The impact of combined inhaled bronchodilator therapy in the treatment of COPD

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ABSTRACT

The introduction of a single inhaler comprising a β_2-agonist and ipratropium (Combivent®) in the treatment of Chronic Obstructive Pulmonary Disease (COPD) should enhance compliance, improve patient outcomes and result in lower medication costs.

Using the Saskatchewan Health databases, a cohort of subjects initiating treatment with Combivent® was identified and followed up to one year. A reference cohort was formed from all subjects who were dispensed, for the first time, two canisters, one of ipratropium and one of inhaled β_2-agonist, on the same day.

Combivent® users presented lower costs associated with inhaled bronchodilators (RR=0.83; 95% CI: 0.76 – 0.92), despite a slight increase in overall use of these medications (RR=1.16; 95% CI: 1.07 – 1.26). Moreover, the use of other respiratory drugs and antibiotics was unchanged (RR=1.03; 95% CI: 0.93 - 1.16).

The availability of a simpler dosing regimen did not alter significantly the treatment of COPD and resulted in appreciable cost savings.

RÉSUMÉ

L'introduction dans le traitement des maladies pulmonaires obstructives chroniques (MPOC) d'un aérosol-doseur composé d'ipratropium et de salbutamol (Combivent®) devrait favoriser l'observance, réduire les hospitalisations et les coûts reliés à l'utilisation des médicaments.

L'utilisation des bases de données de l'assurance-santé de la Saskatchewan a permis l'identification et le suivi d'une cohorte composée de patients initiant un traitement avec Combivent®. Une cohorte de référence a été formée avec tous les patients ayant rempli, au cours d'une même journée, deux prescriptions, une pour de l'ipratropium et l'autre pour un β_2-agoniste.

Malgré une légère augmentation de l'utilisation des bronchodilatateurs en inhalation (RR=1.16; 95% CI: 1.07 – 1.26), l'analyse ajustée démontre que l'utilisation de Combivent® est associée à une diminution des coûts de ces médicaments (RR=0.83; 95% CI: 0.76 – 0.92). L'utilisation des autres médicaments respiratoires et des antibiotiques est demeurée inchangée (RR=1.03; 95% CI: 0.93 - 1.16).

La disponibilité d'un régime posologique plus simple n'a pas modifié significativement le traitement des MPOC et représente une économie substantielle.

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TABLE OF CONTENTS

LIST OF TABLES, FIGURES AND APPENDICES

CHAPTER 2

CHAPTER 3

CHAPTER 4

APPENDICES

CHAPTER 1 – INTRODUCTION

1.1 Burden of COPD

1.1.1 Epidemiology of COPD

Current and past smokers are at risk of developing significant chronic impairment of lung function and the clinical syndrome that results is usually referred to as Chronic Obstructive Pulmonary Disease (COPD) (Chapman, 1992). In Canada, COPD and related disorders are the sixth leading cause of death in men and the eight leading cause of death in women, thereby accounting for 3.6 percent of all deaths (Manfreda, 1992). COPD claimed 87,000 lives in 1992 in the USA. In North America, COPD is the only leading cause of death that is increasing in prevalence (Higgins, 1989). According to statistics produced by the American Lung Association, 13.6 percent of males and 11.8 percent of females aged 65-74 years in the USA may have developed features of COPD (National Centre for Health Statistics, 1995; Benson, 1994).

Despite the high prevalence and the worsening situation, COPD has received scant attention in the medical community, particularly when compared with the other prevalent obstructive airway disease, asthma. Because of the strong association between cigarette smoking and COPD, there is perhaps a widespread perception that with the decline in cigarette smoking, COPD will disappear. This is certainly not the case in the foreseeable future because the increase in prevalence is occurring despite a decrease in the number of people smoking cigarettes. Even though smoking has declined amongst most groups in the population, silent pulmonary damage due to years of smoking made popular in postwar years may become apparent only many years later when the effects of aging are added (Chapman, 1992). COPD is also thought of as a self-inflicted disease with few effective treatments, mainly affecting the elderly, possibly a less vocal population. However, respiratory physicians around the world now believe that this defeatist attitude can no longer be justified (Taylor, 1998).

1.1.2 Costs and outcomes of COPD

For the nearly 16 million Americans estimated to suffer from COPD, previous studies have found the medical and economic costs to be substantial. Oster et al. (1984) reported the average medical costs per patient year to range from $587 to $6,238 (1990 US dollars) depending on the number of years after onset of symptoms. In a prospective study of the medical costs for treatment of COPD, Strauss et al. (1986) and Bergner et al. (1988) reported costs averaging $14,647 per year (1990 US dollars). However, the Bergner et al. study sample was limited to a severely impaired homebound group of patients. Pharmacotherapy is the principal form of treatment and entails high costs, accounting for more than 30 percent of the direct medical care expenditure on chronic respiratory disease. Adding in indirect costs, the annual cost to the American nation for COPD is approximately $18.1 billion (National Centre for Health Statistics, 1995; Benson, 1994).

COPD accounts for 12 percent (297,000 first-listed discharge diagnosis) of all hospitalisations with an average length of stay of 7 days, and 42 percent (13,760,000) of all physician office visits (National Centre for Health Statistics, 1995; Benson, 1994). Therefore, COPD poses an enormous burden to society both in terms of direct cost to heath care services and indirect costs through loss of productivity. Moreover, COPD represents, from the public health point of view, a frequent potentially fatal and disabling disease.

1.2 Combined inhaled bronchodilator therapy – Study hypothesis

COPD patients whose airflow is significantly limited despite smoking cessation are usually prescribed bronchodilators (Ferguson, 1993). Currently, there are three main classes of bronchodilators available for the treatment of COPD, each with specific clinical benefits: anticholinergics (ipratropium bromide), β_2-agonists (e.g. salbutamol) and methylxanthines (e.g. theophylline). The former two, ipratropium bromide and salbutamol, are administered by inhalation, the preferred route of administration due to rapid onset of action and minimal systemic side effects. As severity of the disease progresses, it is appropriate according to treatment guidelines to use ipratropium bromide therapy and to add inhaled β_2-agonists (Chapman, 1991). Even in the absence of a synergistic effect, this dual therapy may have benefits by virtue of the site of actions and differing time courses of the bronchodilator effect (Ohrui, 1992; Phillips, 1984).

Combivent® is a combination therapy comprising two existing medications, ipratropium bromide and salbutamol, in a single metered dose inhaler. By providing a treatment that is less complex and more convenient, we hypothesise that Combivent® may enhance patient compliance with prescribed therapy, increase symptomatic relief, and possibly improve patient outcome (Tashkin, 1995). Moreover, if the prescription habits and patterns of bronchodilator use remain unchanged, the introduction of combined bronchodilator therapy in the treatment of COPD can result in substantial cost savings to both the patient and the health care system since the total average cost per prescription of Combivent®, including distribution costs and professional fees, is estimated to be $29.41. This is 28.6 percent lower than the total average salbutamol/ipratropium bromide combination therapy ($41.27) (weighted for generic brands of salbutamol) (Brogan Consulting Inc., 1996).

1.3 Objectives

1.3.1 General Objective

The objective of this study was to evaluate the impact of the introduction of combined inhaled bronchodilator therapy in the treatment of COPD on:

- use of respiratory medications and antibiotics
- costs related to use of bronchodilators
- hospitalisations
- mortality

1.3.2 Specific Objectives

Specifically, the aims of this study are:

1. Primarily to compare the incidence rates of drug use and costs related to use of bronchodilators according to the treatment initiation with combined inhaled bronchodilator or with the two-canister bronchodilator therapy.
2. Secondarily to compare the incidence rate of hospitalisations and death according to the contrasted groups.
3. To identify patterns of bronchodilator use.

These proposed objectives will be performed for the overall population and for the various exposure categories identified and defined subsequently.

CHAPTER 2 – REVIEW OF THE LITERATURE

This chapter provides a review of the literature on the pharmacotherapy of COPD. The condition is first defined, its risk factors described, followed by a summary of the diagnostic features and the pharmacological treatment of COPD with special emphasis on bronchodilator therapy and compliance.

2.1 Definition of COPD

COPD is a nonspecific term that refers to a spectrum of chronic respiratory diseases that may occur individually or in combination. According to various guidelines, COPD is defined as a chronic, slowly progressive disorder characterised by airflow obstruction (reduced maximal volume of air forcefully expelled in one second (FEV_1) and FEV_1/forced vital capacity (FVC) ratio). Most of the lung function impairment is fixed, although some reversibility can be obtained by bronchodilator therapy (Canadian Thoracic Society Workshop Group, 1992; Celli, 1995; COPD Guidelines Group of the Standards of Care Committee of the BTS, 1997; European Respiratory Society Task Force, 1995; National Lung Health Education Program Executive Committee, 1998).

The main components included within the COPD designation are chronic bronchitis (excess mucus secretion) with obstruction of small airways and emphysema (loss of lung elasticity of the airways due to alveolar disruption). There may also be a reversible component of airway limitation but if significant, this signals asthma which is not included as part of COPD. Chronic bronchitis is defined clinically by the presence of excessive cough and chronic productive bronchial secretions, on most days for a minimum of three months a year during at least two consecutive years. Emphysema has an histological definition, which is a condition where there is permanent destructive enlargement of the airspaces distal to the terminal bronchioles without obvious fibrosis, resulting in a reduction

in the surface area for gas exchange. However, the attempts of identifying specific forms of COPD, such as chronic bronchitis and emphysema is probably of minimal value, because these disease entities are poorly distinguishable clinically and their identification may offer little pathophysiologically or clinically useful information. Indeed, most patients with COPD have features of both conditions, although one maybe more prominent than the other. Rather than attempting to categorise patients with COPD, it may be more sensible to view them as suffering from some combination of pathophysiologic processes associated with COPD (Canadian Thoracic Society Workshop Group, 1992).

2.2 Risk factors for COPD

Cigarette smoking is undoubtedly the major risk factor for the development of COPD through several related mechanisms. Overall, tobacco smoke accounts for an estimated 80 to 90 percent of the risk of developing COPD (U.S. Surgeon General, 1984). Certain risk factors besides smoking have been identified. Genetic deficiency of α_1-protease inhibitor contributes importantly to the development of emphysema in a small percentage of very young patients (Laurell, 1963). Family clustering of COPD also exists in the absence of the α_1-antitrypsin deficiency state. Other contributing factors in COPD include air pollution, childhood respiratory tract infections, and nonspecific bronchial hyperreactivity (Silverman, 1996). The risk factors are summarised in Table 2.1.

Table 2.1. Risk factors for the development of COPD (Silverman, 1996; Dantzker, 1993)

Major	**Minor**
Smoking	Air pollution
Age over 45 years	High alcohol intake
Male	Race (higher incidence in white)
Existing lung impairment	Poor nutritional status
Dusty work environment	Family history
α_1-antitrypsin deficiency	Low socioeconomic status
	Frequent respiratory tract infections
	Bronchial reactivity

2.3 Diagnosis

Significant overlap exists in signs and symptoms of the three major diseases of airflow obstruction: asthma, chronic bronchitis and emphysema. This relationship have been summarised by Snider and colleagues (1994) as a nonproportional Venn diagram (Figure 2.1). Nevertheless, signs and symptoms of COPD have been well characterised and can be identified from an appropriate patient history (e.g., symptoms, smoking and family history), physical examination and laboratory tests (e.g., pulmonary function tests, especially spirometry, arterial blood gases) (Celli, 1995). However, due to a large reserve of pulmonary function, symptoms often appear at advanced ages in patients with COPD and the deterioration in airflow obstruction can proceed undetected for many years if pulmonary function are not done. In fact, except in those individuals who engage in vigorous exercise, quite severe airflow obstruction is often present before any symptoms of COPD develop. A firm diagnosis can best be made by objective measurement of airway obstruction with spirometric tests (COPD Guidelines Group of the Standards of Care Committee of the BTS, 1997). The simple measurement of FEV_1 is as sensitive and specific as more complex measurements, even in the early stages of COPD. Since mild disease may be present in completely asymptomatic patients, spirometry is recommended annually for smokers, for those with significant occupational exposure to

respiratory irritants, for patients with recurrent or chronic respiratory symptoms and for those with a family history of pulmonary diseases (Canadian Thoracic Society Workshop Group, 1992). The normal decline in FEV_1 in healthy subjects is approximately 25 mL/year. In patients with COPD, the decline in FEV_1 may be as high as 75-80 mL/year and even more drastic among smokers (Kesten, 1989).

Despite the simplicity of the test, spirometry appears to be underused, because many cases of COPD remain undiagnosed until the disease is advanced. In a recent study, primary-care physicians were confronted with a hypothetical case of a smoker with recurrent respiratory symptoms and physical findings suggestive of airflow limitation; only 5 percent of the physicians surveyed would have requested a spirometric measurement (Kesten, 1993).

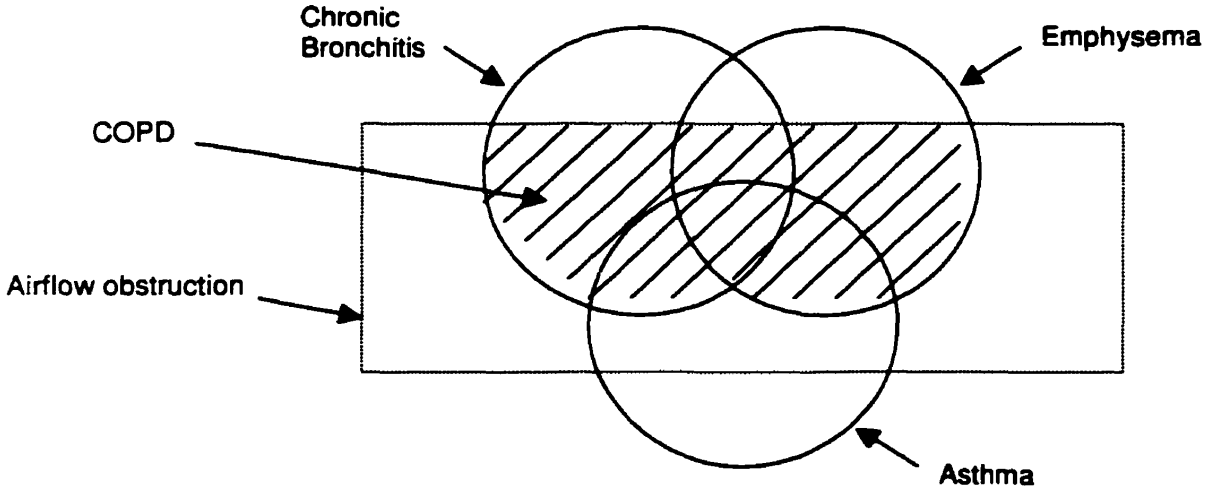

Figure 2.1. Venn diagram of overlap between asthma, chronic bronchitis and emphysema

2.4 Pharmacotherapy

Once the diagnosis has been established and because it is impossible to reverse the damage done to the lungs, the aims of treatment are to alleviate symptoms, minimise any further progression of the condition, preserve optimum lung function, improve performance of activities of daily living and enhance

quality of life. More specifically, the outpatient pharmacotherapy of COPD should be organised according to the severity of disease and the patient's tolerance for specific drugs with the aim of inducing bronchodilation, decreasing the inflammatory reaction and facilitating expectoration (Ferguson, 1993). In general, a stepwise approach should be considered (Figure 2.2) (Chapman, 1991). The initial approach relies heavily on bronchodilator therapy, and symptomatic benefit may be obtained in the absence of significant spirometric changes.

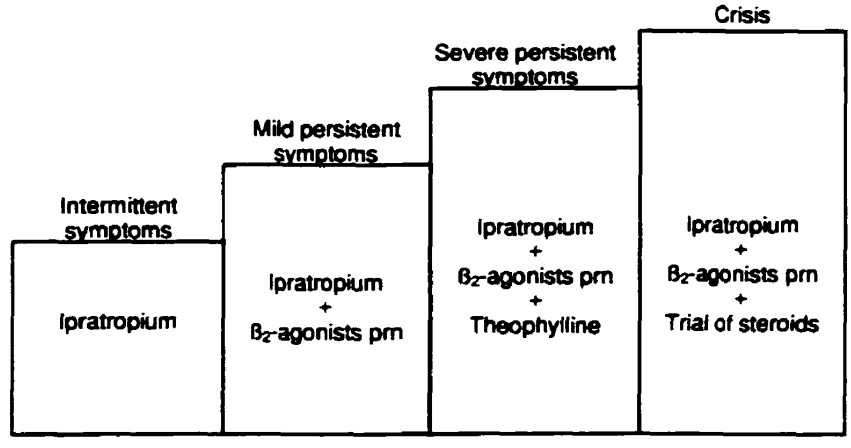

Figure 2.2. Stepwise pharmacologic management of COPD (adapted from Ferguson, 1993)

2.4.1 Smoking cessation

Although smoking cessation is part of nonpharmacological therapy, the various guidelines place great emphasis on cessation of smoking as the single most important therapeutic intervention. Stopping smoking will slow the rate of lung function decline. The rate of FEV_1 decline in exsmokers is lower than that of current smokers and may approach that of nonsmokers (Fletcher, 1977). Unfortunately, only about 20 to 30 percent of patients, even after extensive counselling, are able to abstain from smoking after one year (Prochaska, 1993).

2.4.2 Bronchodilator therapy

COPD patients whose airflow is significantly limited despite smoking cessation are usually prescribed bronchodilators. Bronchodilators, the cornerstone of symptomatic treatment for the reversible component of airways obstruction, relax smooth muscles in the airways. Even if they can improve the FEV1, FVC, or exercise tolerance independently of each other, acute bronchodilator challenges do not usually produce in COPD the marked responses that they do in asthma (Anthonisen, 1987). This does not mean that airflow obstruction is "irreversible", notes the Canadian Thoracic Society Workshop Group (1992). A small improvement in airflow in COPD patients with severe obstruction may be of significant clinical benefit, particularly if it reduces the effort of breathing by decreasing gas trapping and hyperinflation.

Currently, there are three main classes of bronchodilators available for the treatment of COPD, each with specific clinical benefits : anticholinergics (ipratropium bromide), β_2-agonists (e.g., salbutamol) and methylxanthines (theophylline). The former two, ipratropium bromide and salbutamol, are administered by inhalation, the preferred route of administration due to rapid onset of action and reduced systemic side effects (European Respiratory Society Task Force, 1995).

Anticholinergics

Whereas in asthma adrenergic agents are preferred, anticholinergic agents are an integral part of COPD therapy and are considered to be the first-line agents by many (Ferguson, 1993). In most patients with COPD, inhaled anticholinergic agents, such as ipratropium bromide, appear to offer bronchodilation at least equal to and often greater than that seen with β_2-agonists, and with fewer side effects (Gross, 1984; Gross, 1987). COPD patients, as an older group, may exhibit less tolerance for sympathomimetic-induced tremor, nervousness, and cardiac side effects. Moreover, ipratropium bromide is a quaternary ammonium anticholinergic agent and, as such, has little systemic absorption. It has excellent safety and side effect profiles. The greater

bronchodilator responsiveness to anticholinergics is thought also to be a consequence of aging, since there is a relative decline in the sensitivity and number of adrenergic receptors with advancing age. As a result, the cholinergic system predominates over the adrenergic system and is more readily manipulated for the purpose of bronchodilation. The efficacy of anticholinergic agents does not appear to change over years of regular uninterrupted use (Gross, 1993). A minor degree (3 to 5 percent) of tolerance, or tachyphylaxis, to the bronchodilator effects of inhaled adrenergic drugs has been documented (Rebuck, 1983). It is not clear whether this modest change is of clinical importance.

Beta$_2$-agonists

Inhaled β_2-agonists have been the mainstay of COPD management for years, although their role as a first-line agent has been challenged by ipratropium bromide in recent years. Short acting inhaled β_2-agonists have a relatively rapid onset of action and are prescribed on an "as needed" (PRN) basis or as maintenance therapy, depending on the severity of symptoms. Used before exercise, they can increase tolerance in some patients with COPD. There is no evidence that prolonged regular therapy with inhaled β_2-agonists leads to worsening of COPD, as has been reported with asthma. There is disagreement, however, as to the occurrence of tachyphylaxis to inhaled β_2-agonists in patients with COPD (Ziment, 1995). Side effects from systemic absorption include tacchycardia, tremors, mild hypokalemia and pulmonary vasodilatation. Pulmonary vasodilatation can negatively affect oxygen exchange in some COPD patients (Gross, 1987).

There is a controversy over the use of home nebuliser treatment in patients with COPD (Van der Palen, 1995; Newhouse, 1987). Most patients can be treated with bronchodilator delivered by metered dose inhalers and spacers or by dry powder devices. A few with severe disease may benefit from high dose bronchodilator treatment which is more conveniently given by a nebuliser (Gross, 1989). The results of clinical trials comparing metered dose inhalers and

nebulisers in stable patients with COPD are inconsistent (Morrison, 1992; Jenkins, 1987). Treatment is expensive and may have major side effects.

Oral β_2-agonists are not recommended as initial therapy because of their high incidence of side effects, but can be tried in patients unable to use inhaled therapies (Skorodin, 1993).

Combined bronchodilator therapy (Appendix 1)

As severity of COPD progresses, it is appropriate to use ipratropium bromide therapy and to add salbutamol as often as needed, up to four times a day. A number of studies have been conducted comparing various strategies for combining anticholinergics and inhaled β_2-agonists in COPD. When looking specifically at ipratropium bromide and salbutamol (the agents which make up Combivent®) delivered by inhalation aerosol, seven studies have compared their concurrent use in patients with COPD with the use of each of the individual drugs alone. In five of these trials, superior bronchodilation, measured by FEV_1, was obtained with the drug combination (Casali, 1979; Lees, 1980; Leitch, 1978; Petrie, 1973; Lightbody, 1978). In the remaining two studies, no additive effects of the second drug were demonstrable despite the use of higher than recommended doses (Easton, 1985; Lloberes, 1988). All of these trials had serious limitations in design. Generally, sample sizes were too small to attain statistical significance. These studies were inadequately blinded, of short duration, and in many of them the combination was administered as the third test drug after treatment with each of the components. A retrospective study showed that in 33 percent of the patients who responded inadequately to β_2-agonists alone, bronchodilation was increased when inhalation of the β_2-agonist was followed by inhalation of ipratropium bromide (Frith, 1986).

A fixed combination of a low dose of another β_2-agonist, fenoterol, and ipratropium bromide in the same metered dose inhaler has been used world-wide, except in North America, for periods ranging up to 10 years. In several controlled trials, patients with COPD responded to this combination with a greater improvement in lung function than when they were treated with either fenoterol or

ipratropium bromide alone (Marlin, 1986; Serra, 1986; Barros, 1990; Wesseling, 1992; Morton, 1984). However, methodological problems also limit the conclusions that can be drawn. For these reasons, an extensive, multicenter clinical trial of long-term administration of combined albuterol and ipratropium bromide delivered in one inhalation was undertaken. Results suggest significant benefit is obtained with the combination without any increase in the incidence of adverse reactions (Combivent Inhalation Aerosol Study Group, 1994). The combined administration of albuterol and ipratropium bromide achieved an average increase in FEV_1 that was 16 to 30 percent greater than the increase with albuterol or ipratropium bromide alone. The Combivent® group maintained a statistically significant increase in FEV1 over ipratropium bromide or albuterol from day 1 through day 85. This additional bronchodilation provided by the combination drug over the single entity agents is especially meaningful in this population since a small improvement in airflow in COPD patients with severe obstruction may be of significant clinical benefit. Therefore, although β_2-agonists, have been shown to be less effective than anticholinergics for bronchodilation in COPD patients, they can provide additional bronchodilation when added to ipratropium bromide therapy.

The superior effectiveness of this drug combination is hardly surprising since the combined use of the anticholinergic and the β_2-agonist bronchodilator brings to bear two different mechanisms of action (Combivent Inhalation Aerosol Study Group, 1994; Levin, 1993). There is also some evidence that, even in the absence of a synergistic mechanistic effect, this combination therapy may have benefits by virtue of the site of actions, meaning that β_2-agonists may be relatively more effective in the distal airways while anticholinergics may be of more benefit in the proximal airways (Ohrui, 1992). As well, these drug components have differing, and possibly beneficial, time courses for their bronchodilator effect not apparent with either drug alone (Phillips, 1984).

Methylxanthines

Theophylline's potential for toxicity and evidence that theophylline offers little additional bronchodilation beyond that of inhaled agents led to a decline in its popularity (Lam, 1990). Recently, interest in theophylline therapy has been rekindled by reports of beneficial nonbronchodilator effects (prevention of respiratory fatigue, respiratory stimulation, stimulation of mucociliary transport) (Murciano, 1984; Murciano, 1989; Wanner, 1985; Berry, 1991). However, it is regarded by many clinicians to be a third line agent, to be considered for use only if standard bronchodilators do not provide optimal results or have failed to control symptoms adequately (COPD Guidelines Group of the Standards of Care Committee of the BTS, 1997). It can also be of particular value for less compliant or less capable patients who cannot use inhaled therapy optimally, but are willing to take an oral long-acting theophylline once or twice a day (McKay, 1993). However, some of theophylline's advantages now can be obtained with a long-acting inhaled β_2-agonists. Presently, the impact of these newer agents on the therapy of COPD is unclear, but theophylline may be further displaced as a commonly used agent in the treatment of COPD (Ramsdell, 1995).

Consideration should be given to avoid theophylline therapy taken orally among patients known to have cardiovascular disease, or at high risk of such disease. There is some evidences that such therapy are associated with an increased risk of cardiac death in patients with underlying cardiovascular disease (Suissa, 1996).

Bronchodilator selection

Beta$_2$-agonists used "as required" can be tried first in view of their more rapid relief of symptoms. If β_2-agonists do not control symptoms adequately or if regular maintenance therapy is desired, an anticholinergic agent can be added or substituted (COPD Guidelines Group of the Standards of Care Committee of the BTS, 1997).

Combination bronchodilator therapy has the potential advantage of convenience and improved patient compliance. However, combinations of a

β_2-agonists and ipratropium bromide should only be used if the single drugs have been tried and have failed to give adequate symptom relief. Combinations should only be continued if there is good subjective or objective evidence of benefit. Symptom severity and subjective benefit as reported by the patient are better guides to improvement of quality of life than are short term changes in spirometric values after bronchodilators (COPD Guidelines Group of the Standards of Care Committee of the BTS, 1997; National Lung Health Education Program Executive Committee, 1998).

The addition of oral theophylline should only be considered if inhaled treatments have failed to provide adequate relief (COPD Guidelines Group of the Standards of Care Committee of the BTS, 1997).

2.4.3 Corticosteroid therapy

While anti-inflammatory therapy is emphasised in asthma management, its role is less important in COPD (Ferguson, 1993). A review of published studies and a recent meta-analysis reveal that even though COPD patients have airway inflammation, only 10 to 20 percent of them benefit from either systemic or inhaled corticosteroid therapy (Blair, 1984; Bourbeau, 1998; Eliasson, 1986; Kerstjens, 1992; Lam,1983; Mendella, 1982; Shim, 1985; Syed, 1991; Weir, 1990). Despite the small number of patients who will benefit from corticosteroid therapy, many COPD sufferers are prescribed these medications, complicating their therapy without offering additional benefit and exposing them to adverse effects and unnecessary expenses (Callaghan, 1991).

Oral corticosteroid therapy may be considered for COPD patients with severe obstruction who remain symptomatic despite maximal bronchodilator therapy and smoking cessation (Callaghan, 1991). However, oral corticosteroids must not be prescribed for the long term unless a response to such therapy has been demonstrated in a carefully monitored therapeutic trial (Ferguson, 1993).

2.4.4 Other agents

Even if patients with COPD have frequent respiratory infections and a high rate of antibiotics consumption, there is no evidence to support the use of prophylactic antibiotics given either continuously or intermittently (Grossman, 1998; Wilson, 1998).

There is no role for other anti-inflammatory drugs such as ketotifen, sodium cromoglycate or nedocromil sodium. Other drugs not found to be effective or requiring further investigations before recommending them in the treatment of COPD include: calcium antagonists, respiratory stimulants, mucolytics, antioxydants and antiprotease replacement (COPD Guidelines Group of the Standards of Care Committee of the BTS, 1997).

2.4.5 Oxygen therapy

Long term oxygen therapy has been proven to reduce mortality among patients with advanced COPD who have persistent hypoxemia (Ferguson, 1993). In patients with hypoxemia resulting in cor pulmonale (hypertrophy or failure of the right ventricule of the heart), supplemental oxygen can increase longevity by six or seven years (Cooper, 1987). Exactly how oxygen reduces mortality is unclear, as most acute physiological changes are small (Anthonisen, 1983). Evidence suggests that both quality of life and neurophysiologic function improve with oxygen administration. Blood gas measurements should be used to guide oxygen prescriptions.

2.5 Compliance

Compliance with prescribed therapy, sometimes referred to as adherence, is defined simply as the extent to which a person's behavior (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice. Compliance can be total, partial, nil or erratic. Patients can also be overcompliers or undercompliers (Haynes, 1979). A number of

factors have been shown to influence compliance with prescribed therapy, as reviewed by Mellins et al. (1992). Factors not believed to be important include age (except if associated with impaired memory), gender, educational level or socioeconomic status, personality traits, and various disease characteristics, such as diagnosis (except for mental illness and alcoholism), severity or frequency of symptoms, medication side effects, and the physician's prediction of compliance. However, a number of factors appear to be associated with improved compliance including a relatively simple treatment regimen (i.e., one in which the frequency of dosing, number of prescribed drugs, duration of treatment, and requirement for behavior change have been minimised). Therefore, whenever possible regimens should be simplified.

Compliance to pharmacological therapy has been reported to be low among patients with COPD and related to poor prognosis (Windsor, 1980). This is a distressing finding considering that pharmacotherapy, administered regularly and for long period of time, is considered an essential component of the management of COPD in both comprehensive rehabilitation programs and ambulatory settings.

Currently, little is known about the extent and management of adherence problems among patients with chronic bronchitis and emphysema. An exhaustive review of the literature identified only a few studies which have specifically assessed compliance with inhaled medication in patients with symptomatic COPD. Chryssidis et al. (1981) reported overcompliance with inhaled medication therapy as measured by canister weight in a sample of 114 patients with COPD. James et al. (1985) also examined patterns of medication by using a questionnaire in 185 patients with either asthma or COPD. The results indicate that both groups displayed poor adherence and that patients with COPD displayed significantly lower adherence levels than asthmatic subjects. The group with COPD was observed to adhere to their maintenance regimen 47 percent of the time and to their full regimen only 19 percent of the time. It is

interesting to note that James et al. also observed overutilisation of inhaled medications among many of their patients.

A more recent report confirmed the poor adherence to pharmacological regimens observed previously (Dolce, 1991). More than half of patients reported missing or skipping doses of their maintenance drugs. In addition, approximately half of the patients reported using more than the prescribed amount of medications during times of distress. When observing the administration of inhaled medications, 31 percent of the sample displayed a technique which delivered an inadequate dose of medication. This study also highlighted the complexity of medication regimens which are frequently prescribed for patients with COPD. It was quite common for patients in this sample to be prescribed a combination of five to eight oral and inhaled time-contingent and as needed medications, with many medications requiring different dosing patterns.

One limitation should be considered in interpreting findings of these investigations. Estimates of compliance relied on self-reports from patients and canister weighting. Most studies on the reliability of self-reports and canister weighting indicate that patients bias information in a positive direction, suggesting that it is more likely that adherence may have been overestimated (Hensen, 1976).

Compliance has also been evaluated during clinical trials. Rand et al (1992) used an electronic monitoring device to assess compliance with inhaled ipratropium or placebo in subjects with mostly mild COPD participating in a clinical trial of early intervention. Their findings indicated that only 15 percent of the participants actually used their inhaler the prescribed number of times a day and that actual compliance with prescribed dosing frequency and the prescribed number of puffs per dosing interval was considerably overestimated by both self-report and canister weighing. In a subsequent report from the same group, the electronic monitoring device was found not only to provide a more accurate assessment of compliance but also to enhance compliance when the participants were given feedback of their monitoring results.

In an another study, the long-term trends in compliance with prescribed pharmacotherapy varied considerably over the 24-month observation period. Compliance decreased during the 4-month intervals between follow-up visits, but increased immediately after each of the visits. This patterns was most pronounced early in the study, with participant who received feedback about their actual MDI usage maintaining a higher level of compliance throughout the trial (Simmons, 1996).

While these studies underline the gradual decline in compliance and are important to evaluate the efficacy of the treatment, they do not reflect the context of actual medical practice. The subject's awareness that medication use is being monitored may in itself be sufficient to improve compliance.

CHAPTER 3 – METHODS

This chapter outlines the study population, the design and methods used to evaluate the impact of combined inhaler bronchodilator therapy in the treatment of COPD on the patterns of use of respiratory medications and to compare the incidence costs related to use of bronchodilators according to the contrasted groups.

3.1 Overview of the design

For the purpose of assessing the objectives, an historical cohort design was used. This non-experimental design was selected to address this question in a sufficiently rapid fashion and to conduct a study in the context of actual medical practice determining the real impact of combined inhaler bronchodilator therapy. The computerised prescription and hospitalisation databases of the Saskatchewan Prescription Drug Plan were used to assemble the cohort. More precisely, prescription codes for various inhaled bronchodilators were used to identify COPD patients under pharmacological treatment in Saskatchewan between the years 1994-1997. All subjects who received a prescription for Combivent® during the study period were entered into the exposed group. A reference group was formed from all the patients who, during the same period, were dispensed two canisters, one of ipratropium bromide and one of an inhaled β_2–agonist. Since no diagnostic code, nor medical history or symptom information was used to identify patients, disease severity was assessed from information on therapy and outcomes during the period immediately prior to the patient's entry into the cohort. Relevant factors taken into consideration were: age, hospitalisation and medication use (including concurrent prescription of other relevant drugs). During the follow-up of up to one year for all the cohort members, incident claims for drugs related to the treatment of COPD and

hospitalisations were obtained through the prescription and hospitalisation databases. The data analysis first generated crude overall rates for the two groups, then multivariate approaches were used, to adjust for the effect of relevant baseline patient characteristics (Figure 3.1).

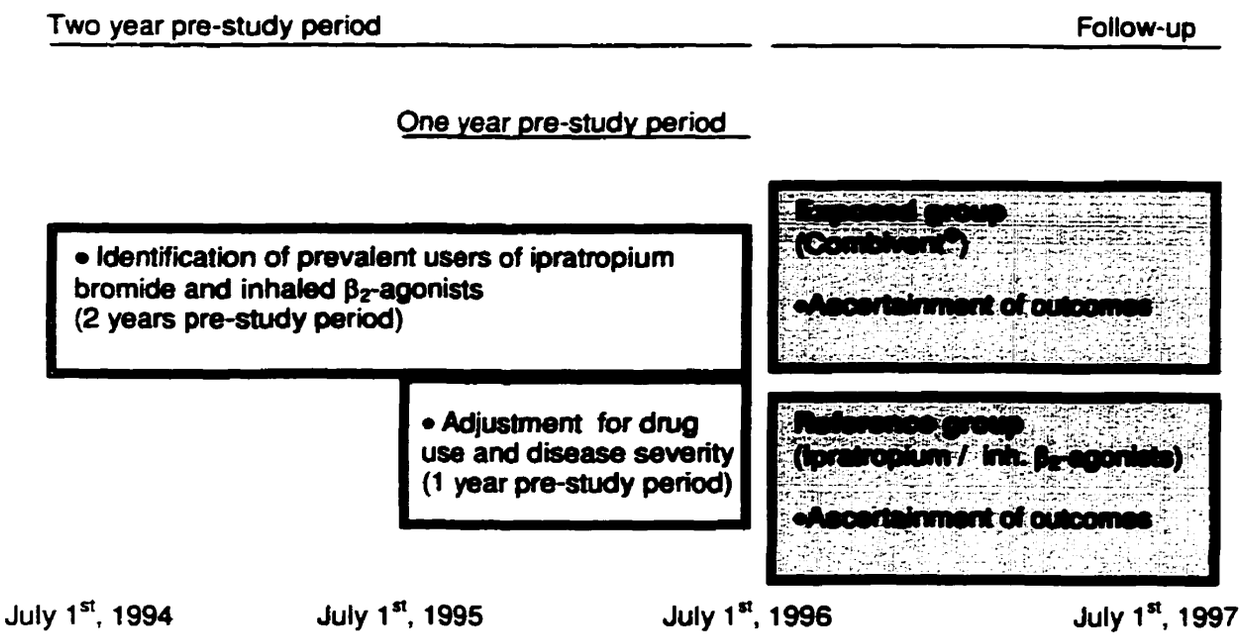

Figure 3.1. Overview of the study design

3.2 Source population

The three main computerised databases of Saskatchewan Health constituted the primary source of data for this study. The computerised administrative health care data files of Saskatchewan have developed as a result of the various health service programs provided to residents of the province since 1975. In almost all of its programs, residents of the province enjoy universal coverage. There is no eligibility distinction based on socioeconomic status. All Saskatchewan residents (over 1 million) with a valid Health Services Card are eligible for coverage with the exception of registered Indians, members of the

Armed Forces, RCMP and veterans, who represent less than 5% of the population. The information on this population has been successfully used in pharmacoepidemiological, market research and post-marketing surveillance studies (Strand, 1989; West, 1987).

Patient identification

The Health Insurance Registration data file contains the identification and demographic details, i.e., gender, age, socioeconomic status and coverage termination (date of migration or death) of all residents eligible for health services in Saskatchewan (approximately 95% of the population). The existence of the Health Services Number, which is a lifetime number that uniquely identifies each resident, has allowed record linkage between the various data files. Eligibility for Saskatchewan health services is updated on an ongoing basis.

The mortality component of this file was used to trace all deaths among members of the study population. This database also indicated whether the subject ever received social assistance during the study period, as a proxy for socioeconomic status.

Prescription Drug data

The Prescription Drug Services Branch data file collects data about out-patient prescriptions on a claim-by-claim basis. All Saskatchewan residents who have a valid Health Services Card are eligible for benefits under the Prescription Drug Plan (after paying for a family deductible). Drugs covered by the plan are listed in the Saskatchewan Formulary. The number of prescriptions for drugs not listed in the formulary is unknown, but believed to be relatively low since the formulary is comprehensive and under continuous review. Information in the data file includes the identity (at the Active Ingredient Number Level and by DIN) of the drug dispensed, strength and dosage form, date and quantity dispensed and total cost data (including mark-up and professional fee).

Hospital Services data

The Hospital Services Branch data file contains data on all hospitalisations in Saskatchewan and includes information on date of discharge, length of stay, vital status at separation, diagnostic and treatment information (e.g., discharge diagnoses and primary surgical procedures). Discharge diagnostic data are coded for both primary and secondary diagnoses using the International Classification of Diseases, Ninth revision (ICD-9) at the four-digit level. Information comes from 6 base hospitals, 1 rehabilitation hospital, 7 regional hospitals and approximately 100 community hospitals.

Oxygen data

For the first time, information on oxygen therapy compiled by Saskatchewan Health was used to help answer the study objectives. The main information encompassed by the database is the oxygen coverage dates. To obtain coverage, patients must have a prescription from a physician and must provide the test results documenting that one or more of the following criteria are met:

- require oxygen continuously at rest ($O_2 \leq 87\%$ or $P_{O2} \leq 55$ as measured with an oximeter)
- require oxygen for exercise (oxygen dips while walking as identified with an exercise test)
- require oxygen at night (measured with an oximeter)

Because the program is universal with no deductible and no criteria with regard to income, patients who meet the medical criteria and whose physician applies for coverage are granted oxygen benefits; therefore, information on use outside hospital should be relatively complete.

3.3 Cohort definition

The study of the impact of combined inhaled bronchodilator therapy was carried out using a historical cohort design of new users of two different bronchodilators (ipratropium bromide and inhaled β_2-agonist) either combined or in two separate canisters. Using the prescription database of the Saskatchewan Prescription Drug Plan, all subjects from the source population aged at least 45 years initiating treatment with Combivent® between July 1st, 1996 and June 30th, 1997 were eligible for cohort entry and represented the exposed group. A reference group was formed of all subjects who, during the same time period, were dispensed, for the first time, two canisters, one of ipratropium bromide and one of inhaled β_2-agonists, on the same day. A subject's date of cohort entry was taken to be the date of receipt of the first prescription for these two medications either combined or in two separate canisters. Entry into the cohort was only possible as of July 1st, 1996 since Combivent® was introduced to the Saskatchewan formulary on this date. Subjects were followed up to June 30th, 1997, death, emigration from the province or end of coverage by the insurance plan, whichever came first.

To confirm the incident nature of the dual bronchodilator therapy (either with Combivent® or ipratropium bromide and inhaled β_2-agonist), past users were excluded from the cohort by ensuring that no enrolled subject had received a prescription for both ipratropium bromide and any of the inhaled β_2-agonists in the 24 months preceding cohort entry. Other criteria for exclusion from the study cohort were:

1) age less than 45 years old
2) past or current use of nedocromil sodium, sodium cromoglycate or ketotifen
3) pre-study period less than 2 years
4) duration of follow-up less than 90 days

The first two exclusion criteria increase the likelihood of restricting the cohort mainly to COPD patients. COPD generally affects middle-aged and older

individuals with a mean age for onset of dyspnea related to COPD of 45 years (Ingram, 1994). Thus patients less than 45 years old will be more likely to have asthma. Nedocromil sodium, sodium cromoglycate and ketotifen are drugs essentially indicated for the treatment of asthma (McCormack, 1995). The last two criteria relate to the duration of the pre-study period for both exclusion of the prevalent users and adjustment factors, and ensure stability of the estimates.

Two hundred and eight of the 1,621individuals in the Combivent® group who responded to the initial definition for cohort entry were found to be aged less than 45 years. Of the remaining 3,198 subjects (1,413 in the Combivent® group and 1,785 in the comparison group), 728 had a follow up of less than 90 days, 32 had an insufficient pre-study period, 91 were users of nedocromil sodium, sodium cromoglycate or ketotifen and 1,295 were prevalent users of ipratropium bromide and inhaled β_2-agonists. All these patients were therefore excluded, leaving a total of 1,052 users of double bronchodilator therapy in the primary study cohort, 641 were Combivent® users while 411 subjects were dispensed the two-canister combination (Figure 3.2).

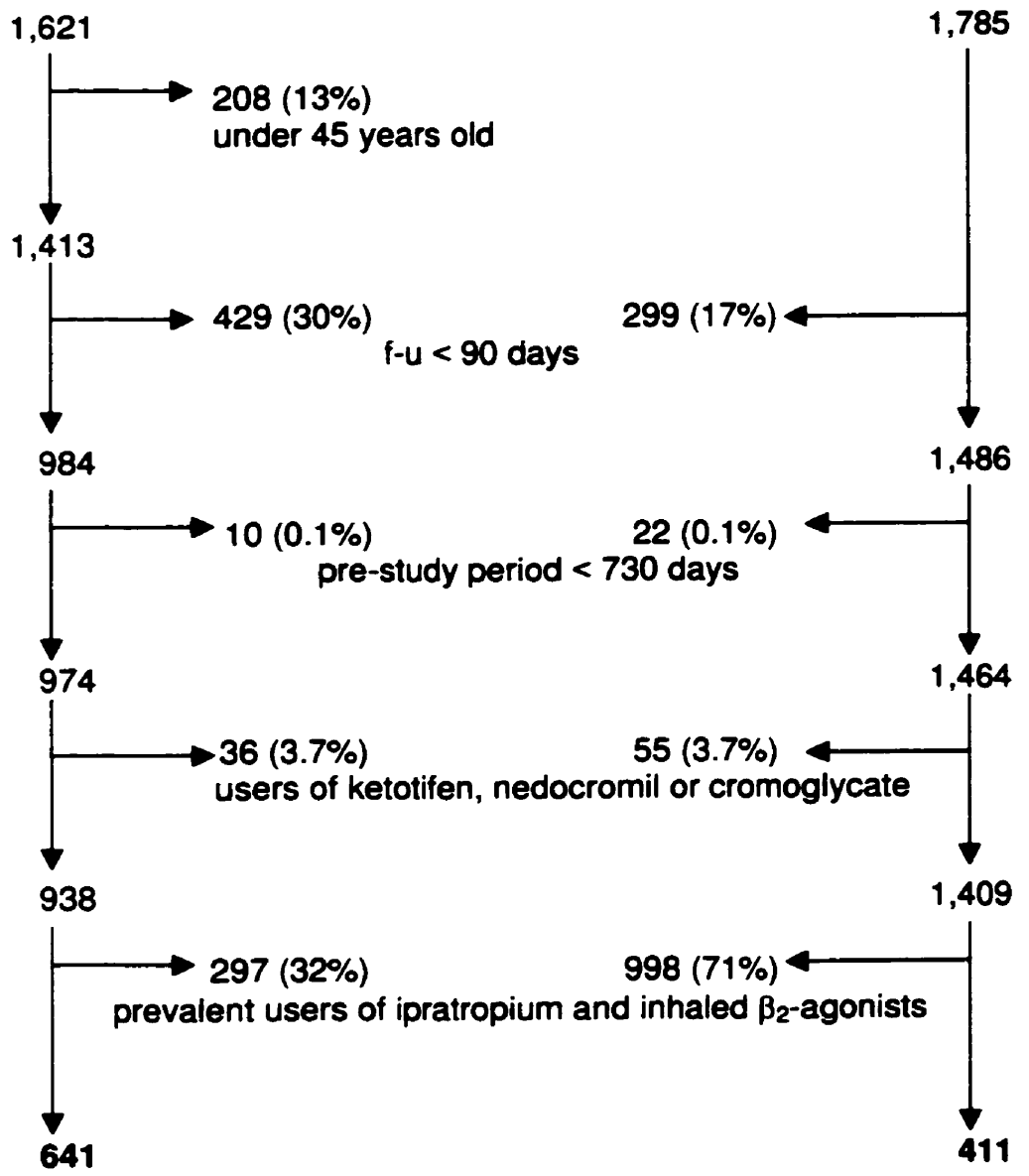

Figure 3.2. Cohort selection

3.4 Definition of the outcome variables

As mentioned, cohort eligibility was restricted to COPD patients with COPD status ascertained on the use of Combivent® or ipratropium bromide and inhaled β_2-agonist combination. Once this cohort of incident COPD treated patients was identified, subcohorts of subjects on Combivent® and ipratropium bromide and inhaled β_2-agonist combination were followed forward in time so as to identify relevant outcomes. Outcome information was obtained through the prescription database (Prescription Drug Services Branch data file) and the hospitalisation database (Hospital Services Branch data file). Exposure to combined inhaled bronchodilator therapy was studied in relation to four distinct outcome variables: 1) use of respiratory medications and antibiotics; 2) costs related to bronchodilator utilisation; 3) hospitalisations; and 4) mortality.

3.4.1 Drug utilisation

The primary outcome to be considered for analysis comprised use of bronchodilator, other respiratory medications and antibiotics during the follow up. First, data to be extracted included: drug information relating to the treatment schedules (i.e., all claims for Combivent®, inhaled ipratropium bromide and all inhaled β_2-agonists). In addition, claims data for other bronchodilators or claims for other inhaled dosage forms (i.e., oral β_2-agonists, nebulised β_2-agonists, nebulised ipratropium bromide, theophylline), all forms of corticosteroids, and selective anti-infective therapy were also obtained. Information collected on a per claim basis included: generic and brand name, strength and dosage form, date and quantity dispensed. A complete list of the drugs of interest is shown in Appendix 2.

Regrouping drugs into bronchodilators and other respiratory drugs and antibiotics allowed the evaluation of the impact of the introduction of combined inhaled bronchodilator on the drugs encompassed by Combivent® (ipratropium bromide and inhaled β_2-agonist), but also on the global therapy of COPD. Therefore, any change in the patients dynamics on dual or combination therapy

were identified. Inhaled corticosteroids were also studied as a distinct outcome because despite the small number of patients who will benefit from inhaled corticosteroids therapy, many COPD sufferers are put on inhaled steroids, exposing them to unnecessary complications and additional expenses.

3.4.2 Costs related to bronchodilators use

Although the average cost per prescription of Combivent® has been shown to be lower than the ipratropium bromide and inhaled β_2-agonist combination, it is necessary to conduct a study in the context of actual medical practice to determine the extent to which combined therapy is prescribed and the impact on the real direct bronchodilator costs following the introduction of Combivent®.

To verify the assumption that the introduction of combined bronchodilator therapy in the treatment of COPD can represent substantial cost savings to both the patient and the health care system, the second outcome of interest is the costs related to the use of bronchodilators. Total costs, including unit costs of drug, dispensing fees and wholesale mark-up, consumer share of total costs, government share of total costs and total costs, of Combivent®, of all inhaled β_2-agonists and ipratropium bromide were compiled and compared for both groups. This information was used to determine the eventual savings attributable to Combivent® during its first year on the Saskatchewan Formulary.

3.4.3 Hospitalisations

The cohort of new users of dual bronchodilator therapy was also used to quantify the frequency of health services utilisation as defined by the occurrence of hospital admissions after treatment initiation. COPD is a chronic disease typically generating multiple acute episodes of worsening respiratory illnesses requiring hospitalisation (which occur later in the course of the disease) and indicate disease progression and poorer prognosis (Ingram, 1994). Hospitalisation is a major outcome, both in terms of disability and costs. Therefore, any therapy that affects this outcome will impact heavily upon total health care costs. First analyses encompassed all hospitalisations following

treatment across the contrasted groups in order to examine potential differences. Then, rates of hospitalisations were restricted only to hospitalisations diagnosed as acute respiratory infections (ICD-9 codes 460-466.1, 480-494) and other diseases of the respiratory system related to chronic airway diseases (ICD-9 codes 496, 512-514, 518-518.8, 519.8, 519.9).

3.4.4 Mortality

Finally, in accordance with general principles, analyses also addressed total mortality between the contrasted groups. Therefore, deaths occurring during follow-up were included as an important outcome. This last outcome, without any distinction of the cause of death, was identified from the Health Insurance Registration data file.

3.5 Data analysis

The study has been designed to emulate a clinical trial with divergence of therapies occurring at cohort entry (since subjects are recruited at initiation of ipratropium bromide and inhaled β_2-agonist either combined or in two separate canisters). Since the study design restricts cohort entry to the time of beginning of dual bronchodilator therapy for COPD patients, confounding by severity of COPD is not expected to affect study validity. This issue is largely discussed in a subsequent chapter.

First, for each member of the cohort of 1,052 COPD patients (section 3.3), univariate analyses of adjustment factors (respiratory medications, hospitalisations and oxygen consumption in the year prior to cohort entry), use of respiratory drugs during the follow-up and each of the outcome variables were carried out.

Crude overall and subgroup comparisons were performed for each outcome. The next stage of the analysis involved stratified analysis for selected adjustment factors to show differences in the estimate of the primary outcome

variable (bronchodilator use) across various strata of these factors. This step is important to identify potential confounders or effect modifiers prior to multivariate analysis.

The study thus lends itself to standard techniques of Poisson regression models for rates, accounting for between-subject variation, to contrast the two therapies, with the two canisters combination therapy as the reference group. These regression techniques were used to address potential confounding by age, gender and socioeconomic status as measured by the receipt of social assistance at any time during the study period. Use of drugs related to the treatment of COPD, respiratory hospitalisations and oxygen administration during the 12-month preceding treatment initiation were used as additional adjustment factors. The first multivariate analysis was carried out under the "intention to treat" principle to emulate the clinical trial paradigm. Here, the specific bronchodilator therapy at treatment initiation, either combined or in two separate canisters, defines the exposure group of the subject, irrespective of the patterns of multiple drug therapy, drug switching and non-compliance, for the duration of the follow-up. However, these patterns are described to help interpret the corresponding results. The second analysis, emulating the evaluation of efficacy, was restricted to "regular" users of each dual bronchodilator therapy. "Regular" users were defined as subjects filling at least one prescription (two for the reference group, one of ipratropium bromide and one of inhaled β_2–agonists) every three months. The subjects were followed until study termination date and the number of outcomes (prescriptions, costs of bronchodilators, hospitalisations and death) were documented. All outcome measures were computed as rates (number of events per person-years) to account for the differing amount of follow-up between the contrasted groups.

Finally, an analysis of the costs associated with inhaled bronchodilators was undertaken. The direct cost impact analysis was conducted from the societal perspective. This perspective provides for the broadest possible evaluation and reflects costs as a whole. This approach also makes it possible, subsequently, to present results according to a more restrictive perspective, such as a private third

party payer. Using multiple regression analysis to adjust for the potential factors identified earlier, estimation of the difference of mean costs per month between the treatment groups was obtained. Furthermore, to overcome the proportionality between the variance of the mean costs and the duration of follow-up, individual values of duration of follow-up were considered as relative weights in the weighted-least-squares regression analysis. Due attention was paid to any distributional assumptions of the data, and logarithmic transformations were used to reduce the skewness and better approximate a normal distribution.

In all cases, 95% confidence intervals were computed for point estimates, crude and adjusted.

CHAPTER 4 – RESULTS

This chapter describes the results of the analyses outlined in the preceding chapter. First, a summary of selected socio-demographic characteristics of the study cohort is presented. This is followed by a description of the medication profiles and the clinical characteristics of the subjects during the year prior to cohort entry and during follow-up. Finally the results of the stratified and multivariate analyses of the use of prescribed respiratory medications and antibiotics, costs related to bronchodilators, hospitalisations and mortality are described. All results are presented for both the entire cohort and the cohort of "regular" users. Definitions of dependent and independent variables are detailed in Appendix 3.

4.1 Socio-demographic description

Among the 1,051 subjects newly treated with two different bronchodilators (ipratropium bromide and inhaled β_2-agonist) between July 1st, 1996 and June 30th, 1997, 641 subjects initiated drug therapy with Combivent® (Combivent® group), and 411 were dispensed, on the same day, ipratropium bromide and inhaled β_2-agonist in two separate canisters (Double users group). In Table 4.1, the socio-demographic characteristics of the study subjects at cohort entry are presented. Patients initiated on Combivent® are slightly younger, included more females and are less likely to receive social assistance. The person-days of follow-up are almost identical for the two groups, with an average of 216 days per subject.

Table 4.1. Socio-demographic characteristics of study subjects according to treatment initiation (full cohort)

	Combivent® (n=641)	**Double users** (n=411)
Age*, n		
45-54	87	34
55-64	136	50
65-74	218	151
≥75	200	176
Mean† (sd)	68 (11)	71 (10)
Male, n	276	189
Social Assistance‡, n	33	27
Person-days of follow-up		
Mean (sd)	218 (80)	215 (76)

* Age is as of the first prescription that qualifies the subject for inclusion in the study.
† Subjects older than 85 years of age are identified as being 85.
‡ Saskatchewan Assistance Plan indicator at any time during study period.

After restricting the cohort to regular users, 451 subjects remained in the cohort. Of these 293 regularly filled a prescription for Combivent® and 158 the two-canister combination therapy (Table 4.2). With this restricted cohort, discrepancies between the two groups become more evident. Again, patients in the Combivent® group are slightly younger, with a mean age over 70 years. For both groups, nearly 75 percent of the cohort members are in the two older age categories (over 65 years). This finding, in agreement with the nature of the disease which affects middle-aged and older individuals, is also present for the entire cohort. Close to 50 percent of the Combivent® group is male as compared with 41 percent in the double users group. Subjects in the Combivent® group received social assistance roughly twice as less during the follow-up. They also satisfied the regular use inclusion criterion for a longer period of time. As a consequence, subjects initiated on Combivent® were followed for a longer time than were those initiated with the two-canister combination therapy.

Overall, when comparing the initial and the restricted cohorts, subjects tended to be older in the latter cohort, with a greater likelihood for patients exposed to Combivent® to receive social assistance and to be followed for a longer period of time. These differences are in the same direction for regular users of the two-canister combination therapy, except for the duration of follow-up which clearly became shorter after applying the last inclusion criteria (215 person-days of follow-up for double users in the initial cohort and 207 person-days in the restricted cohort). However, when taking into consideration the difference in the sizes of the two cohorts, these changes remain minor, except for the duration of follow-up.

Table 4.2. Socio-demographic characteristics of regular users according to treatment initiation (restricted cohort)

	Combivent® (n=293)	**Double users** (n=158)
Age*, n		
45-54	24	9
55-64	63	18
65-74	104	53
≥75	102	78
Mean† (sd)	70 (10)	73 (9)
Male, n	138	65
Social Assistance‡, n	13	15
Person-days of follow-up		
Mean (sd)	228 (82)	207 (79)

* Age is as of the first prescription that qualifies the subject for inclusion in the study.
† Subjects older than 85 years of age are identified as being 85.
‡ Saskatchewan Assistance Plan indicator at any time during study period.

4.2 Descriptive analysis

This section describes the results of the univariate analyses for the variables of interest. The next eight tables contain information regarding drug use and clinical characteristics of the subjects during the year prior to cohort entry (adjustment factors at baseline) and also for the first year following the index date. Again, all results are presented and discussed for the entire cohort and the cohort restricted to regular users.

4.2.1 Baseline data

Drug utilisation

Table 4.3 provides information regarding the use of different respiratory drugs and antibiotic categories related to the treatment of COPD during the 12-month period preceding treatment initiation. For each drug category, the first line represents the monthly rate of drug use per 100 subjects for all subjects of the contrasted groups, including non users. The second line shows the same rate, but only for the patients who were dispensed at least one prescription for the drug of the identified category. Subjects initiated on Combivent® tended to be more likely to receive a prescription for inhaled β_2-agonists, nebulised β_2-agonists, nebulised ipratropium, oral β_2-agonists, theophylline, inhaled corticosteroids, oral corticosteroids and antibiotics, whereas a greater proportion of subjects initiated on the two-canister combination therapy received inhaled ipratropium. However, among users of nebulised β_2-agonists, inhaled ipratropium, nebulised ipratropium, oral β_2-agonists, theophylline, inhaled corticosteroids, oral corticosteroids and antibiotics, rates of utilisation are similar for both groups, with less than one prescription filled every two months. The rates of inhaled β_2-agonists in the one year period is lower for the double users group at 39 (95 CI: 33 – 45) per 100 patients per month and highest for the Combivent® group at 47 (95 CI: 42 – 52) per 100 subjects per month. These findings have implications on the first rate which encompass also non-users. These unadjusted rates show a lower consumption of inhaled β_2-agonists, inhaled corticosteroids and antibiotics

in the double users group and a tendency to fill less prescriptions for all other respiratory drugs, except inhaled ipratropium, suggesting that they have a less severe airway respiratory disease.

The same comparisons are repeated for the regular users cohort in Table 4.4. It appears that patients initially prescribed Combivent® are using more inhaled β_2-agonists, nebulised ipratropium, oral β_2-agonists, theophylline, inhaled corticosteroids, oral corticosteroids and antibiotics. It is noteworthy that almost all rates of prescription of primary interest have increased when compared to the rates presented for the entire cohort. Therefore, by restricting the cohort to regular users more severe patients were selected.

Table 4.3. Monthly rates of prescription in the year preceding cohort entry, per 100 subjects (full cohort)

	Combivent®		Double users	
	N	Rate (95% CI)	N	Rate (95% CI)
Inh. β_2-agonists				
all subjects	641	16 (14 – 18)	411	11 (8 – 14)
users	222	47 (42 – 52)	121	39 (33 – 45)
Neb. β_2-agonists				
all subjects	641	4 (3 – 5)	411	3 (2 – 4)
users	54	43 (33 – 53)	29	47 (34 – 60)
Ipratropium				
all subjects	641	3 (2 – 4)	411	4 (3 – 5)
users	51	36 (26 – 46)	47	32 (23 – 41)
Neb. Ipratropium				
all subjects	641	3 (2 – 4)	411	2 (1 – 3)
users	40	44 (33 – 55)	20	43 (26 – 60)
Oral β_2-agonists				
all subjects	641	0.6 (0.3 – 0.9)	411	0.5 (0.02 – 1)
users	26	15 (9 – 21)	7	29 (5 – 53)
Theophylline				
all subjects	641	4 (3 – 5)	411	3 (2 – 4)
users	64	42 (34 – 50)	29	43 (32 – 54)
Inh. Corticosteroids				
all subjects	641	12 (10 – 14)	411	9 (7 – 11)
users	220	34 (30 – 38)	116	31 (26 – 36)
Oral Corticosteroids				
all subjects	641	6 (5 – 7)	411	5 (4 – 6)
users	134	27 (23 – 31)	70	28 (22 – 34)
Antibiotics				
all subjects	641	14 (13 – 15)	411	11 (9 – 13)
users	430	21 (19 – 23)	230	20 (18 – 22)

Table 4.4. Monthly rates of prescription in the year preceding cohort entry, per 100 regular users (restricted cohort)

	Combivent®		Double users	
	N	Rate (95% CI)	N	Rate (95% CI)
Inh. β_2-agonists				
all subjects	293	26 (22 – 30)	158	12 (8 – 16)
users	136	55 (49 – 61)	55	35 (27 – 43)
Neb. β_2-agonists				
all subjects	293	5 (3 – 7)	158	4 (1 – 7)
users	35	44 (31 – 57)	11	52 (25 – 79)
Ipratropium				
all subjects	293	5 (3 – 7)	158	6 (3 – 9)
users	32	43 (30 – 56)	27	35 (25 – 45)
Neb. Ipratropium				
all subjects	293	4 (2 – 6)	158	2 (0 – 4)
users	29	37 (26 – 48)	8	45 (14 – 76)
Oral β_2-agonists				
all subjects	293	0.7 (0.1 – 1)	158	0.1 (-0.04 - 0,2)
users	11	18 (5 – 31)	2	8
Theophylline				
all subjects	293	6 (5.8 – 6.2)	158	2 (0.1 – 4)
users	41	45 (35 – 55)	10	39 (20 – 58)
Inh. Corticosteroids				
all subjects	293	17 (14 – 20)	158	10 (7 – 13)
users	137	37 (32 – 42)	55	28 (23 – 33)
Oral Corticosteroids				
all subjects	293	7 (5 – 9)	158	3 (2 – 4)
users	73	30 (24 – 36)	23	21 (14 – 28)
Antibiotics				
all subjects	293	16 (14 – 18)	158	11 (8 – 14)
users	202	23 (20 –26)	85	20 (16 – 24)

Hospitalisations and oxygen therapy

Clinical characteristics, as defined by hospitalisations and oxygen therapy, also differed across the contrasted groups (Table 4.5). Again, for both the entire cohort and the restricted cohort, the results are first presented for the complete groups and restricted to the subjects who were hospitalised at least once. These figures indicate that the double users group are hospitalised twice as often. The rate for hospitalisations from all causes among the double users group is 10 admissions per 100 patients per month, compared with 5 for the Combivent® group. The difference persists when considering respiratory hospitalisations only with an overall rate of approximately 3 hospitalisations per 100 subjects per month for the two groups. Rates of oxygen use, as measured by the delivery of any home oxygen on a monthly basis, are comparable for the contrasted groups.

For regular users of the treatments contrasted, although the rates of hospitalisations present more similarity between the two groups, subjects who were dispensed two canisters at treatment initiation are hospitalised more frequently during the baseline year (Table 4.6). However when comparing results obtained from the entire cohort and the restricted cohort, no clear differences are observed.

Despite the fact that they had more hospital admissions in the year preceding treatment initiation, subjects initiated with the two-canister bronchodilator therapy used less prescription drugs. This finding complicates the interpretation of the results due to the differential disease severity between the two groups.

Table 4.5. Monthly rates of hospitalisation and oxygen use in the year preceding cohort entry, per 100 subjects (full cohort)

	Combivent®		Double users	
	N	Rate (95% CI)	N	Rate (95% CI)
All hospitalisations				
all subjects	641	5 (4 – 6)	411	10 (9 – 11)
subjects hospitalised	202	16 (14 – 18)	279	15 (13 – 17)
Respiratory hospitalisations*				
all subjects	641	2 (1.6 – 2.4)	411	4 (3 – 5)
subjects hospitalised	89	11 (9 – 13)	151	10 (9 – 11)
Oxygen use†				
all subjects	641	3 (2 – 4)	411	5 (3 – 7)
users	32	68 (56 – 80)	32	65 (54 – 76)

* ICD-9 codes 460-466.1, 480-494, 496, 512-514, 518-518.8, 519.8, 519.9

† Refers to any home oxygen use on a monthly basis

Table 4.6. Monthly rate of hospitalisation and oxygen use in the year preceding cohort entry, per 100 regular users (restricted cohort)

	Combivent®		Double users	
	N	Rate (95% CI)	N	Rate (95% CI)
All hospitalisations				
all subjects	293	6 (5 – 7)	158	9 (8 – 10)
subjects hospitalised	108	16 (13 – 19)	116	12 (11 – 13)
Respiratory hospitalisations*				
all subjects	293	2 (1 – 3)	158	4 (3 – 5)
subjects hospitalised	53	12 (9 – 15)	61	10 (9 – 11)
Oxygen use†				
all subjects	293	5 (3 – 7)	158	6 (3 – 9)
users	23	70 (56 – 84)	15	62 (40 – 84)

* ICD-9 codes 460-466.1, 480-494, 496, 512-514, 518-518.8, 519.8, 519.9

† Refers to any home oxygen use on a monthly basis

4.2.2 Outcomes

Using the same format as the previous tables, drug use and selected clinical characteristics after treatment initiation are documented.

Drug utilisation

Table 4.7 presents the rates of drug use of primary interest in the first year of follow-up. The introduction of Combivent® makes comparison of inhaled bronchodilators between the two contrasted groups difficult. For these drugs (Combivent®, inhaled β_2-agonists and inhaled ipratropium bromide) subjects of the two groups are filling on average just less than one prescription every two months (0.47 prescription per subject per month). An important proportion (18 percent) of the patients initiated on Combivent® were also dispensed one prescription of inhaled β_2-agonists every two months. As expected, the proportion and the rate of use of ipratropium bromide are smaller in the Combivent® group. Part of these figures could easily be explained by drug switching or stopping. For all the other drugs described, the Combivent® group tends to be more likely to receive prescriptions of nebulised β_2-agonists, nebulised ipratropium, oral β_2-agonists, inhaled corticosteroids and antibiotics, whereas subjects initiated on the two-canister combination therapy are more likely to be dispensed oral corticosteroids.

Among regular users, similarly to what was observed in the year prior to cohort entry, almost all rates of prescriptions for COPD related drugs are higher when compared to the rates for the entire cohort (Table 4.8). Regular users of Combivent® filled 80 prescriptions of Combivent® per 100 subjects per month, whereas the reference group was dispensed 76 and 74 prescriptions per 100 subject-months of inhaled β_2-agonists and ipratropium respectively. Still, a fairly large proportion of Combivent® users also filled prescriptions for inhaled β_2-agonists. Overall, the results of the univariate analyses indicate that regular use of Combivent® seems to be associated with higher crude rates of drug use during follow-up.

During follow-up, 46 percent of the patients in the exposed group used Combivent® only once, while 39 and 43 percent of patients in the reference group for one prescription for inhaled β_2-agonists and ipratropium, respectively, therefore justifying the need for the analyses restricted to regular users of these drugs.

The rates of drug use before and after the index date appear to differ as indicated by Tables 4.3 and 4.7. Combivent®users clearly filled more prescriptions for inhaled bronchodilators during the follow-up period. Among this group, the increase in drug use over time is also more evident for inhaled corticosteroids and antibiotics. In the group initiated on the two-canister combination therapy, the increase in drug use affects the same drug categories with the addition of theophylline and oral orticosteroids. However, the magnitude of the rise is similar for the contrasted groups. This increasing pattern over time is even more pronounced in the cohort restricted to regular users (Tables 4.4 and 4.8). This observation is concordant with the clinical need to add a second bronchodilator, which is the entry criterion into the cohort.

Table 4.7. Monthly rates of prescription during follow-up, per 100 subjects (full cohort)

	Combivent®		Double users	
	N	Rate (95% CI)	N	Rate (95% CI)
Combivent®				
all subjects	641	47 (44 – 50)	-	-
Users	-	-	-	-
Inh. β_2-agonists				
all subjects	641	9 (7 – 11)	411	47 (43 – 51)
users	114	50 (42 – 58)	-	-
Neb. β_2-agonists				
all subjects	641	6 (4 – 8)	411	4 (2 – 6)
users	67	62 (52 – 72)	37	49 (38 – 60)
Ipratropium				
all subjects	641	2 (1 – 3)	411	44 (41 – 47)
users	40	40 (30 – 50)	-	-
Neb. Ipratropium				
all subjects	641	5 (3 – 7)	411	4 (2 – 6)
users	53	66 (56 – 76)	30	59 (47 – 71)
Oral β_2-agonists				
all subjects	641	1 (0.5 – 2)	411	0.3 (-0.1 - 0.7)
users	20	31 (18 – 44)	4	29 (-3 – 61)
Theophylline				
all subjects	641	6 (4 – 8)	411	6 (4 – 8)
users	72	49 (40 – 58)	52	47 (38 – 56)
Inh. Corticosteroids				
all subjects	641	23 (20 – 26)	411	19 (16 – 22)
users	303	48 (44 – 52)	178	44 (40 – 48)
Oral Corticosteroids				
all subjects	641	8 (6 – 10)	411	11 (9 – 13)
users	136	40 (34 – 46)	127	37 (32 – 42)
Antibiotics				
all subjects	641	17 (15 – 19)	411	14 (12 – 16)
users	373	30 (28 – 32)	204	29 (26 – 32)

Table 4.8. Monthly rates of prescription during follow-up, per 100 regular users (restricted cohort)

	Combivent®		Double users	
	N	Rate (95% CI)	N	Rate (95% CI)
Combivent®				
all subjects	293 (100)	80 (76 – 84)	-	-
users	-	-	-	-
Inh. β_2-agonists				
all subjects	293	9 (6 – 12)	158	76 (71 – 81)
users	53	48 (36 – 60)	-	-
Neb. β_2-agonists				
all subjects	293	9 (6 – 12)	158	3 (1 – 5)
users	46	60 (48 – 72)	11	47 (27 – 67)
Ipratropium				
all subjects	293	2 (1 – 3)	158	74 (69 – 79)
users	18	38 (26 – 50)	-	-
Neb. Ipratropium				
all subjects	293	7 (4 – 10)	158	3 (1 – 5)
users	36	56 (45 – 67)	10	45 (30 – 60)
Oral β_2-agonists				
all subjects	293	1 (-0.03 – 2)	158	0
users	12	30 (10 – 50)	0	0
Theophylline				
all subjects	293	9 (6 – 12)	158	7 (4 – 10)
users	47	56 (45 – 67)	20	55 (39 – 71)
Inh. Corticosteroids				
all subjects	293	32 (28 – 36)	158	27 (22 – 32)
users	170	56 (51 – 61)	80	53 (48 – 58)
Oral Corticosteroids				
all subjects	293	11 (8 – 14)	158	12 (8 – 16)
users	81	40 (33 – 47)	51	39 (31 – 47)
Antibiotics				
all subjects	293	18 (15 – 21)	158	14 (11 – 17)
users	176	30 (27 – 33)	76	29 (24 - 34)

Hospitalisations and oxygen therapy

When looking at hospitalisations during follow-up, the differences between the two groups observed in the baseline year for both all causes and respiratory hospitalisations is less obvious (Table 4.9). Resulting from an average duration of follow-up of less than one year, the proportion of patients hospitalised has declined, to a lesser extent for the double users group. However, all patients have been hospitalised more often. As a consequence, patients initiated on the two-canister combination therapy had slightly more all cause and respiratory hospitalisations, with an overall rate of 9 and 3 hospitalisations per 100 subjects per month, respectively, compared to 7 and 2 hospitalisations per 100 subjects per month for the Combivent® group. As well, the patients used home oxygen during 8 and 22 months per 100 subjects, the higher rates being for the reference group. These differences are similar for the regular users (Table 4.10).

Table 4.9. Monthly rates of hospitalisation and oxygen use during follow-up, per 100 subjects (full cohort)

	Combivent®		**Double users**	
	N	Rate (95% CI)	N	Rate (95% CI)
All hospitalisations				
all subjects	641	7 (6 – 8)	411	9 (7 – 11)
subjects hospitalised	176	26 (23 – 29)	143	27 (24 – 30)
Respiratory hospitalisations*				
all subjects	641	2 (1 – 3)	411	3 (2 – 4)
subjects hospitalised	81	18 (15 – 21)	61	18 (15 – 21)
Oxygen use†				
all subjects	641	8 (6 – 10)	411	22 (18 – 26)
users	56	93 (83 – 103)	99	92 (85 – 99)

* ICD-9 codes 460-466.1, 480-494, 496, 512-514, 518-518.8, 519.8, 519.9
† Refers to any home oxygen use on a monthly basis

Table 4.10. Monthly rates of hospitalisation and oxygen use during follow-up, per 100 regular users (restricted cohort)

	Combivent®		Double users	
	N	Rate (95% CI)	N	Rate (95% CI)
All hospitalisations				
all subjects	293	7 (5 – 9)	158	9 (6 – 12)
subjects hospitalised	84	25 (21 – 29)	57	26 (22 - 30)
Respiratory hospitalisations*				
all subjects	293	3 (2 – 4)	158	3 (2 – 4)
subjects hospitalised	50	16 (14 – 18)	28	18 (15 – 21)
Oxygen use†				
all subjects	293	13 (9 – 17)	158	32 (24 – 40)
users	41	91 (78 – 104)	54	95 (86 – 104)

* ICD-9 codes 460-466.1, 480-494, 496, 512-514, 518-518.8, 519.8, 519.9
† Refers to any home oxygen use on a monthly basis

4.3 History of bronchodilator use

Based on the univariate analyses of drug use during the year prior to cohort entry, three exclusive strata of history of bronchodilator use were identified:

- naive patients (i.e., subjects on neither ipratropium bromide nor inhaled β_2-agonists)
- patients on inhaled β_2-agonists only
- patients on inhaled ipratropium bromide only

This choice of mutually exclusive strata has the added advantage of including all patients and provides an opportunity to identify patients at risk of overusing bronchodilators. These strata will first guide stratified analyses and then will be taken into consideration in the multivariate models.

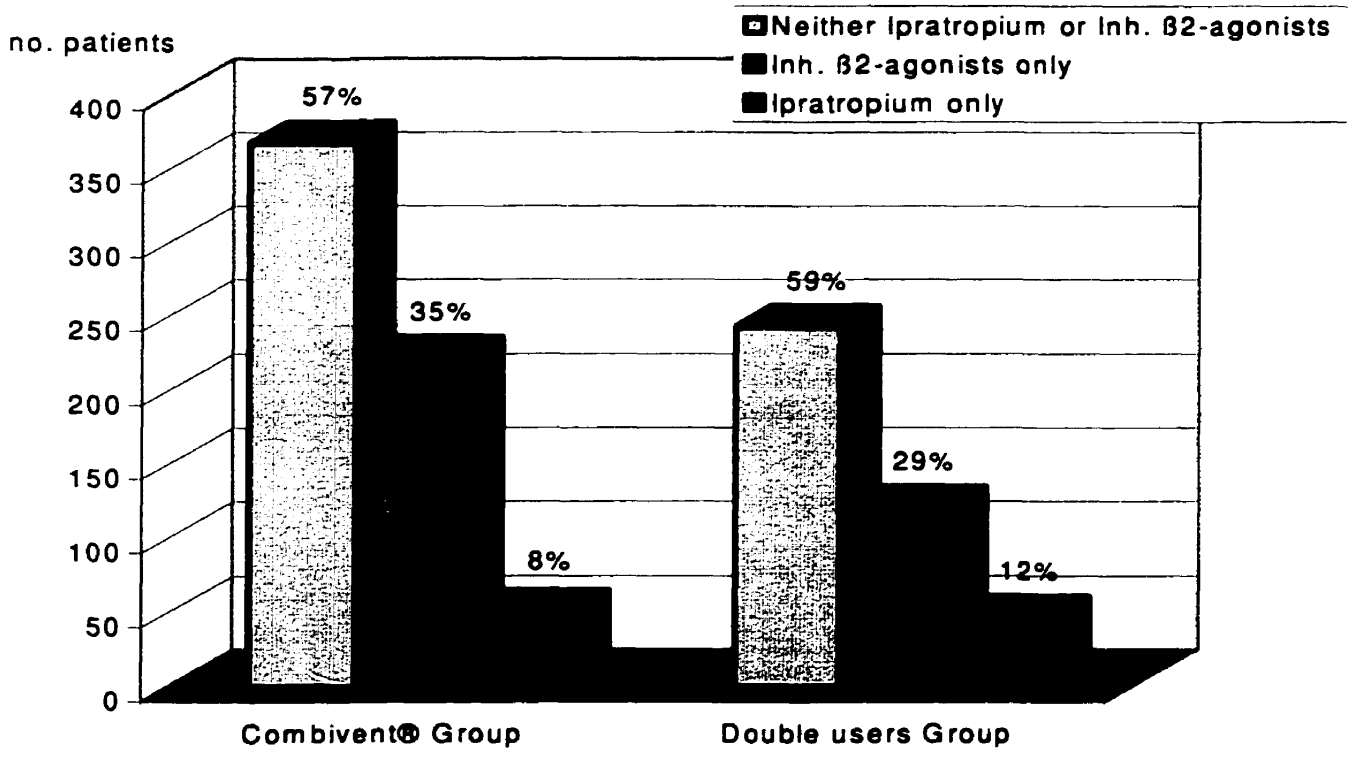

Figure 4.1. History of bronchodilator use in the year prior to cohort entry (full cohort)

The distribution of subjects within the strata is similar for the two contrasted groups (Figure 4.1). A significant important proportion of subjects, around 60 percent of subjects, are started on ipratropium bromide and inhaled β_2-agonists, either combined or in two different canisters, without any prescription for single agents in the previous years. The distribution of subjects within the strata for regular users did not differ significantly from the preceding description (Figure 4.2).

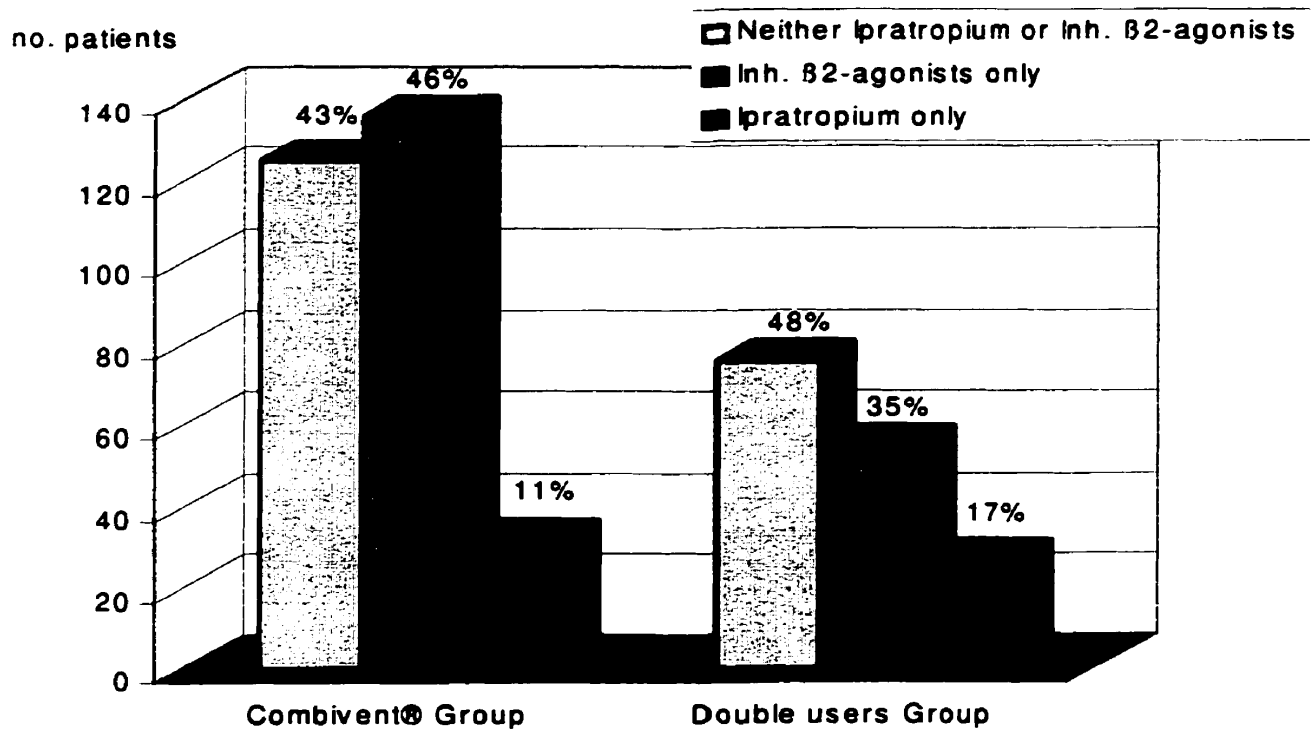

Figure 4.2. History of bronchodilator use in the year prior to cohort entry for regular users (restricted cohort)

4.4 Bivariate analysis

The next stage of the analysis involved unadjusted estimation of rate ratios of the various outcomes through bivariate analysis. The relation between exposure to combined inhaled bronchodilator therapy and use of bronchodilators, other respiratory medications and antibiotics, costs related to bronchodilators utilisation, hospitalisations and mortality is shown in Table 4.11. The double users group is the reference. In this table, frequencies of each distinct outcome measure as well as duration of follow-up are presented for the exposed and the reference groups, with unadjusted rate ratios and corresponding 95 percent confidence intervals. The double users group and the Combivent® group generated a total of 2,899 and 4,582 person-months of follow-up, respectively. The crude rate ratios indicate a higher use of bronchodilators among users of Combivent®. Although rate estimates failed to reach statistical significance, the results also indicate greater use of other respiratory drugs and inhaled corticosteroids among subjects using Combivent®. On the other hand, the overall costs associated with these inhaled bronchodilators are reduced in the same group. For the clinical outcomes, hospitalisations and death are 22 and 51 percent lower, and respiratory hospitalisations tended to be less in the Combivent® group.

Results for the restricted cohort are almost identical, with a cost reduction of 13 percent for Combivent® users (Table 4.12). The increase in use of other respiratory medications and antibiotics became significant while the decrease in hospitalisation lost statistical significance.

Table 4.11. Crude rate ratios of outcome measures according to treatment initiation (full cohort)

Outcome	Number of events	Follow-up (months)	RR[¶]	95% CI
Bronchodilators*				
Double users	2,582	2,899	1.00	Reference
Combivent®	4,921	4,582	1.21	1.10 – 1.32
Other Rx†				
Double users	1,818	2,899	1.00	Reference
Combivent®	3,172	4,582	1.10	0.96 – 1.27
Inh. Corticosteroids				
Double users	589	2,899	1.00	Reference
Combivent®	1,094	4,582	1.17	0.99 – 1.40
Costs‡				
Double users	$ 52,567	2,899	1.00	Reference
Combivent®	$ 79,833	4,582	0.96	0.87 – 1.06
All hospitalisations				
Double users	251	2,899	1.00	Reference
Combivent®	311	4,582	0.78	0.64 – 0.96
Resp hospitalisations§				
Double users	76	2,899	1.00	Reference
Combivent®	108	4,582	0.90	0.70 – 1.15
Death				
Double users	22	2,899	1.00	Reference
Combivent®	17	4,582	0.49	0.35 - 0.68

* Prescriptions for Combivent®, inhaled ipratropium bromide and inhaled β_2-agonists.

† Prescriptions for nebulised β_2-agonists, nebulised ipratropium, oral β_2-agonists, theophlline, inhaled corticosteroids, macrolides, cephalosporins, penicillins, tetracyclines, sulfonamides, quinolones

‡ Total costs for Combivent®, ipratropium bromide and inhaled β_2-agonists in Canadian dollars.

§ ICD-9 codes 460-466.1, 480-494, 496, 512-514, 518-518.8, 519.8, 519.9

¶ Unadjusted rate ratio

Table 4.12. Crude rate ratios of outcome measures according to treatment initiation of regular users (restricted cohort)

Outcome	Number of events	Follow-up (months)	RR[¶]	95% CI
Bronchodilators*				
Double users	1,604	1,070	1.00	Reference
Combivent®	3,776	2,191	1.15	1.06 – 1.25
Other Rx†				
Double users	722	1,070	1.00	Reference
Combivent®	1,969	2,191	1.33	1.09 – 1.62
Inh. Corticosteroids				
Double users	288	1,070	1.00	Reference
Combivent®	716	2,191	1.21	0.95 – 1.55
Costs‡				
Double users	$ 32,765	1,070	1.00	Reference
Combivent®	$ 61,714	2,191	0.87	0.79 – 0.95
All hospitalisations				
Double users Group	88	1,070	1.00	Reference
Combivent® Group	156	2,191	0.87	0.63 – 1.18
Resp hospitalisations§				
Double users	33	1,070	1.00	Reference
Combivent®	66	2,191	0.98	0.68 – 1.41
Death				
Double users	11	1,070	1.00	Reference
Combivent®	11	2,191	0.49	0.31 – 0.78

* Prescriptions for Combivent®, inhaled ipratropium bromide and inhaled β_2-agonists.

† Prescriptions for nebulised β_2-agonists, nebulised ipratropium, oral β_2-agonists, theophlline, inhaled corticosteroids, macrolides, cephalosporins, penicillins, tetracyclines, sulfonamides, quinolones

‡ Total costs for Combivent®, ipratropium bromide and inhaled β_2-agonists in Canadian dollars.

§ ICD-9 codes 460-466.1, 480-494, 496, 512-514, 518-518.8, 519.8, 519.9

¶ Unadjusted rate ratio

4.5 Stratified analysis

Prior to performing the multivariate analyses, stratified analyses of the primary outcome variable were performed to identify potential sources of confounding or effect modification. Table 4.13 presents rate ratios of bronchodilator use for various strata of selected adjustment factors. Comparison between the rate ratios obtained in the various strata and the crude rate ratio computed in the previous section help to identify potential confounders by looking for clinically meaningful changes (greater than 20 percent) in the rate ratios of the variables examined. To identify any modification of the relation between exposure to Combivent® and bronchodilator use, consistency of the rate ratios obtained in the various strata was studied using Breslow-Day's homogeneity test. Age, gender, history of bronchodilator use and hospitalisations were considered as potential confounders because clinically significant differences between the crude estimates and the stratified estimates were seen. Consumption of bronchodilators was elevated in the two extremes of the age distribution ($RR_{\text{under 55 years}}$ = 1.27; 95% CI: 0.90 – 1.81 and $RR_{\text{over 76 years}}$=1.41; 95% CI: 1.20 – 1.65), in males (RR=1.32; 95% CI: 1.14 – 153), in previous users of inhaled β_2-agonists (RR=1.41; 95% CI: 1.21 – 1.63) and among patients who were hospitalised at least once ($RR_{\text{all hospitalisations}}$=1.38; 95% CI: 1.22 – 1.56 and $RR_{\text{respiratory hospitalisations}}$=1.53 95% CI: 1.28 – 1.82). When looking specifically at history of bronchodilator use, it is noteworthy that the higher bronchodilator use observed seems to be confined to patients previously using inhaled β_2-agonists. However, although rate ratios in the strata showed differences, none of the variables emerged as a strong effect modifiers.

Using the same techniques for regular users, age, history of bronchodilator use and hospitalisations remained as possible confounders in the restricted cohort (Table 4.14). These observations will be verified in the multivariate analysis.

Table 4.13. Rate ratios of bronchodilator* use stratified by selected adjustment factors (full cohort)

Stratification	n	RR	95% CI
Overall	1052	1.21†	1.10 – 1.32
Age			
≤ 55	136	1.27	0.90 – 1.81
56 – 65	204	1.10	0.89 – 1.36
66 – 75	377	1.12	0.96 – 1.30
≥ 76	335	1.41	1.20 – 1.65
Gender			
Female	577	1.12	0.99 – 1.26
Male	475	1.32	1.14 – 1.53
Social Assistance Program			
No	992	1.22	1.11 – 1.35
Yes	60	0.99	0.66 – 1.48
Bronchodilator use			
None	611	1.03	0.91 – 1.17
Inhaled $ß_2$-agonists only	343	1.41	1.21 – 1.63
Ipratropium only	98	1.07	0.84 – 1.38
Hospitalisation			
None	571	1.14	0.98 – 1.33
at least one	481	1.38	1.22 – 1.56
Respiratory hospitalisation			
none	812	1.16	1.04 – 1.31
at least one	240	1.53	1.28 – 1.82
Oxygen use			
no	988	1.21	1.09 – 1.33
yes	64	1.25	0.95 – 1.63

* Prescriptions for Combivent®, inhaled ipratropium bromide and inhaled $ß_2$-agonists.
† Unadjusted rate ratio using double users as group of reference.

Table 4.14. Rate ratios of bronchodilator* use stratified for selected adjustment factors (restricted cohort)

Stratification	n	RR	95% CI
Overall	451	1.15†	1.06 – 1.25
Age			
≤ 55	36	1.48	1.04 – 2.16
56 – 65	92	1.03	0.85 – 1.26
66 – 75	166	1.02	0.91 – 1.16
≥ 76	157	1.30	1.14 – 1.48
Gender			
Female	248	1.13	1.02 – 1.25
Male	203	1.16	1.02 – 1.33
Social Assistance Program			
No	423	1.15	1.06 – 1.25
Yes	28	1.21	0.85 – 1.72
Bronchodilator use			
None	201	1.00	0.90 – 1.13
Inhaled β_2-agonists only	191	1.32	1.15 – 1.51
Ipratropium only	59	1.05	0.88 – 1.26
Hospitalisation			
None	227	1.06	0.92 – 1.22
at least one	224	1.22	1.10 – 1.36
Respiratory hospitalisation			
none	337	1.12	1.02 – 1.24
at least one	114	1.26	1.08 – 1.46
Oxygen use			
no	413	1.14	1.05 – 1.24
yes	38	1.25	0.95 – 1.63

* Prescriptions for Combivent®, inhaled ipratropium bromide and inhaled β_2-agonists.
† Unadjusted rate ratio using double users as group of reference.

4.6 Multivariate analysis

The last section of this chapter presents the adjusted rate ratios obtained by multivariate techniques, including adjustment for age, gender, socio-economic status, previous use of bronchodilators, number of prescriptions filled for nebulised β_2-agonists, nebulised Ipratropium, oral β_2-agonists, theophylline, inhaled corticosteroids and antibiotics, as well as oxygen use and number of respiratory hospitalisations during the year prior the cohort entry. Table 4.15 shows the adjusted rate ratios for each outcome variable during the entire follow-up, contrasting subjects who initiated treatment with ipratropium bromide and inhaled β_2-agonist in two separate canisters (the reference group), to those initiated on Combivent®. Adjustment for confounders abolished the crude association between the use of Combivent® and other respiratory drugs, inhaled corticosteroids or hospitalisations. However, prescribing Combivent® resulted in lower costs associated with inhaled bronchodilator use (RR=0.83; 95% CI: 0.76 – 0.92), despite a slight increase in the overall use of these medications (RR=1.16; 95% CI: 1.07 – 1.26). In most analyses, crude and adjusted rate ratios were similar, suggesting that none of the adjustment factors acted as strong confounders of these associations.

The second multivariate analysis, emulating the evaluation of efficacy, was restricted to "regular" users of each dual bronchodilator therapy (Table 4.16). Only the reduction in costs remained statistically significant (RR=0.80; 95% CI: 0.74 – 0.87).

Table 4.15. Adjusted rate ratios of outcome measures according to treatment initiation (full cohort)

		Adjusted[¶]	
	Crude RR[§]	**RR[§]**	**95% CI**
Bronchodilators*	1.21	1.16	1.07 – 1.26
Other Rx†	1.10	1.03	0.93 – 1.16
Inh. Corticosteroids	1.17	1.10	0.95 – 1.28
Costs‡	0.96	0.83**	0.76 – 0.92
All hospitalisations	0.78	0.92	0.76 – 1.12
Resp. hospitalisations	0.90	0.88	0.70 – 1.12
Death	0.49	0.57	0.41 – 0.79

* Prescriptions for Combivent®, inhaled ipratropium bromide and inhaled β_2-agonists

† Prescriptions for nebulised β_2-agonists, nebulised ipratropium, oral β_2-agonists, theophlline, inhaled corticosteroids, macrolides, cephalosporins, penicillins, tetracyclines, sulfonamides, quinolones

‡ Total costs for Combivent®, ipratropium bromide and inhaled β_2-agonists in Canadian dollars.

§ Double users group is the reference group

¶ Adjusted for age, gender, socio-economic status, strata of history of bronchodilator use, use of inhaled ipratropium bromide, inhaled β_2-agonists, nebulised β_2-agonists, nebulised ipratropium bromide, oral β_2-agonists, theophlline, inhaled corticosteroids, antibiotics, oxygen and respiratory hospitalisations during the year prior to cohort entry

** Weighted for the duration of follow-up

Table 4.16. Adjusted rate ratios of outcome measures according to treatment initiation for regular users (restricted cohort)

		Adjusted[¶]	
	Crude RR[§]	**RR[§]**	**95% CI**
Bronchodilators*	1.15	1.07	0.99 – 1.16
Other Rx[†]	1.33	1.04	0.87 – 1.25
Inh. Corticosteroids	1.21	0.97	0.77 – 1.23
Costs[‡]	0.88	0.80**	0.74 – 0.87
All hospitalisations	0.87	0.86	0.63 – 1.17
Resp. hospitalisations	0.98	0.81	0.56 – 1.19
Death	0.49	0.49	0.30 – 0.80

* Prescriptions for Combivent®, inhaled ipratropium bromide and inhaled β_2-agonists

† Prescriptions for nebulised β_2-agonists, nebulised ipratropium, oral β_2-agonists, theophlline, inhaled corticosteroids, macrolides, cephalosporins, penicillins, tetracyclines, sulfonamides, quinolones

‡ Total costs for Combivent®, ipratropium bromide and inhaled β_2-agonists in Canadian dollars.

§ Double users group is the reference group

¶ Adjusted for age, gender, socio-economic status, strata of history of bronchodilator use, use of inhaled ipratropium bromide, inhaled β_2-agonists, nebulised β_2-agonists, nebulised ipratropium bromide, oral β_2-agonists, theophlline, inhaled corticosteroids, antibiotics, oxygen and respiratory hospitalisations during the year prior to cohort entry

** Weighted for the duration of follow-up

4.6.1 Cost savings estimation

The total cost impact for the introduction of Combivent® is presented in Table 4.17. During the 4,582 person-months of follow-up, total actual costs for bronchodilators in the Combivent® group reached $79,833, corresponding to $209.08 per patient-year. However, as computed in the multivariate analysis section (4.6), the use of Combivent® is associated with a 17 percent cost reduction. Accordingly, we computed the annual cost savings in Canadian dollars in this cohort based on the subjects initiated with the two-canister combination therapy. As shown in the first column of the table, the annual cost savings associated with the use of Combivent® in the cohort is obtained by multiplying the expected annual expenditure per patient for bronchodilators when treatment is not initiated with Combivent® (obtained from the reference group) by the adjusted estimation of costs reduction between the contrasted group (0.83) as estimated by the multivariate analysis. In this cohort of 641 subjects, initiation with Combivent® would represent an annual savings of $23,711. In column two of the table, we are extending the cost savings estimation to all subjects initiating treatment with Combivent® between July 1st, 1996 and June 30th, 1997, representing the cost impact associated with Combivent® users in Saskatchewan. Using the same figures, it is estimated that the savings over a one year period associated with use of Combivent® corresponds to $103,468 (95% CI: 48,694 – 146,082). This estimation is made under the assumption that Combivent® users excluded from the cohort present patterns of bronchodilator utilisation similar to the subjects included in the cohort. This issue will be addressed in the following section.

We also investigated the potential cost impact associated with a switch to Combivent® for all subjects using two-canister therapy. This estimation was possible inasmuch as the introduction of Combivent® did not alter significantly patterns of use of bronchodilators. For these patients a switch to Combivent® represents a saving of $64 per subject per year which corresponds to an overall saving of approximately $200,000.

Table 4.17. Savings associated with Combivent® use

	Combivent® users included in the cohort n=641	**All Combivent® users[¶]** n=1,621
Actual costs[*] per patient-year	209.08	271.34
Expected costs[†] per patient-year	217.59	375.49
Adjusted cost savings[‡] per patient-year	36.99	63.83
Total adjusted cost savings[§] per year	23,711	103,468

[*] Costs per subject per year for Combivent®, ipratropium bromide and inhaled β_2-agonists generated by patients initiated on Combivent®

[†] Costs per subject per year for inhaled bronchodilators in the reference group (patients initiated on the two-canister bronchodilator therapy)

[‡] Cost savings per subject per year associated with Combivent®use (based on an adjusted rate ratio of 0.83)

[§] Total cost savings per year for the entire group

[¶] All subjects initiating treatment with between July 1st, 1996 and June 30th, 1997 (before exclusion criteria) including the 641subjects used in the cohort

CHAPTER 5 – DISCUSSION

This chapter contains a discussion of the principal results described in Chapter 4 regarding both the patterns, and costs for the use of respiratory medications in the treatment of COPD. In addition, the limitations of this study are discussed.

5.1 Patterns of respiratory medications and antibiotics use

Although drug prescribing is one of the most important components of medical care, little is known about how prescribing practices are determined and how they can be influenced (Carter, 1996; Avorn, 1982). Concerns about potential misuse of a combination therapy comprising two existing medications, ipratropium bromide and salbutamol, are therefore justified. We conducted a study, in the context of actual medical practice, to determine the impact on heath care utilisation of the inclusion in the Saskatchewan drug formulary, of a combination product hypothesised to improve patient compliance by offering a less complex and more convenient regimen. We found that the introduction of Combivent® did not significantly alter patterns of use of bronchodilators, other respiratory drugs and antibiotics commonly used for the treatment of COPD. This study highlights three principal points regarding consumption of bronchodilators.

The first important result of this study is that the subjects initiated on Combivent® slightly increase their overall use of bronchodilators. More detailed analysis, however, found that the higher consumption of bronchodilators observed among users of the combined product is confined to previous users of inhaled β_2-agonists (Tables 4.13 and 4.14). On clinical grounds, this is likely related to the frequent "as needed" use of inhaled β_2-agonists to relieve acute symptoms. When changing therapy subjects previously using only a β_2-agonist inhaler to relieve their symptoms, some patients may continue their β_2-agonists

initially prescribed or utilised on an "as needed" basis in addition to their regular use of Combivent®. This will not be apparent among patients prescribed bronchodilator therapy for the first time and will be less apparent among patients previously using ipratropium bromide alone, an agent usually prescribed four to six times daily for best results (Pakes, 1980). For these patients a switch to Combivent® represents a minimal behavioural change. Moreover these patient do not have the opportunity to fill an old prescription for a β_2-agonist inhaler. It would be of interest to evaluate whether the subgroup using inhaled β_2-agonists during the year prior to cohort entry sustained an increase in use of inhaled bronchodilators over a longer period of time.

Two other factors may help explain the increase in overall use of inhaled bronchodilators among subjects started on combined bronchodilator therapy: 1) some patients may still require a separate β_2-agonist inhaler for breakthrough symptoms such as shortness of breath (COPD Guidelines Group of the Standards of Care Committee of the BTS, 1997), and 2) the criteria used to define the cohort does not allow for drug switching in the exposed group. For example, patients initiating therapy with Combivent® who later switch to two-canister combination therapy will still be considered as part of the Combivent® category. However, patients receiving a prescription of Combivent® after initiating treatment with ipratropium bromide and inhaled β_2-agonists in two separate canisters would be excluded from the cohort as prevalent users of the two products of interest. This is illustrated in part by the analysis restricted to regular users, where the differences observed were no longer significant. In this cohort, drug switching among users of Combivent® is minimised since subjects have to fill at least one prescription every three months for the drugs of interest in order to be included.

In order to ensure the rational use of bronchodilators, physicians and pharmacists have a crucial role to play when prescribing and dispensing a prescription for Combivent®. These health professionals have a key role in educating COPD patients. Before using Combivent®, patients should understand that it is intended to replace the combination of β_2-agonist and ipratropium

bromide therapy and because of this last component, the combined therapy must be taken regularly to result in an improvement of symptoms. Although some patients may require an additional β_2-agonist inhaler for breakthrough shortness of breath, a well-educated patient will be more responsible for his bronchodilator use.

A second feature of this study is that it provides evidence that Combivent® does not significantly affect market growth for combination therapy beyond that expected for patients switching from single agent to dual agent therapy, or initiating dual therapy. Since Combivent® includes two existing medications for a treatment that was previously available for physicians to prescribe, there are two likely scenarios leading to Combivent® use. Natural disease progression may require additional therapy or patients diagnosed later may have require combined therapy of treatment initiation. Such patients would have been prescribed two bronchodilators regardless of whether or not Combivent® was introduced. The second scenario is that patients switch therapy because Combivent® has become recently available (non-natural progression). As shown in Figures 4.1 and 4.2, the history of bronchodilator use of patients on combination therapy is comparable for the two contrasted groups, suggesting a natural progression to combined bronchodilator therapy either as Combivent® or as two separate inhaler devices. Therefore, in this population, non-natural initiation did not occur.

Finally, the third point concerning bronchodilator use that this study highlights is the large proportion of patients initiating dual therapy, either combined or in two different canisters, without any previous use of a single agent in the previous years. This might indicate a late diagnosis at a more advanced stage of disease. This finding might reflect the under use of spirometry (Kesten, 1993). Because there is such a large reserve of pulmonary function, the presence of symptoms can be extremely variable in patients with COPD, and the deterioration in airflow obstruction can proceed undetected for years if pulmonary function tests are not done. In fact, except in those individuals who engage in vigorous exercise, quite severe airflow obstruction is often present before any symptoms of COPD develop (National Lung Health Education Program Executive

Committee, 1998). COPD is a progressive disorder that necessarily passes through mild and moderate phases before becoming severe. From the 60 percent who were initiated directly on dual therapy, it is clear that an undefined number of patients presenting with severe disease have been "missed" by the health care system and did not have the opportunity to benefit from early interventions like smoking cessation or bronchodilator therapy. The rate of decline of FEV_1 following smoking cessation is less than that of current smokers and may approach that of non smokers (Fletcher, 1977). Interventions with bronchodilator and anti-inflammatory therapy have also been proposed as possibly interfering with the natural history of the disorder and studies are currently evaluating the effect of these agents on the course and the prognosis of COPD (Rennard SI, 1996; Dompeling, 1993; Connett, 1993; Wedzicha, 1993).

One of the initial hypotheses was that combining two frequently prescribed and regularly scheduled inhaled bronchodilator medications into one MDI would improve patient compliance. By rendering the treatment regimen less complex and more convenient, it would result a reduction of respiratory drugs and antibiotics use. Although Combivent® may have helped to reduce the complexity and increase the convenience of multidrug treatment regimens, we did not find any reduction in drug use. The rate of use of inhaled corticosteroids, a drug category exposing patients to unnecessary complications and additional expense, was also unchanged. These findings can be a sign of an inability to link improved symptom relief and drug utilisation.

5.2 Costs related to bronchodilator use

Our secondary outcome variable was costs related to bronchodilator use. We found a 20 percent per month reduction in total medication costs among patient using regularly the combination product. This is similar to an estimated cost savings of 28.6 percent when comparing the total average cost per prescription of Combivent® to the weighted average salbutamol/ipratropium bromide combination (Brogan Consulting Inc., 1996). This cost saving was possible only because, as seen in the previous section, the prescription habits and patterns of bronchodilator use remain unchanged with the introduction of Combivent®. The difference in the magnitude of the two estimates is explained mainly by the fact that subjects were dispensed less than one prescription per month (or two prescriptions in the reference group) and Combivent® users tended to use more bronchodilators. The pressing need for more efficient allocation of resources in health care has stimulated interest in economic evaluation studies. Whereas the first studies tended to concentrate on the most visible applications of modern advanced diagnostic and therapeutic technology in medicine, the focus is gradually shifting to more routinely applied treatment. Although these are less expensive per unit of output, they often lead to much higher costs, because of their wide application in much larger populations, who often need long-term care. The treatment of COPD is characterised by long-term drug therapy, therefore, any therapy, like Combivent®, that affects the cost of this common respiratory ailment, impacts upon total health care costs. This is well illustrated when translating the monthly difference in mean costs between the two groups into actual annual cost savings. In Saskatchewan, the introduction of Combivent® reduced expenses related to inhaled bronchodilator use by an estimated $104,000. However, this result is based on the following assumption: patient dynamics of bronchodilator therapy, as determined by the users of Combivent® included in the cohort, are the same for all Combivent® users. This assumption is not problematic for prevalent double users initially excluded, since they represent a more severely impaired group of subjects consuming more

bronchodilators. Therefore we believe that this provides a conservative estimate, of cost savings underestimating the cost reduction associated with Combivent® in this group. However, it is possible that patterns of bronchodilator use differ among Combivent® users excluded for a follow-period of less than 90 days. This limitation is inherent to the study design evaluating the impact of Combivent® in the year following its introduction; only a longer period of follow-up could answer this uncertainty.

The resources allocated to COPD hospitalisations represent an important part of the total costs associated with this disease. Although the tendency of reduced hospitalisations observed could not clearly be related to the use of Combivent®, as discussed in the preceding section, we can not entirely eliminate the hypothesis that the availability of Combivent®, by facilitating patient compliance and enhancing symptomatic relief may reduce patient outcomes such as hospitalisations and mortality.

5.3 Hospitalisation and mortality

Our last objective was to evaluate the eventual impact of Combivent® on patient outcomes such as hospitalisations and mortality. A lower mortality rate and a tendency to decrease respiratory-related hospitalisations were associated with the use of Combivent®. A slightly younger age and shorter follow-up period in the double users group may partially explain these findings. We think that it is unlikely that the introduction of Combivent® is responsible for these improvements in patient outcome. These results suggest rather a difference in the severity of the disease among the contrasted groups. Up to now, interventions with bronchodilators have never been reported as interfering with the natural history of this disorder and the goals of this therapy are limited to the relief of symptoms and an improvement in the quality of life. The Lung Health Study suggested that bronchodilator therapy, in the form of ipratropium bromide, does not slow the gradual decline in lung function, even though there is a

potentially useful and prolonged pharmacological effect that is undiminished over 5 years (Anthonisen, 1994). However, knowing that symptoms (more than pulmonary functions results) drive health care utilisation, a possible link between greater symptom relief and improvement of outcomes, as observed in this study, can not completely be ruled out. Further research will have to be carried out to answer this question.

5.4 Limitations

There are several limitations inherent in the design and the source of data for this study. The limitations, which include possible confounding, misclassifications, bias in selection of the cohort and quality of the computerised data are discussed in some detail in the sections that follow.

5.4.1 Confounding

Our cohort approach, attempted to emulate a clinical trial. Clearly, however, subjects were not randomised to their intervention group and may consequently have differed with respect to their disease status, comorbidity and unmeasured confounders. The cohort was selected so as to exclude subjects for whom the main indication for treatment initiation with bronchodilators was not COPD. Study subjects were identified using the Saskatchewan prescription database. While the two drugs of interest are used for the treatment of both COPD and asthma, ipratropium bromide combined with inhaled β_2-agonist is used primarily for the treatment of COPD. Current asthma treatment guidelines, relegate ipratropium bromide to fourth line therapy (British Thoracic Society, 1993; Ernst, 1996; National Heart, Lung, and Blood Institute, National Institutes of Health, 1992; National Institutes of Health, 1991). Patients who were dispensed drugs indicated essentially for the treatment of asthma (such as nedocromil sodium, sodium cromoglycate and ketotifen) in the two years prior to cohort entry

or during the follow-up, were also excluded. Knowing that COPD generally affects middle-aged and older individuals with a mean age of onset for dyspnea related to COPD of 45 years, inclusion of only older patients minimized the number of asthmatic subjects included in the cohort.

Comorbidity and the use of health services in the year preceding initiation of therapy, being the strongest predictors of health services utilisation during follow-up, were quantified using prescription drug and hospitalisation data and adjusted for in all analyses. Nonetheless, the results might still be influenced by other factors not documented such as the smoking status, physician characteristics or severity of COPD. It is clear that the clinical presentation of COPD can vary in severity from simple chronic bronchitis without disability to a severely disabled state with chronic respiratory failure. Having no access to diagnostic codes, or medical history to quantify patients severity of disease, and knowing that pharmacotherapy is initiated based on the severity of the disease, to maximize the comparability of the contrasted groups, we restricted cohort entry to incident users of dual bronchotherapy. Patients were expected to present similar degrees of severity requiring the addition of a second bronchodilator or the initiation of combined inhaled bronchodilator therapy for patients diagnosed later in the course of the disease. Moreover, considering that COPD generally affects middle-aged and older individuals and the course of the disease is characterized by a slowly progressive airways obstruction, age is likely to be an important marker of disease severity. The last aspect to consider is hospitalisations. Hospitalisations following acute respiratory failure usually occur later in the course of the disease and are associated with a poor long-term prognosis and therefore also reflect disease severity.

Non-experimental studies are susceptible to bias from confounding by indication of the prescribed drugs, whereby selective prescribing of a specific agent may lead to a lack of comparability between the contrasted groups with regard to the outcomes under study (Miettinen, 1983). In our analysis, COPD is likely to be the main indication for the selection of a specific agent. Having no access to clinical or physiological measures of the severity of COPD, potential

confounding by indication had to be addressed with solely prescription and hospitalisation data. Restricting comparisons to one therapeutic class can minimise confounding by indication (Strom, 1983). Furthermore, since neither official guidelines nor medical textbooks discriminate between the two alternatives compared in our study when recommending bronchodilator agents at treatment initiation, confounding by indication appears unlikely to present a large threat. To further reduce the likelihood that confounding by indication might bias the results, we controlled for factors believed to be determinants of drug use and health services. Despite all these adjustments, however, residual differences may have remained between the contrasted subjects.

Furthermore, the adopted "intention-to-treat" principle used in the main analysis does not take into account the different patterns of use such as multiple drug therapy, drug switching or stopping, duration of use and adherence to treatment. Consequently, the assumed treatment may not have held true for all subjects and may have distorted the results, especially when non-adherence to initial treatment is systematically associated with the use of health services. However to overcome this limitation, we conducted an analysis confined to regular users of the treatment of interest which gave substantially the same results.

5.4.2 Exposure and outcome misclassifications

The validity of information contained in the health care utilisation databases of Saskatchewan Health has been assessed in different ways. Validity studies have shown excellent concordance (99 per cent) between procedures documented in the Hospital Services Branch data file and medical charts (Rawson N, 1994). Similarly, concordance between diagnoses in the hospital file and those in medical charts (of patient with acute myocardial infarction) was extremely high (97 per cent) (Rawson N, 1994). There are also a multiple of checks carried out on each field of information on the claim submitted to the drug plan before the claim is approved for payment (Strand, 1994). The checks include verification that the person was eligible for benefits under the

program and that the drug dispensed was eligible for benefits under the program. In addition, on a regular basis, a sample of paid claims is selected and the beneficiaries are requested to confirm that the service paid for had been provided and that all the information on the claim was correct. It is for this reason that the Saskatchewan databases have come to be recognized as a major resource in epidemiologic research.

Potential misclassification of the exposure is possible due to the fact that dispensed prescriptions, as indicated by the database, may not correspond exactly to the medications actually taken. Therefore a subject classified, for example, as a Combivent® user, may in fact be a non-user or could use actually only one bronchodilator. However this situation is unlikely to occur in the restricted cohort, since it is hard to imagine a subject regularly filling a prescription and then not taking the drug.

The possibility of outcome misclassification with regard to any of the outcomes in this study is extremely remote. Respiratory related hospitalisations have been broadly selected, encompassing not only respiratory hospitalisations classified as due to COPD. Moreover, acute respiratory failure in COPD patients is a condition easily diagnosed with the degree of change from the usual state of the individual patient (Ingram RH, 1994). Some outcome misclassification is to be expected, although this is not expected to be differential across the two groups. Thus, any non-differential misclassification of outcomes would bias the result in the direction of the null and provide a conservative estimate of costs (Rothman KJ, 1986).

5.4.3 Selection bias

It is clear that when restricting the cohort to regular users of two bronchodilators, we selected a more impaired group of patients, with monthly rates of drug use almost doubling. Of more concern is the appearance of a discrepancy in the duration of follow-up between the two groups. This resulted from the requirement that the reference group sustain the regular use of separate drugs, inhaled β_2-agonist and ipratropium bromide, compared to only

one canister in the case of those prescribed Combivent®. Subjects included in the reference group of the restricted cohort are therefore a group of highly compliant patients, and thus their number is limited. This, however, confirms the hypothesis that by combining two frequently prescribed regularly scheduled inhaled bronchodilator medications into one MDI, patient compliance with prescribed therapy improved by rendering the treatment regimen less complex and more convenient. A useful conceptual distinction between selection bias and confounding is whether or not the bias can be removed in the analysis (Rothman, 1986). While it is possible to control for the duration of follow-up in the analysis and the problem of selection bias is better viewed as one of confounding, measurements of compliance in this cohort are unavailable, therefore introducing a selection bias.

Computing the rate of regular use over the entire period of follow-up favoured the inclusion of subjects with a shorter period of follow-up. Ideally one would have liked to define a period of exposure up to 90 days from the day following the dispensation of the prescription through to the day following the last scheduled day of supply or until another drug of interest is dispensed. Alternatively, where no other drug were to be dispensed, the subject would then be censored after the 90 day period, ensuring a more realistic contribution to person-time. This longer period of follow-up for the Combivent® group should have generated more drug use, and by the same extent, more costs, therefore biasing the results against the initial hypothesis.

5.4.4 Limitations of the data

Another limitation of this study stems from the use of computerised databases of drug dispensation. Dispensed medication may not represent actual intake of these drugs, which could result in a dilution of the measures of effect. Whereas reliance on data from computerized databases has inherent weaknesses, and the use of non-experimental designs can be problematic, the strengths of such studies are being increasingly recognized. Besides the obvious advantage of a large sample size, there is the added merit of a prolonged follow-

up at a relatively inexpensive cost. If the non-experimental study is well-designed and properly analysed, it can produce useful information at a fraction of the time and cost needed by the experimental design. An additional methodologic advantage of database studies is that, being set in the context of actual medical practice, they provide information of greater relevance than what is obtained within the artificial confines of a clinical trial. It is in fact for these reasons that the outcomes research movement has advocated the creation of databases, recording routine medical practice information, for the purpose of appropriate medical research (Elwood PM, 1988; Relman 1988; Epstein AM, 1990).

Finally, because this study was carried out using data from only one year, with a follow-up ranging from 3-12 months, it was not possible to investigate whether a cohort effect existed in the outcomes under study; that is, the question of whether there have been any changes in the extent to which is Combivent® substituted for dual bronchodilator therapy, rates of drug utilisation and hospitalisation during the time period of the study could not be addressed.

CHAPTER 6 – CONCLUSION

This last chapter provides a summary of the conclusions drawn from the results and discussion of the previous two chapters.

1) This study shows that the introduction of Combivent® did not alter the patterns of use for bronchodilators, other respiratory drugs and antibiotics related to the treatment of COPD and did not increase the market growth for combination therapy beyond the natural rate of progression expected for patients switching from single agent therapy to dual agent therapy. Previous users of inhaled β_2-agonists tend to continue to fill prescriptions for these drugs in addition to their regular use of Combivent®. Moreover, some patients may still require a separate β_2-agonist inhaler for breakthrough shortness of breath, partially explaining the slight increase in overall use of inhaled bronchodilators associated with Combivent®.

Regular users of Combivent® were more numerous and were followed for a longer period of time, confirming the hypothesis that by combining two frequently prescribed regularly scheduled inhaled bronchodilators into one metered dose inhaler, patient compliance would improve.

2) The availability of a single metered dose inhaler that produces both anticholinergic and β_2-adrenergic bronchodilating effects provides substantial cost savings to both the patient and the health care system. The costs reduction may even be more considerable when taking into account the eventual reduction in patient outcomes such as hospitalisations and mortality realised through improved better symptomatic relief associated with better compliance.

3) Despite a lower mortality rate, and a tendency to decrease respiratory related hospitalisations associated with the use of the combination product, we were unable to entirely control for confounders and clearly demonstrate a link between better symptom control, and a reduction in health care utilisation and drug use. Further studies are needed to evaluate the role of the intervention of bronchodilator therapy on these major outcomes.

4) Participation of health care professionals is essential to ensure rational use of bronchodilators. The act of prescribing or dispensing a prescription represents a good opportunity for physicians and pharmacists to educate COPD patients regarding the disease and its treatment. Patients have to understand that Combivent® replaces the combination of a β_2-agonist and ipratropium bromide and should be taken regularly to observe any improvement in symptoms. Although some patients may require an additional β_2-agonist inhaler for breakthrough shortness of breath, a well educated patient will be more responsible for his bronchodilator use.

Lastly, further study is required to address issues in diagnosis and early detection since a large proportion of patients initiated dual bronchodilator therapy, either combined or in two different canisters, without prior use of a single agent, possibly indicating that some patients may have been identified late in the course of illness.

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Appendix 1. Summary of the studies evaluating combined inhaled bronchodilator therapy

Authors	Design	Sample size	Disease	Bronchodilators	Follow-up (days)	Main results
Barros, 1990	Retrospective cohort	296	Not specified	Ipratropium Salbutamol	-	For 33% of subjects who responded inadequately to salbutamol, bronchodilation was increase after the addition of ipratropium*
Casali, 1979	Randomized crossover	27	Chronic bronchitis Asthma	Ipratropium Salbutamol	3	Strong bronchodilating activity (↑ FEV_1 and V_{60}) with the combination
CIASG, 1994	Randomized double-blind controlled trial	534	COPD	Ipratropium Salbutamol	85	Combination is superior in peak effect, during the first 4 hour and in the total area under the curve of the FEV_1 response*
Easton, 1986	Double-blind placebo controlled trial	11	COPD	Ipratropium Salbutamol	4	Subsequent effect of a second inhaled bronchodilator was not greater than that of placebo
Frith, 1986	Double-blind placebo controlled trial	24	Chronic airway obstruction	Oxitropium Fenoterol	6	Combination produced more prolonged bronchodilation*
Lees, 1980	Crossover	35	Chronic bronchitis	Ipratropium Salbutamol	3	Bronchodilation with combination tended to be greater and lasted longer, in some cases >20% ventilory improvement
Leitch, 1978	Double-blind placebo controlled trial	24	Chronic bronchitis	Ipratropium Salbutamol	5	Greater increase in FEV_1 and FVC with the combination

* Results statistically significant

Appendix 1. Summary of the studies evaluating combined inhaled bronchodilator therapy (continuation)

Authors	Design	Sample size	Disease	Bronchodilators	Follow-up (days)	Main results
Lightbody, 1978	Crossover	21	Chronic bronchitis Bronchial asthma	Ipratropium Salbutamol	3	Combination therapy more than double the FEV_1 *
Lloberes, 1988	Single-blind crossover	13	COPD (exacerbation)	Ipratropium Salbutamol Aminophylline	3	The addition of a second bronchodilator did not result in significant increments of bronchodilation
Marlin, 1986	Double-blind placebo controlled trial	8	Chronic airway obstruction	Ipratropium Fenoterol	4	Improved FEV_1 with combination at various times*
Morton, 1984	controlled trial	122	Chronic bronchitis Asthma	Ipratropium Fenoterol	42	Global rating by physicians and patients showed that 76% of the patients improved with combination*
Petrie, 1973	Double-blind controlled trial	16	Bronchitis Asthma	Ipratropium Salbutamol	4	Slightly greater and longer response with the combination
Serra, 1986	Prospective cohort study	15	COPD	Ipratropium Fenoterol	84	Combination produced clear improvements in respiratory function and symptomatology*
Wesseling, 1992	Double-blind crossover	22	COPD	Ipratropium Fenoterol	3	Increase of 38% in FEV_1 after the combination*

* Results statistically significant

APPENDIX 2

Appendix 2. Drugs of primary interest

Description	Dosage form
INHALED BRONCHODILATORS	
Combivent®	MDI*
Ipratropium	MDI
Inhaled β_2-agonists	
Salbutamol	MDI
Fenoterol	MDI
Terbutaline	MDI
Isoproterenol	MDI
Procaterol	MDI
Metaproterenol	MDI
OTHER RESPIRATORY DRUGS	
β_2-agonists	
Ipratropium	NEB†
Salbutamol	NEB, TAB‡, LIQ§
Fenoterol	NEB, TAB
Terbutaline	TAB
Metaproterenol	TAB, LIQ
Corticosteroids	
Beclomethasone	MDI
Betamethasone	TAB
Budesonide	AER, NEB
Dexamethasone	TAB
Fludrocortisone	TAB
Flunisolide	AER
Fluticasone	AER
Hydrocortisone	TAB
Methylprednisone	TAB
Prednisolone	LIQ
Prednisone	TAB
Triamcinolone	AER, TAB
Theophyllines	
Aminophylline	TAB
Oxtriphylline	TAB, LIQ
Theophylline	TAB, LIQ

* Metered dose inhaler, including capsule powder and disk powder for inhalation
† Liquid for inhalation by nebulisation
‡ Tablet, including oral and capsule sustained release capsule
§ Oral liquid, including oral suspension and oral syrup

Appendix 2. Drugs of primary interest (continuation)

Description	Dosage form
ANTIBIOTICS	
Cephalosporins	TAB[‡], LIQ[§]
Macrolides	TAB, LIQ
Tetracyclines	TAB, LIQ
Sulfonamides	TAB, LIQ
Fluoroquinolones	TAB

[‡] Tablet, including oral and capsule sustained release capsule
[§] Oral liquid, including oral suspension and oral syrup

APPENDIX 3

Appendix 3. Definition of dependent and independent variables

Variable definition	Unity / Coding	Characteristics
Age	years	Continuous variable
Antibiotics	Number of prescriptions	Continuous variable
Bronchodilators	Number of prescriptions	Continuous variable
Costs of bronchodilators	Canadian dollars	Continuous variable
Death	0 = no death 1 = death during follow-up	Dichotomous variable
Gender	0 = female 1 = male	Dichotomous variable
Hospitalisations	Number of hospitalisations	Continuous variable
Inhaled corticosteroids	Number of prescriptions	Continuous variable
Nebulized β_2-agonists	Number of prescriptions	Continuous variable
Nebulized ipratropium	Number of prescriptions	Continuous variable
Oral corticosteroids	Number of prescriptions	Continuous variable
Other respiratory drugs	Number of prescriptions	Continuous variable
Oxygen therapy	Oxygen use on a monthly basis	Continuous variable
Respiratory hospitalisations	Number of hospitalisations	Continuous variable
Social Assistance	1 = yes 0 = no	Dichotomous variable
Strata	0 = naive patients 1 = previous use of inh. β_2-agonists 2 = previous use of ipratropium	Categorical variable
Thephyllines	Number of prescriptions	Continuous variable