}$ on the risk of arrhythmia.

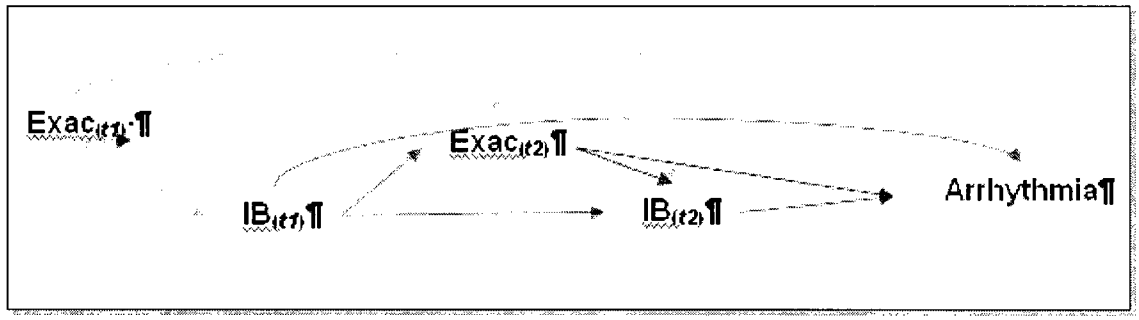

Figure 6-1 A simple DAG of a hypothetical COPD cohort study under the assumption of no confounding

As shown in Figure 1, treatment received in a particular period affects arrhythmia as well as treatment and exacerbations at subsequent periods. Treatment within a given period is also affected by treatment and exacerbations in previous periods as well as exacerbations within the same time period. This DAG therefore illustrates that exacerbation is a time-dependent confounder since exacerbation ($Exac_{t2}$) affects both treatment (IB_{t2}) and arrhythmia, and is also an intermediate variable in the pathway from treatment (IB_{t1}) and arrhythmia.

It should be noted that inherent in the above diagram is the assumption of no unmeasured confounders, which implies that that the selection of treatment during each month can be totally explained by variables which have been measured and included in the diagram. This assumption, however, is clearly violated by any common causes of exacerbation and outcome such as that presented in Figure 6-2 below:

In Figure 6-2, a variable such as a genetic marker (or set of variables), which is a causal risk factor for arrhythmia and which is also associated with exacerbation has been included. There are no direct arrows from this genetic marker into Ipratropium at any time period since unless we specifically screened for this variable (thereby rendering it measured as opposed to unmeasured as stated), there would be no possibility for it to be associated with exposure. In this

scenario, however, by controlling for ($Exac_{t2}$) we would artificially induce an association between $U_{(t2)}$ and Ipratropium bromide at time 1 at least within one stratum and therefore induce bias. (collider stratification bias) [350;351]

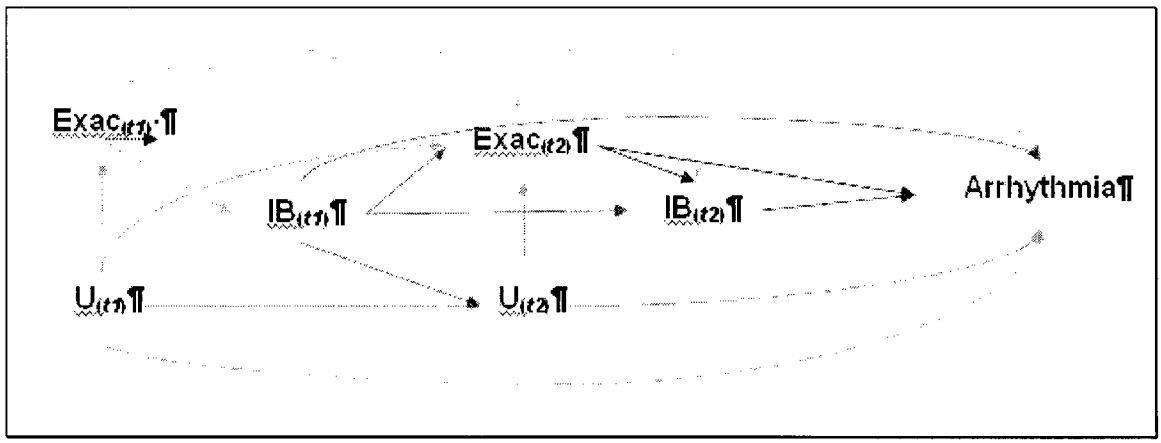

Figure 6-2 A more complex DAG of a hypothetical COPD cohort study in which there is unmeasured confounding

There are a number of candidate time-dependent confounding variables which should be considered when modeling the risk of serious arrhythmia requiring hospitalization or sudden death attributable to the use of ipratropium bromide in COPD. The purpose of this study, therefore, is to identify exactly which (if any) of these variables actually result in a biased estimate of effect when modeled using standard methods as compared with a marginal structural model.

METHODS

Subjects

To estimate the causal effect of bronchodilator use on cardiac arrhythmia in patients with COPD, we took advantage of a large cohort of new bronchodilator users aged 67 and older using the health administrative databases of Quebec [352] Briefly, subjects had a minimum of three prescriptions for a bronchodilator, on at least two different dates, within any one period after January 1, 1990 and December 31, 2002, with the data of cohort entry defined as the date of the third of this sequence of prescriptions. Subjects were excluded if they had received any bronchodilator, anti-asthma drug (cromoglycate, nedocromil, montelukast,

zafirkulast, or ketotifen), or nasal or inhaled corticosteroids in the 2 years prior to cohort entry, or if they had less than 2 years of history since their enrolment. A total of 76,648 subjects were then followed until the date of their arrhythmic event, December 31, 2003, or the date of their death from any cause, whichever came first.

Exposure:

All ipratropium bromide prescriptions that were dispensed to the cases and controls during follow-up were identified and classified according to month obtained. Canisters of ipratropium bromide either alone (Atrovent) or combined with albuterol (Combivent) contain 200 puffs per canister, and presuming that on average 4 puffs are administered per day, we assume that each ipratropium bromide dispensing results in approximately 50 days of exposure. We therefore considered a subject to be currently exposed during both the month the medication was dispensed as well as the month immediately following. New exposure pertains to any current exposure period which was preceded by ten months of non-exposure to ipratropium bromide.

Outcome:

The study end point was the earliest event corresponding to either death with an underlying cause of death of arrhythmia, or a hospital admission with a primary discharge diagnosis of arrhythmia (ICD-9 codes 427x, ICD-10 codes I46x-I49x, R000 and R001) occurring any time after cohort entry.

Baseline covariates

Central to IPW estimation is the inclusion of a set of baseline covariates which are distinguished from the set of time-varying covariates, the latter which are to be included only in the two logistic models specified for the purposes of estimating the inverse probability treatment weight (IPTW) and inverse probability censoring weight (IPCW) denominators. As described elsewhere,[353;354] the process of determining the set variables to include as baseline covariates in a marginal

structural model requires a delicate balance of both parsimony and completeness. Completeness speaks to the issue of the exchangeability assumption which assumes that there is no unmeasured confounding within the model being estimated. In order to satisfy this assumption, it is therefore necessary to ensure that all confounders are measured and appear within the model. Parsimony, however, is also recommended since rare combinations of covariates can result in a situation where violations of the positivity assumption (also known as the *experimental treatment assumption*[344]) which requires that there must be both exposed and unexposed individuals at every level of the confounders.[354] When the estimated probability of exposure is close to 0 within in some subset of the data, the resulting inverse probability weights attributed to those subjects whose treatment levels are inconsistent with the majority of subjects with the same values of their covariates, will be large.[355] Since large and variable weights can lead to unstable estimates the practice of stabilization is carried out via a process where the weights are multiplied by the numerator probabilities of the models estimating exposure and censoring on the baseline covariates only.[356-358]

Variables that were identified as being known or potential risk factors of arrhythmia and known or potential confounders of the association between bronchodilators and arrhythmia were measured at baseline. Previous history of arrhythmia at baseline was captured by means of a four-level ordinal variable denoting the number of sources from which the condition was identified (range from 0 to 3). The three variables pertaining to cardiovascular conditions at baseline were included in the model based on the presence of diagnoses contained in either the hospital or physicians services files were : congestive heart failure, a variable which captured any of anemia, atherosclerosis, cerebrovascular disease or cardiomegaly which are the four other cardiovascular conditions which are considered to be high risk factors for arrhythmia, and a third variable which captured all other cardiovascular conditions. In addition, a variable pertaining to the use of cardiovascular medications (either digitalis, nitrates or vasodilators, ACE inhibitors, beta blockers or calcium channel blockers) was included.

In the interest of parsimony in variable selection, variables flagging the other comorbid conditions associated with arrhythmia from any data source (i.e. from medical services, hospitalisations or pharmacy records) were pooled such that if a subject was identified amongst any of these files, that subject was coded as having had that condition at baseline. Comorbid conditions for which pooling occurred include hypertension, diabetes, hyperlipidemia, thyroid disease, and renal failure. Additional baseline variables included the use of drugs that decrease potassium levels such as inhaled corticosteroids; aspirin /non-steroidal anti-inflammatory drugs (NSAIDs)/narcotics; and drugs that are hypothesized to lengthen the Q-T interval thereby causing Torsades de Pointes such as macrolides antibiotics (not prescribed on the same day as an oral corticosteroid), antidepressants, cisipride, and antipsychotics. Use of inhaled or oral corticosteroids (the latter when not prescribed in conjunction with an antibiotic) were also included as a measure of respiratory severity, as were previous history of a moderate COPD exacerbation, a COPD hospitalisation, or any other hospitalisation during the baseline year. The remaining baseline variables included in the analyses were age, sex, and the year of cohort entry.

Data analysis

The data for our cohort were configured in order to be compatible with a pooled logistic regression format with each observation corresponding to a person-month under study. Pooled logistic regression and the grouped Cox regression with time dependent variables are asymptotically equivalent as long as the necessary conditions of short intervals for grouping of the outcome events, small probability of an event in the intervals, and equal intercepts of the pooled logistic model for each interval are met. [359]

The approach used to performed our marginal structural model closely followed the method as described by Hernan et al (2000)[356] with one exception worth noting. Hernan modeled the benefit of zidovudine on the survival of HIV positive

men using an intention to treat analysis, such that it was assumed that once starting zidovudine a patient does not stop. This assumption would not make sense in the case of bronchodilator therapy in COPD seeing as these bronchodilator exposures are much more transient in nature, and what is relevant is the particular exposure(s) which occur in the time-period immediately adjacent to the event.

Thus, we fit four pooled logistic models (two for the probability of being dispensed ipratropium bromide, and two for the probability of being censored during each person-month) and obtained their predicted values. The predicted values from the four pooled logistic models were used to produce inverse propensity treatment and censoring weights such that a pseudo-population was created in which the exposure is independent of the measured confounders (assuming that both the assumption of no unmeasured confounders was satisfied and the model used to create the treatment weights was not miss-specified).[357] In order to both reduces the range of weight values (which can have an effect on model stability) as well as improves both statistical efficiency and the coverage,[337] the weights were then stabilized using the predicted values produced by the models including the baseline covariates only. The processes by which this was accomplished was by multiplying the weights for person moments associated with current use by the product of probability of being treated with the probability of being censored, and by multiplying the weights for the person moments associated with no current use by the product of probability of not being treated with the probability of being censored.

In this longitudinal analysis, time is a key variable which must be accounted for and modeled appropriately, and while some longitudinal studies implement categorization of time using the usual step-function, this could produce bias introduced by the process categorization.[360;361] In a pooled logistic model, each person-time unit is represented by an observation, where the unit is usually equal to a week or a month. Intrinsic to this format is an assumption that the risks of the

outcome are constant within each time interval, although it is possible that this is untrue, rendering cut-points influential on both the estimates of effect and their associated precision.[362] In order to avoid assumptions regarding constant risk over time, time-dependent intercepts were estimated as a smooth function of the time since beginning of follow-up (MONTH) using natural cubic splines with six knots.[356;363]

In our previous study,[352] we excluded subjects who had either been hospitalized or had experienced a moderate exacerbation during the 60 day "current" time window leading up to the index date. These exclusions were to limit our analysis to subjects with stable disease, and because we were concerned that exacerbations could be potential time-dependent confounders. We eliminated person moments associated with current hospitalisations, however, to minimize misclassification of exposure since medication use during hospitalisation is not captured in these data. In order then to avoid immeasurable time bias[185] in these analyses, we deleted any person month where a hospital admission was recorded as well as the person month immediately following. All analyses were conducted on the post-deletion dataset.

This study assessed the time-varying confounding status for the following four candidate time-dependent covariate categories:

1. Current moderate COPD exacerbation: identified via record for a prescription for an oral corticosteroid and an antibiotic dispensed on the same day;
2. Current minor arrhythmias: identified via either a diagnostic code for arrhythmia within the physician services file or the dispensing of an anti-arrhythmic medication;
3. Ever minor arrhythmia: a variable assigned to one commencing the first month a minor arrhythmia occurs and remaining pegged at unity throughout person time thereafter; and

4. Current use of other (non-ipratropium bromide) bronchodilators: This model includes three variables corresponding to the use of short-acting beta-agonists, long-acting beta-agonists, and methylxanthines.

Estimates of the MSM-based causal parameters of interest and their robust standard errors were produced by running a final weighted pooled logistic model using Proc GENMOD from SAS version 9.1 invoking the repeated statement (using subject ID as the clustering variable). In order to compare each MSM to their corresponding relevant (unweighted) time-dependent Cox proportional hazards model, the vector of time-dependent variables which were used to produced the denominators for both inverse probability weight models were included as covariates in the analysis.

Results

The characteristics of the COPD cohort during the one year baseline period prior to cohort entry comparing subjects by exposure to ipratropium bromide during their first month of follow-up are presented in Table 6-1. Approximately 20% of the cohort entered with a prescription for ipratropium bromide. This group exposed to ipratropium bromide during their first month of follow-up were more likely to have had a previous moderate COPD exacerbation, a previous history of arrhythmia, more cardiovascular conditions at baseline, been exposed to oral corticosteroids (not prescribed on the same day as an antibiotic) and were more likely to have had a previous COPD hospitalisation.

The distributions of the stabilized weights which combine information on both current ipratropium and censoring history are presented in Figures 6-3 and 6-4. Figure 6-3 presents the stabilized weights for current ipratropium exposure at months 24, 48 and 72 for the four models corresponding to the inclusion of each of our four candidate time-dependent confounder categories individually. The mean values of the stabilized weights calculated using all person months were all equal to one (with some variation at the second or third decimal place). Our model

with the highest variation in stabilized weights corresponded to the model which evaluated other bronchodilators as time-dependent confounder (minimum and maximum estimated weights were 0.012 and 10.88 respectively) which is to be expected[354] since this was the only of the four models which included not one but three time-varying confounding variables (corresponding to current exposure to either methyl xanthines or to short or long-acting β-agonists). The distribution of stabilized weights corresponding to new ipratropium exposure was very similar to that for current exposure (not shown).

The distributions of the stabilized weights at eight points of follow-up time from the models for both current and new ipratropium exposure which included all four time-dependent confounder categories are presented in Figure 6-4. The distribution of stabilized weights was found to be relatively symmetric and centered around 1 at all times and for both exposure categories. Whereas the distribution associated with new exposure was much tighter than that for current exposure, the highest observed stabilized weights in the overall sample for both samples were small at 13.9 and 4.8 for current and new exposure respectively.

The estimated causal hazard rate ratio of arrhythmia for current and new exposure to ipratropium bromide exp (β_1) ranged from 1.14 to 1.33 and from 1.35 to 1.50 respectively (Table 6-2)depending on the model indicating that, under our assumptions, both current and new ipratropium therapy appear to increase the risk of arrhythmia. When comparing the marginal structural model results to the relevant comparison time-dependent Cox model, we observe that the inclusion of other bronchodilators as time-dependent covariates had the single largest impact than did moderate exacerbations or minor arrhythmia for models assessing the risk of both current and new ipratropium exposure. In the final model which included all candidate time-dependent confounders, the change in estimate of effect as calculated by $(\beta_{1MSM} - \beta_{1TDCox})/\beta_{1\ MSM}$ was -36.6% and -16.9% for current and new exposure to ipratropium bromide respectively, indicating a bias towards the null produced by standard techniques. None of current moderate

exacerbations, current minor arrhythmia or ever minor arrhythmia, however, displayed a change in estimate of effect of greater than 6% when considering these variables individually as potential time-dependent confounders.

Discussion

The purpose of this study was to determine whether minor exacerbations, minor arrhythmia, or the use of other bronchodilators were potential time-dependent confounders when modeling the risk of serious arrhythmia requiring hospitalization or sudden death attributable to the use of ipratropium bromide in COPD. We assessed this by comparing the estimates of effect produced when they are modeled using standard techniques as compared with a marginal structural model.

Since a time varying confounder is, by definition, in the causal pathway between exposure and outcome, we would expect that adjusting for them using traditional techniques would remove their indirect component of effect and thereby result in a bias towards the null. Whereas for the most part our findings show this to be the case as indicated by a negative value associated with change in estimate of effect, our findings also indicate that individually, none of current moderate exacerbation, current minor arrhythmia, or ever minor arrhythmia is powerful enough as time-dependent confounders for the modeling technique to make any difference. When comparing the impact of including variables corresponding to methyl xanthine and short- and long-acting β-agonist use, however, the differences between the models diverged, and in the models where all of the candidate time-dependent confounders were combined, the observed change in estimates of effect were -37% and -17% for current and new use of ipratropium respectively.. These observed differences are relatively small; it is questionable as to whether or not differences in hazard ratios of 1.1 vs. 1.2, for example, are either clinically or epidemiologically meaningful.

Although the estimates of effect from both methods produced similar results, it is important to note that the parameters themselves are fundamentally different and that they, in fact have a very different interpretation. The coefficients from the conventional Cox analysis have a conditional (i.e. stratum-specific) interpretation whereas those from the MSMS model analysis have the direct population-level counterfactual causal interpretation " if contrary to fact, everyone in the population were to initiate ipratropium bromide, then the hazard ratio associated with this exposure would be 1.42".[364]

There are a number of limitations which should be noted in this study which impact on the interpretation of the marginal structural model results as causal. First, the estimates of risk associated with ipratropium bromide use have a causal interpretation only under the assumption of no unmeasured confounding. This assumption may not be true in this case, as this is a database study and some clinical and laboratory information used by physicians as indications for such as dyspnea or spirometry values were not available for use in the models for the estimation of the weights.

Second, it is essential that there be no informative censoring in our data, such that these results are based on the assumption that dropout is ignorable, conditional on measured covariates. In this study, censoring only occurred if a subject died from an underlying cause unrelated to arrhythmia, or reached the study end date. It seems unlikely that this would be an issue, but there are circumstances under which treating death as a censoring event in the analysis may be inappropriate[365].

The third condition which must be satisfied is that of no model misspecification. In the current model as specified, we demonstrated that the stabilized weights have a mean of one, which is a necessary condition for correct model specification.[357] While we can assume that our model is not optimally specified, we did test for nonlinearity and effect modification before settling on the final model, and the set of baseline covariates for which we explained earlier was

driven by both the need for completeness and parsimony. It is possible that a more complete model which introduced for example, a vector of cardiovascular conditions as time-dependent covariates would more completely specify the model. Unfortunately, doing so may likely result in a violation of the positivity assumption.

Conclusion

In conclusion, we have found that individually, none of current moderate exacerbation, current minor arrhythmia, or ever minor arrhythmia is powerful enough as time-dependent confounders to meaningfully bias the association between current or new use of ipratropium bromide on the risk of cardiac arrhythmia in patients with COPD. When introduced as a group and when also combined with time-dependent covariates corresponding to other bronchodilator use, however, we did observe a difference between the hazard rate ratios from the traditional time-dependent Cox and Marginal structural Model results in the order of -37% and -17% for current and new use of ipratropium respectively. These finding suggest an important role for the use of inverse probability weighting techniques when investigating the association between cardiovascular outcomes and drug use in patients with COPD.

Table 6-1 Characteristics of the COPD cohort during the one year baseline period prior to cohort entry comparing subjects by exposure to ipratropium bromide during their first month of follow-up

	Exposed to Ipratropium Bromide	Unexposed to Ipratropium Bromide
Subjects n (%)	15,782 (20.6%)	60,866 (79.4%)
Age mean ± SD*	76.9 (6.3)	75.3 (5.9)
Male %*	58.2	50.6
Year of Cohort Entry(mean ± SD	1996.8 (3.7)	1992.7 (3.4)
Use of other Respiratory Therapy		
Inhaled Corticosteroids	1.4	2.0
Oral Corticosteroids (not prescribed on the same day as an antibiotic)	10.1	4.5
Experienced a Moderate COPD Exacerbation	8.4	2.2
Previous History of Arrhythmia	19.1	10.0
Use of medications possibly associated with Arrhythmia		
Cardiotonic Drugs (including Digitalis Glycosides, Nitrates and Vasodilators, ACE Inhibitors, Beta Blockers, and Calcium Channel Blockers)	61.6	52.0
Macrolide antibiotics (not prescribed on the same day as an Oral Corticosterod)	13.4	10.2
Cisapride	2.8	1.5
ASA/NSAID or Narcotics	62.8	65.3
Antidepressants	12.8	9.7
Benzodiazepines or other Psychotherapeutic agents	48.1	54.9
Comorbidity:		
CHF	19.4	8.4
Any of: Enlarged Heart, Cerebrovascular disease, Atherosclerosis, or Anaemia	22.4	11.5
Hypertension	60.5	52.6
Other Cardiovascular disease	44.1	27.5
Diabetes	15.7	11.9
Thyroid Disease	13.3	9.03
Hyperlipidemia	15.2	9.4
Renal Disease	2.1	0.35
COPD hospitalisation	30.1	10.1
Other hospitalisation	6.6	7.7

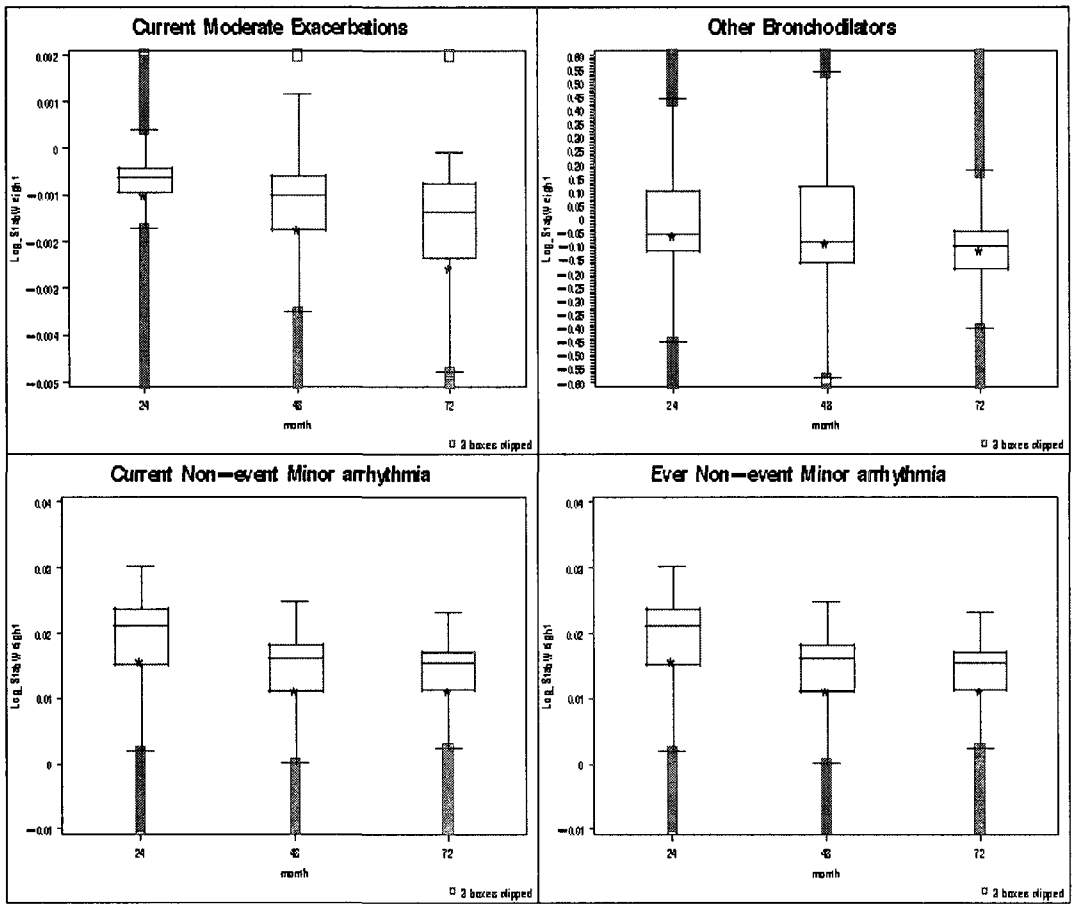

Figure 6-3 Distribution of the Stabilized Inverse Propensity Weights for the four candidate time-dependent confounder categories for models assessing Current use of Ipratropium Bromide.

The box for each group shows the location of the mean (*), median (middle horizontal bar) and quartiles (border horizontal bars). Vertical lines extend to the most extreme observations which are no more than 1.5x 3 IQR beyond the quartiles. Observations beyond the vertical lines are plotted individually, if they lie within the limits of the frame.

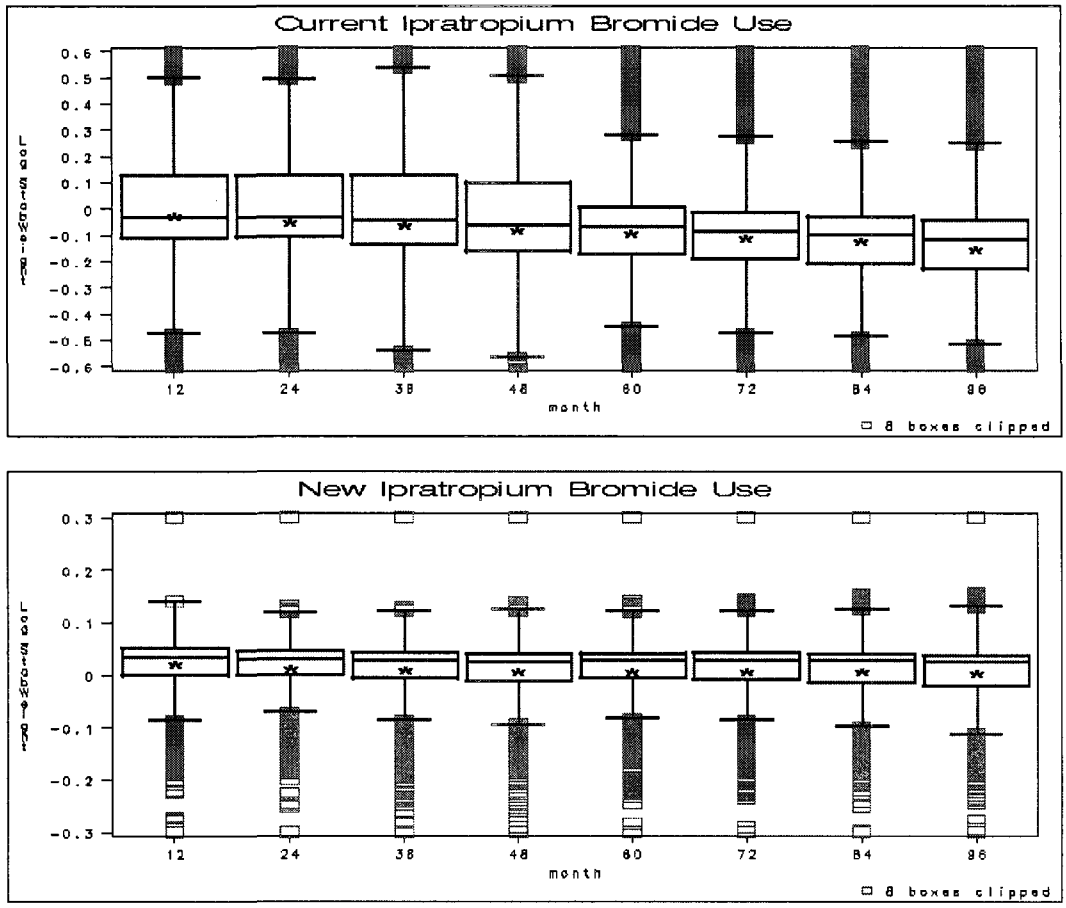

Figure 6-4 Distribution of Stabilized Inverse Propensity Weights for the model including all four candidate time-dependent confounder categories comparing current use to new use of Ipratropium Bromide. The box for each group shows the location of the mean (*), median (middle horizontal bar) and quartiles (border horizontal bars). Vertical lines extend to the most extreme observations which are no more than 1.5x 3 IQR beyond the quartiles. Observations beyond the vertical lines are plotted individually, if they lie within the limits of the frame

Table 6-2 Comparison of Marginal Structural Model Results with time-dependent Cox for the risk of arrhythmia associated with Current and New Use of Ipratropium Bromide in COPD

	Marginal Structural Model			Comparison Time-dependent Cox Model			% Δ estimate of effect‡
Model Time-Dependent Confounders	HR	95% confidence intervals†,		HR	95% confidence intervals†		
		Lower	Upper		Lower	Upper	
Current Exposure to Ipratropium Bromide							
- none -	--	--	--	1.330	1.190	1.487	--
Current Moderate Exacerbations	1.318	1.178	1.474	1.320	1.180	1.477	0.7%
Current Non-event (minor) Arrhythmia	1.329	1.187	1.488	1.323	1.183	1.479	-1.6%
Other Bronchodilator use	1.263	1.064	1.498	1.208	1.061	1.374	-23.6%
Ever Non-event (minor) Arrhythmia	1.272	1.137	1.423	1.254	1.122	1.402	-6.2%
All 4 selected time-dependent variables	1.198	1.006	1.427	1.141	1.002	1.300	-36.6%
New Exposure to Ipratropium Bromide							
- none -	--	--	--	1.521	1.151	2.009	--
Current Moderate Exacerbations	1.485	1.119	1.971	1.503	1.138	1.985	2.9%
Current Non-event (minor) Arrhythmia	1.499	1.128	1.992	1.479	1.119	1.955	-3.4%
Other Bronchodilator use	1.441	1.005	2.065	1.406	1.361	1.453	-7.0%
Ever Non-event (minor) Arrhythmia	1.495	1.131	1.977	1.486	1.125	1.964	-1.5%
All 4 selected time-dependent variables	1.417	0.975	2.058	1.347	1.018	1.782	-16.9%

†Empirical standard error estimates produced using the sandwich estimator account for the within-subject covariances induced by weighting and the clustering within subject.
‡The difference in the beta parameter estimate on the natural log scale

6.3 Discussion

In this study, results derived from time-dependent Cox and marginal structural models were contrasted in order to determine whether or not moderate exacerbations, minor arrhythmia, and use of other bronchodilators were time-dependent confounders in the relationship between ipratropium bromide use and serious arrhythmia in COPD. Our findings suggest that there is an important role for the use of these novel inverse probability weighting techniques when investigating these associations.

As a practical application of marginal structural models (MSMs), and more importantly, one which explicitly contrasts the results from both MSMs as well as those from classical modeling techniques, our hope is that we have contributed to understanding the conditions where these newer causal models are of benefit. It is also our hope that in future, researchers will consider investigating the time-dependent confounder status of other important variables both within the realm of respiratory epidemiology and beyond.

In the context of determining the causal effect of ipratropium bromide use on the risk of serious arrhythmia in patients with COPD, despite using causal techniques, we remain uncertain as to the extent to which our analysis might still be biased due to unmeasured confounding. To the extent, for example, that COPD severity might have been insufficiently controlled for in the analysis, violations of the 'no unmeasured confounding' assumption may have occurred.

Assuming that it would be possible to measure all possible confounders of interest, future research for determining the causal effect of bronchodilator use on the risk of arrhythmia or other cardiovascular outcomes in COPD should not considered to be limited to using MSMs alone. MSMs were developed as an alternative to structural nested models (SNMs),[366] the parameters of which are estimated through the method of g-estimation in which the effect of a final "blip" of exposure at a point in time is modeled among subjects with a given covariate

history who received that exposure. The essential difference between MSMs and SNMs is that SNMs model the magnitude of the effect of a treatment given at time *t* as a function of the prognostic factor history up until that point. In contrast, MSMs model the causal effect of treatment given at time *t* only as a function of baseline prognostic factors.[367]

In clinical practice, COPD management is conducted by individualizing pharmacotherapy which involves routinely adjusting treatment based on increasing severity of symptoms and disability.[341] As such, COPD management can be viewed as being a dynamic treatment regime in which both treatments and covariate history are used as input, in order to output an action to be taken, providing a list of decision rules for how treatment should be allocated over time.[368] In this context, future research should pursue the use of SNMs to determine optimal COPD treatment regimes in which not only on the best treatment choices from the beginning but also on treatment choices that maximize outcomes from a later time, even if a suboptimal regime had been followed up to that point.[368]

7 Chapter 7 Discussion and Conclusions

This research was precipitated by results from the Lung Health Study, a large randomized trial, which suggested an increased risk of cardiac arrhythmia associated with the use of ipratropium bromide in patients with COPD. Their finding was unexpected given the fact that ipratropium, an anticholinergic bronchodilator, is generally more poorly absorbed into the systemic circulation and therefore not expected to induce cardio toxicity.

We therefore set out to examine relationship from within two pharmacoepidemiology databases using observational methods. In doing so, we addressed a number of methodological challenges posed by the study of adverse drug effects in chronic diseases including confounding by time, immortal time bias and immeasurable time bias. We also addressed the specific methodological challenge associated with the study of cardiovascular risks in COPD, namely the appropriate handling of acute exacerbations.

We found an increased risk of cardiac arrhythmia for individuals newly initiated with ipratropium bromide within both COPD cohorts. We also detected increased risks associated with treatment initiation with short-acting (Québec only) and long-acting β-agonists. From a clinical perspective, there results suggest that patients should be warned and /or monitored for the onset of arrhythmia when instituting any new bronchodilator therapy.

We excluded subjects who had recently had an exacerbation, and therefore these results are specific to the population with stable COPD. We can not, however, entirely rule out the presence of residual confounding by severity of illness. Some of the increase in risk may therefore be explained by progressively worsening (yet stable) COPD.

That we did not detect an effect associated with new use of methyl xanthines might seem initially counterintuitive. While historically, xanthines were the bronchodilator class more commonly associated with cardiovascular adverse effects, by the year 1990, they were being prescribed in doses low enough to avoid cardiac toxicity.[369]

Each cohort had their own distinct advantages and disadvantages. While the Québec cohort was substantially larger which facilitated investigation of the risks associated with atrial fibrillation, the Saskatchewan cohort contained information pertaining to home oxygen use, a proxy for end-stage COPD. This gave the smaller cohort somewhat of an advantage in terms of better adjustment for severity of illness. In addition, while the restricted use of long-acting β-agonists in Saskatchewan made it difficult to analyse them as an exposure category, we expect that conditioning on long-acting β-agonist use further improved adjustment for adjustment for severity of illness within this cohort.

The adjusted independent rate ratios associated with treatment initiation with ipratropium although consistently elevated within both cohorts, were different in magnitude (1.4 vs. 3.0). The rate ratios for the effect of ipratropium treatment initiation without concurrent short-acting β-agonists initiation, however, were more similar (1.9 vs. 2.4). Given that there exists a plausible clinical mechanism for the reported negative interaction between these two bronchodilator classes, we recommend that this effect be investigated in both additional populations as well as for other possible cardiovascular outcomes.

The application of marginal structural models (MSMs) in pharmacoepidemiologic research has been surprisingly limited outside the realm of HIV to date. There has been a call for more studies to compare MSMs to standard techniques.[370] In response, the final methodological issue dealt with in this thesis had to do with the handling of variables such as exacerbations which predict both arrhythmia and bronchodilator use, and are themselves predicted by prior bronchodilator use. It is

known that longitudinal cohort analyses in the presence of time-dependent confounders will yield invalid estimates when analysed using standard techniques. There is therefore a need for researchers to be able to identify time-dependent confounder status among their study covariates. By comparing results from both MSM and time-dependent Cox models, we showed that exacerbations were moderate time-dependent confounders of the arrhythmia-ipratropium association. As newer methods such as MSMs become better understood it is hoped that their use will become commonplace such that hypotheses about the time-dependent confounder status of other covariates in different settings can be tested.

Appendix 1: Ethics Approval

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