ADHERENCE TO MEDICATION IN PATIENTS WITH HEART FAILURE: EFFECT ON MORTALITY AND HOSPITALIZATION

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By
Darcy Alan Lamb

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ABSTRACT

Heart failure is a chronic condition that increases the risk for death and disability. Beta blockers and ACE inhibitors have become standard treatments in heart failure because clinical trials have demonstrated their beneficial effect on mortality and morbidity in these patients. As not much is known about adherence to these medications, the main objectives of this project were to determine long term adherence to ACE inhibitors and beta blockers and determine how various degrees of adherence to a beta blocker can affect major health outcomes in patients with heart failure.

Data was obtained from Saskatchewan health from January 1, 1994 to December 31, 2003 for all heart failure patients from their first hospitalization for heart failure. Adherence was calculated using the fill frequency measure of adherence, and all survival analyses were completed using the Cox proportional hazards model.

Although 14, 000 patients were admitted to hospital for a first admission for heart failure, only 1143 subjects started a beta blocker and 5084 subjects started an ACE inhibitor within 3 months of the index hospitalization. Within the first year, adherence was excellent for both beta blockers (80.8 percent) and ACE inhibitors (82.5 percent). The proportion of patients remaining adherent slowly decreased to reach approximately 60 percent, for both medication classes, after 4 years. There was no significant difference in all-cause mortality between patients with high adherence and low adherence, but there appeared to be a trend towards decreased survival time in

those remaining adherent throughout the study period [HR = 1.18 (95% CI: 0.98 to 1.43; p=0.07)].

Since the overall rate of adherence to beta blockers was excellent in most patients during the first year, it is possible that non-adherence is not responsible for a significant burden of mortality in Saskatchewan heart failure patients, and perhaps and the focus of quality improvement should be optimal prescribing of evidence-based therapies, and continued adherence over time.

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1. INTRODUCTION

1.1 Rationale

Heart failure is a progressive disease that is associated with a significantly shortened lifespan as well as debilitating symptoms that often require hospitalization. [1] The average lifespan of a patient diagnosed with heart failure is approximately two years, and 50 percent will be hospitalized within the first year of diagnosis [2-4]. Recent reports estimate the prevalence to be between 1 and 7 percent, however, the number of afflicted individuals is expected to rise as the population ages. [4-8]

Specific classes of medications are known to decrease the risk of hospitalization and death in heart failure patients. [1, 9, 10] Of these medications, certain beta blockers seem to have the most pronounced effect on decreasing mortality as demonstrated by several high quality randomized controlled trials. However, not much is known about the success of these agents in a real world setting. Currently, there is only one trial examining adherence rates to beta blockers, and one trial examining the effect of non-persistence to beta blockers on mortality rates.

1.2 Purpose of the Study

The purpose of the study was to determine the real world adherence to beta blockers and ACE inhibitors in subjects after an initial hospital diagnosis of heart failure, and evaluate if poor adherence to beta blockers in these patients is associated with an increased risk for death or hospitalization in Saskatchewan.

1.3 Objectives

The Primary Objectives of this study are as follows:

A) Determine long term adherence to the major medications used in heart failure, namely ACE inhibitors and beta blockers.

B) Determine how various degrees of adherence to beta blockers can affect major health outcomes.

The Secondary Objectives of this study are as follows:

A) Determine predictors of beta blocker adherence.

B) Determine average doses of beta blockers used in heart failure in Saskatchewan.

C) Examine trends in the initiation rates for beta blockers and ACE inhibitors in Saskatchewan over a 10 year period (1994 to 2004).

1.4 Study Hypothesis

The majority of heart failure patients receiving beta blockers do not continue this therapy for the long term. This lack of adherence negates the full mortality benefit that might accompany improved prescribing rates observed in recent years.

Heart failure patients who are non-adherent to beta blocker therapy will exhibit greater morbidity and mortality than adherent patients but less morbidity and mortality than those not prescribed this drug therapy.

1.5 Significance of the Study

Despite the wealth of controlled clinical trials demonstrating benefits of heart failure medications, very little is known about the use of these drugs, especially beta-blockers, in real world settings. This study provides information about both

prescribing and subsequent adherence to heart failure medications that will reflect the extent to which clinical evidence has been translated into usual clinical practice in Saskatchewan. Care-gaps identified by this study may direct action on the part of health care professionals to ensure that heart failure patients in the community are receiving the best possible medical care.

1.6 Abbreviations

ACE: angiotensin converting enzyme

ARB: angiotensin receptor blocker

RAAS: Renin-Angiotensin-Aldosterone System

EF: ejection fraction

OR: odds ratio

1.7 Disclaimer

This Study is based in part on de-identified data provided by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

2. LITERATURE REVIEW

2.1 Heart Failure

Heart failure is a progressive clinical syndrome resulting from a cardiac disorder that impairs the ability of the heart to pump blood throughout the circulatory system to meet the metabolic demands of the body. [1, 10-13] This impaired ability is due to a problem with ventricular relaxation and filling during diastole, ventricular contractile dysfunction during systole, or a combination of the two. As such, heart failure is broken into two broad categories, systolic and diastolic heart failure. [1, 10-13] Approximately twenty to fifty percent of incident cases of heart failure have preserved systolic function, [14, 15] but this may not be apparent in clinical practice if diagnostic testing is not performed.[1, 10, 16] The demographics, prognosis, left ventricular structure and function between these two groups differ significantly. [17] Treatment of diastolic heart failure is similar to that of systolic heart failure, although this has not been firmly assessed by clinical trials. [1]

The clinical syndrome of heart failure is characterized by signs and symptoms that can include fatigue, pulmonary and peripheral edema, bibasilar rales, pleural effusion, dyspnea, orthopnea, cough, wheezing, and decreased exercise tolerance. [1, 10, 11, 18, 19] Based on a patient's symptoms, their condition can be categorized into one of four functional classes developed by the New York Heart Association (NYHA). Patients in NYHA class I have symptoms of heart failure only at levels of exertion that would limit normal individuals. As a patient's class increases, so does their severity of

heart failure such that patients with NYHA class IV have symptoms at rest. [1, 11, 18] Symptoms of heart failure decrease patient quality of life especially when compared to both the normal population and other disease groups in regards to physical, mental and social functioning. Patients with heart failure report more severe physical impairment then patients with a history of arthritis or chronic lung disease. [20]

Heart failure usually begins with some primary insult and a resultant change to the myocardium. Major causes include coronary artery disease, hypertension, valve disease and dilated cardiomyopathy, of which genetics can play a role in up to thirty percent of patients. [1, 16, 19, 21] Control of risk factors that can damage the heart, such as hypertension, atherosclerotic disease and diabetes mellitus can help to prevent or delay the development of the disease. [1, 22] In fact, treatment of hypertension has shown a relative risk reduction of twenty-nine to over fifty percent. [23-26] Once developed, progression of heart failure is most influenced by activation of certain neurohormonal systems, such as the sympathetic nervous system and the renin-angiotensin-aldosterone system. These systems, which offer benefit to the failing heart in the short term, adversely affect myocardial function over time, resulting in increased hospitalization and death rates. [1, 10, 11, 15, 27]

2.2 Epidemiology of Heart Failure

2.2.1 Incidence and Prevalence

Currently, the average age of heart failure patients at first presentation ranges from 73 to 80 years, with women being older when first diagnosed compared to men. [3, 21, 28-30] The overall incidence of heart failure has been estimated to be between 4.2

and 14.4 per 1000 person-years, with the rates consistently higher among males in all age groups studied, [3, 5, 28-30] whereas, prevalence rates for heart failure range from 12 to 70 per 1000 people, with prevalence being roughly equal between the sexes. [4-8] Both incidence and prevalence increase dramatically with age such that 17 percent of the population over the age of 85 have heart failure. [3, 5-8, 21] With new therapies prolonging the life of heart failure patients, and the mean age of the population increasing, it is expected that the prevalence of heart failure will increase over time. [1, 2]

2.2.2 Hospitalization

The number of patients hospitalized with a principal diagnosis of heart failure has seen an increase of up to 53 percent over the last 2 decades for both men and women. [31, 32] Rates of hospitalization for heart failure also increase with age, such that at least 75% of patients hospitalized for heart failure are over the age of 65. [2, 31-33]

In Canada, heart failure accounts for a total of 1.38 million hospital days over a one year period. [34] When heart failure was compared to other major disease states, it was shown to have the second highest total number of hospital days and the third highest number of patients affected. [34] Two-thirds of the cost of heart failure is due to hospitalizations, with health care utilization rising with increasing disease severity. [35] The economic impact of heart failure is enormous in the developed world, accounting for 1-2% of global health care budgets. [35]

2.2.3 Mortality

From the initial diagnosis of heart failure, epidemiological studies have shown that mean survival time is approximately 24 months. [3] Case-fatality rates appear to be highest during the first 3 months after diagnosis, with 4 to 11 percent of people dying within the first 30 days, 17 to 28 percent within 1 year, and 46 to 59 percent within 5 years. [3, 29, 30] Fortunately, trends in death rates have shown a decrease over the last 50 years with a decline of approximately 12 percent per decade. [29, 30] This improvement in survival can be attributed to new therapies for treating heart failure. [36]

2.3 Neurohormonal Activation in Heart Failure

The first step in the development of heart failure is usually some kind of initial injury to the myocardium that results in a prolonged decrease in both cardiac output and function. [1, 37] To counteract this decreased cardiac output, certain neurohormonal systems are activated, primarily the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), which provide a transient maintenance of normal cardiac output. [37] Over time, constant activation of these systems cause progression of heart failure and increase the risk of hospitalization and death. [15, 19, 37, 38] Cardiac remodeling also occurs, usually causing dilation of the ventricle, resulting in a more spherical shape to the heart. This not only increases myocardial wall stress, but can cause mitral regurgitation, and increase the risk of arrhythmia. [15, 39]

The adverse pathophysiologic effects of RAAS seen in heart failure are mostly driven by angiotensin II and aldosterone. [37, 38] Activation of the angiotensin-1 receptor by angiotensin II brings about vasoconstriction, and release of aldosterone,

catecholamines and vasopressin, leading to sodium and water retention, and increased sympathetic bombardment. Angiotensin II can activate growth response genes leading to hypertrophy of the myocardium, and can also cause alterations in the collagen make-up of the heart. [37] Aldosterone increases sodium and water retention, and stimulates collagen production resulting in myocardial fibrosis. Aldosterone also increases potassium and magnesium excretion, and may prevent uptake of norepinephrine by the heart, thus promoting arrhythmia formation. [37]

It has been shown that there is both an increased and sustained sympathetic stimulation of cardiac tissue in patients with heart failure. Although short term activation helps maintain cardiac performance, long term activation leads to many alterations in the beta adrenergic signal transduction system, one of which is down regulation of beta receptors. [37, 39-42] As a result of these and other changes that occur in the heart over time, routine contraction becomes suboptimal. In addition to cardiac myocyte contractile dysfunction, chronic elevated sympathetic activity also leads to myocardial necrosis and induction of apoptosis. [39, 42]

2.4 Use of Drug Therapy in Heart Failure

In addition to diuretics, which regulate fluid volume and control symptoms, beta blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and aldosterone antagonists have become the mainstay of drug therapy in heart failure. These medications block the neurohormonal systems in the body most responsible for the progression and worsening of heart failure and can prolong the life

of many patients. In addition, they have been shown to improve symptoms over time, and increase patient quality of life. [1, 9, 10]

2.4.1 Use of ACE Inhibitors in Heart Failure

ACE inhibitors have been part of the drug regimen of heart failure for the last two decades. [1] They work by inhibiting the ACE enzyme responsible for conversion of angiotensin I to angiotensin II, and also the breakdown of bradykinin, a vasodilatory hormone. Through this action, ACE inhibitors cause vasodilation, and help to attenuate the rest of the RAA system. [37] Various ACE inhibitors have been studied in both chronic heart failure and in left ventricular dysfunction following a myocardial infarction. They have not only been found to provide improvements in signs and symptoms of heart failure, but to decrease mortality and hospitalizations. [43-48] When used in heart failure, it is suggested that the benefits of ACE inhibitors are due to a class effect, and thus any one could be used. [49]

Several randomized controlled trials have demonstrated the significant benefits of ACE inhibitors in patients with heart failure [Table 2.1]. [43-48] Three of the trials, CONSENSUS[46], SOLVD[43], and ATLAS[45] examined patients with chronic heart failure whereas AIRE[44], TRACE[47], and SAVE[48] were trials involving patients with left ventricular dysfunction following a myocardial infarction. Seventy to eighty-two percent of all trial subjects were male with a mean age of approximately 65 years, and most patients were in class II or III heart failure, with the exception of CONSENSUS which included only class IV patients. [43, 45, 46]

Table 2.1. Summary of Landmark ACE Inhibitor Heart Failure Trials [43-48]

Trial	CONSENSUS	SOLVD	ATLAS	AIRE	TRACE	SAVE
Sample Size (size in treatment)	253 (127)	2569 (1285)	3164 (1568 HD**) (1596 LD**)	1986 (1004)	1749 (876)	2231 (1115)
Description of Patients	Chronic HF; NYHA IV	Chronic HF; Mostly NYHA II-III	Chronic HF; Mostly NYHA III	Post-MI HF	Post-MI HF	Post-MI HF
Drug	Enalapril	Enalapril	Lisinopril	Ramipril	Trandolapril	Captopril
Mean Dose Achieved / day	18.4mg	16.6mg	HD – 33.2mg LD – 4.5mg	Not reported (10mg target)	Not reported (4mg target)	Not reported (150mg target)
Mean/Median Follow-up	188 days	41.4 months	45.7 months	15 months	Not reported	42 months
Total Mortality (%)*	39 vs 54 RRR = 27%	35 vs 40 RRR = 16%	43 vs 45 NS	17 vs 23 RRR = 27%	35 vs 42 RRR = 22%	20 vs 25 RRR = 19%
CV Death (%)*	35 vs 51 RRR = 31%	31 vs 36 RRR = 18%	37 vs 40 NS	-----	26 vs 33 RRR = 25%	17 vs 21 RRR = 21%
Sudden Death (%)*	11 vs 11 NS	-----	-----	-----	12 vs 15 RRR = 24%	9 vs 11 NS
Admission to Hospital*	-----	69 vs 74 RRR = 7%	RRR = 13%	-----	-----	-----

HR = heart failure; MI = myocardial infarction; RRR = relative risk reduction; CV = cardiovascular; NS = not statistically significant
* percentage of events in active treatment versus placebo
** LD = low dose and HD = high dose. There was no placebo control in this trial

2.4.2 Use of Beta Blockers in Heart Failure

Beta blockers exert their beneficial effects by blocking the sympathetic nervous system at beta receptors. [1, 11, 39, 40, 42] Blocking these receptors in the heart reduces the negative impact norepinephrine has on cardiac remodeling and myocyte survival. Furthermore, in contrast to traditional concerns that beta blockers may be detrimental because they reduce heart rate and cardiac output, these agents actually can improve myocardial function by prolonging ventricular filling time, resulting in a more productive heartbeat. [50]

Three beta blockers have been extensively studied and have shown a decrease in morbidity and mortality in heart failure patients. These beta blockers are metoprolol

and bisoprolol, which are beta-1 specific, and carvediolol, a non-specific beta blocker with alpha-1 blocking properties. [1, 11, 51-57] Atenolol, a beta-1 specific beta blocker has not been studied in heart failure, but is widely used for the condition, and is assumed to work due to properties similar to metoprolol and bisoprolol. [58] However, it is generally accepted that the benefits of beta blockers in heart failure are not a class effect and the use of proven drugs is recommended. [1, 9, 40, 59]

Table 2.2 gives a brief summary of major landmark trials of beta blockers used in heart failure and their major outcomes. [52-56, 59] For the most part, these trials included patients in NYHA class II and III, with the exception of COPERNICUS [54], which had class IV patients. Three quarters of all study patients were male and the vast majority were white. The mean age of patients in these trials was approximately 62 years. Total mortality was shown to be reduced by 23 to 65 percent. [51-56, 59]

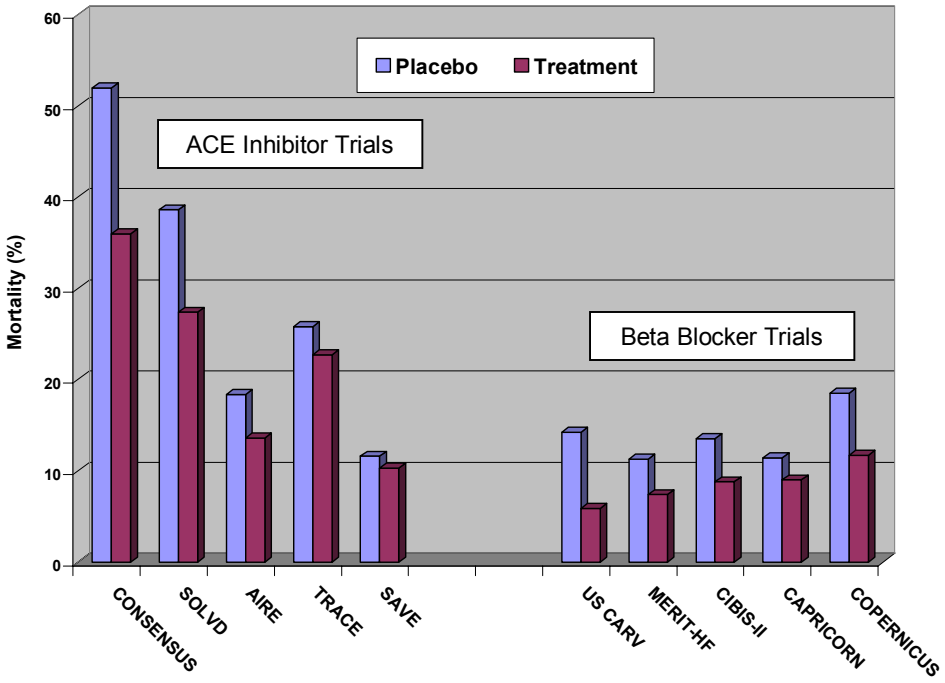
The main reason for using both beta blockers and ACE inhibitors in heart failure is their ability to reduce mortality and hospitalizations. Prior to the introduction of beta blocker use in heart failure, the only medications proven to consistently reduce mortality were ACE inhibitors, which decreased death rates by approximately 23 percent. [43-48, 60] In the beta blocker trials, significant mortality benefits were observed despite the fact that over 95 percent of patients were already taking an ACE inhibitor [Figure 2.1]. [51-56, 59] With the introduction of both these medications into the drug therapy regimen of heart failure patients, great strides have been made in reducing the death rate. One year mortality can now approach 11.5 percent compared to 17 to 28 percent seen prior to beta blocker use. [3, 29, 30, 52-56]

Table 2.2. Summary of Landmark Beta Blocker Heart Failure Trials [52-56]

Trial	US Carvedilol HF Study	MERIT-HF	CIBIS-II	COPERNICUS	CAPRICORN
Sample Size (size in treatment)	1094 (696)	3991 (1990)	2647 (1327)	2289 (1156)	1959 (975)
Drug	Carvedilol	Metoprolol CR/XL	Bisoprolol	Carvedilol	Carvedilol
Description of Patients**	Mostly NYHA II-III; EF~23%	Mostly NYHA II-III; EF~28%	Mostly NYHA III; EF~27%	NYHA IV; EF~20%	Post-MI HF; EF~33%
Mean Dose Achieved	45mg/day	159mg/day	50% of pts reached target of 10mg/d	37mg/d	74% of pts reached target of 50mg/d
Mean/Median follow-up	6.5 months	12 months	16 months	10.4 months	12 months
Total Mortality*	3.2 vs 7.8 RRR=65%	7.2 vs 11 RRR=34%	12 vs 17 RRR=34%	11.2 vs 16.7 RRR=35%	12 vs 15 RRR=23%
CV Death*	2.9 vs 7.8 RRR=63%	6.4 vs 10.1 RRR=37%	9 vs 12 RRR=29%	----	11 vs 14 RRR=25%
Sudden Death*	1.7 vs 3.8 RRR=55%	4.0 vs 6.6 RRR=39%	4 vs 6 RRR=42%	----	5 vs 7 RRR=26%
Admission to Hospital*	14.1 vs 19.6 RRR=27%	-----	33 vs 39 RRR=20%	----	----

CR/XL = controlled release formulation; MI = myocardial infarction; HF = heart failure; EF = ejection fraction; RRR = relative risk reduction; CV = cardiovascular
* percentage of events happening in active treatment versus placebo
** EF = mean ejection fraction

Figure 2.1. One year mortality in ACE Inhibitor and Beta Blocker Trials [43, 44, 46-48, 52-56]



2.4.3 Angiotensin Receptor Blockers (ARBs)

Angiotensin receptor blockers have been studied as alternative agents to ACE inhibitors and also as add-on therapy. [61-69] Like ACE inhibitors, angiotensin receptor blockers cause vasodilation, and help to attenuate the effects of angiotensin II, but instead of inhibiting the production of angiotensin II, ARBs block the angiotensin II receptor to inhibit its physiologic effects. [1] Since angiotensin II can be produced by other pathways besides the ACE enzyme, it had been postulated that ARBs may provide superior protection against its detrimental effects. [1, 61-63] However, ACE inhibitors also promote the accumulation of bradykinin which may be responsible for some clinically important benefits (as well as adverse effects such as cough) that are not observed with ARBs. [1, 37, 38]

Of the ARBs that have been studied in heart failure patients, only valsartan and candesartan have shown significant benefits in mortality and hospitalization and are approved as acceptable agents. [61-66, 69] Overall, there is not enough evidence to conclude that these ARBs are completely equivalent to ACE inhibitors but they are good alternatives in patients who cannot tolerate an ACE inhibitor for various reasons. [1] In addition, some benefit has been shown when an ARB is added to ACE inhibitor therapy, [63, 65] and this combination *may* be used in patients who are unable to tolerate a beta-blocker or who have continued symptoms while receiving ACE inhibitor and beta-blocker therapy. [1, 9]

2.4.4 Aldosterone Antagonists

With the increased production of aldosterone in heart failure and its adverse effects on the heart, the RALES trial was completed to test the benefits of spironolactone, an aldosterone antagonist. It was shown that in patients with NYHA class III and IV heart failure, the use of spironolactone in addition to usual heart failure medication decreased mortality by 30 percent. [70] Based on this trial, spironolactone is recommended in a select group of heart failure patients. [1, 12]

2.5 Adherence to Medications in Heart Failure

Despite the evidence showing a benefit for neurohormonal blockers in patients with heart failure, two barriers may stand in the way of optimal therapy: utilization and adherence. For a medication to provide a benefit, it must first be prescribed to a patient with an indication for that drug. In addition to being prescribed a medication for heart failure, a patient must fill the prescription and then continue to use it over the long term to retain its beneficial effects.

2.5.1 Utilization of Heart Failure Medications

Guidelines recommend the routine use of ACE inhibitors or ARBs, and beta blockers in heart failure patients due to their proven benefits. [1, 10, 11, 27] However, recent studies indicate that these recommended medications are underused. The major reason for underutilization of heart failure medications is assumed to be a result of physician under-prescribing. However, other factors, such as unfilled discharge prescriptions, likely also play a role. [71]

European, American and Canadian studies report that 28 to 75 percent of heart failure patients are prescribed an ACE inhibitor and only 11.8 to 41 percent are prescribed beta blockers. [58, 72-81] The prescribing rates for beta blockers are even lower in elderly patients [58, 77-79] and over half of all beta blocker prescriptions for heart failure are written by a cardiologist. [58, 79, 80] Prescription rates for combined use of beta blockers and ACE inhibitors is even lower at approximately 17 percent of the heart failure population, with one paper reporting 31 percent. [58, 72, 80] ARBs are considered a reasonable alternative to using an ACE inhibitor [1, 9], and combined utilization rates of either of these drug classes range from 61.7 to 82 percent. [36, 58, 72, 74, 77, 80]

Since the publication of major landmark heart failure trials, utilization rates have been increasing. In North America, ACE inhibitor utilization rates have remained relatively constant over the last 14 years, but the use of beta blockers has increased from approximately 5.9 percent in 1992 to 30 percent in 2001. ARB utilization has also increased from approximately 0 percent in 1992 to 7 percent in 2001. [36, 76, 81] Considering that most heart failure patients have an indication for both an ACE inhibitor and a beta blocker, these numbers although increasing, show a large gap in the optimal care of these patients.

In addition to prescribing rates, up-titration of these medications is an essential component of the optimal use of heart failure medications. In clinical trials, up to 89 percent of patients are able to maintain their beta blocker therapy, and about 70 percent of patients can maintain ACE inhibitor therapy once it is initiated and titrated to target doses. [43-48, 51, 52, 54, 55] In the real world, it has been shown that only 50 to 60 percent of patients reach target doses of these medications. This may mean that many patients

are not receiving the maximum benefits seen in the large randomized controlled trials. [58, 72, 77, 78, 80] Obviously, dosage level of many heart failure medications is a key component to evaluating the quality of care provided to these patients.

2.5.2 Adherence to Drug Therapy

Adherence is usually defined as the degree to which patients are taking their drug therapy as prescribed by their physician, [82-84] but poor prescribing and lack of patient follow undoubtedly contributes to this problem. Patient characteristics such as race, sex or socioeconomic status have not been consistently associated with adherence. Instead, factors such as depression, cognitive impairment, poor relationships with the physician, or side effects of a medication have been cited as barriers to adherence. [82, 83] It is interesting to note that complexity of the drug therapy regimen in terms of multiple dosing and the use of multiple concomitant medications has frequently been cited as a major barrier to optimal adherence. [82, 83]

There are various ways of measuring adherence, [82] including self-report via questionnaire or interview, [85, 86] pill counts, [87] electronic medication monitors, [88] testing of serum drug levels, [89] and calculation through administrative databases. [47, 90-94] Each method of measuring adherence has both advantages and disadvantages, but no method is considered to be the gold standard. [82, 95]

Administrative databases use rates of refilling prescriptions in order to calculate adherence on a large number of subjects in an objective manner. [82, 95] Although, there is no one perfect way of calculating adherence from these databases, it has been shown that taking the total days supply of a medication and dividing it by the

number of days of study participation is a reasonable way of calculating adherence. [95] In the case, where days supply is not available, a fill frequency (or fills per month) measure of adherence has been used with comparable results. [96]

2.5.3 Adherence and Discontinuation Rates with Heart Failure Medications

Although adherence rates can vary depending on the type of measurement instrument used and the type of heart failure patient studied, various observational studies show adherence rates to be between 61 and 80 percent for *all heart failure medications*. [85, 97, 98] Evangelista and colleagues found self reported medication adherence rates of 96 percent in a heart failure clinic. [99] Although this report clearly highlights the success of a specific heart failure clinic, it is unlikely that adherence rates reach this level in the general heart failure population.

Monane et al. reported digoxin adherence in heart failure patients from the 1980s. [100] It was found that the average patient had enough medication on hand to last for only two-thirds of a year. Only 10 percent of patients had enough medication on hand to last them the whole 12 month follow up period. [100]

Studies of ACE inhibitors show more promising rates of adherence. ACE inhibitor adherence trials using both prescription databases and electronic monitoring have found the average adherence rate for ACE inhibitors range from 67 to 92.9 percent. [88-91, 93, 94] Approximately 50 to 73 percent of these patients had adherence rates greater than 80 percent. [88-90, 93]

There is currently only one trial examining adherence rates to beta blockers in heart failure. Cole et al. examined adherence rates of ACE inhibitors and beta

blockers and the effect of drug copayment on these adherence rates using a database from a large, national health insurance plan in the United States. [91] Median adherence for beta blockers and ACE inhibitors was calculated to be 91.6 and 92.9 percent, respectively. [91]

Other studies have examined beta blocker discontinuation rates. [81, 97, 101] In one study of a heart failure clinic where approximately 70 percent of patients were on beta blockers, maintenance of therapy was followed over a two year period through a retrospective chart review. Of the patients prescribed beta blockers at the beginning of the trial, rates of continued therapy at 6, 12 and 24 months were 69, 70 and 74 percent. The most common reason for discontinuing the beta blocker was failure to reinitiate therapy after discharge from a hospitalization, which occurred in about 28 percent of patients. Side effects and intolerance accounted for one-third of all discontinuations, and 40 percent of patients stopped the beta blocker for unknown reasons. There was no significant difference between the mean ages of patients in whom therapy was stopped compared to those who remained on beta blockers. [101] Again, this report summarizes an apparently successful heart failure clinic, however, the majority of heart failure patients in Saskatchewan do not have access to such a program.

A community based heart failure study examining trends in prescribing rates of beta blockers also reported on continuation of beta blocker use in patients. Heart failure patients who were started on a beta blocker were followed for ten years, and the average proportion of patients continuing with their therapy was 73 to 83 percent. [81] However, adherence rates were not specifically examined over this period.

A recent study examined the persistent use of evidenced based drug therapy in heart failure and included information on the use of beta blockers. [92] Gislason et al. analyzed over 100,000 patients discharged alive from their first hospitalization for heart failure using an administrative database. Of all patients starting a beta blocker within three months of discharge, 69, 46 and 37 percent of patients had a break in therapy lasting at least 30, 90 and 180 days, respectively. For breaks of 90 days or longer, approximately 50 percent of subjects reinitiated beta blocker treatment within one year, and of patients with a break of more than 180 days, only 27 percent reinitiated therapy.

Even if patients are prescribed ACE inhibitors and beta blockers, poor adherence or non-persistence with these medications play a role in causing decompensation and admission to hospital. [102-104] It is generally unknown whether poor adherence to these neurohormonal blockers can negatively affect mortality rates. Miura et al. studied the effects of non-adherence with digoxin and its effect on hospitalization and mortality in heart failure. [105] With a mean follow up of almost 6 years, the number of hospitalizations was 2.5 times higher and risk of death was doubled in non-adherent patients. [105] Gislason et al studied non-persistence with heart failure medications and the effect this has on mortality. [92] Using a large population database to monitor frequency of prescription refill, it was found that patients who had a break in beta blocker therapy of at least 90 days had a 1.25 times higher risk of death (95% CI: 1.19 to 1.32; $p<0.0001$). Patients with a break in ACE inhibitor or ARB therapy of at least 90 days had a 1.37 times higher risk of death (95% CI: 1.31 to 1.42;

$p<0.0001$). Non-persistence with spironolactone did not result in a significant effect on mortality.

2.5.4 Reasons for Non-adherence

There are numerous studies examining reasons for poor patient compliance with medications in both the general population and in heart failure patients.

Patients diagnosed with heart failure are inherently at risk of non-compliance due to a variety of factors, such as the presence of psychological or cognitive problems, medication related side effects, complexity of the medication regimen, patient's lack of insight into their disease, cost of medications, concomitant diseases and inadequate follow-up from health care providers. [82, 83, 106, 107]

When patients are asked about their reasons for not taking their prescribed medications, the most common answers are forgetfulness, other priorities preventing them from taking their medications, intentionally deciding to skip doses, lack of information about their prescribed medications, and certain emotional factors. [82]

Over 70 percent of heart failure patients are prescribed three or more medications solely for heart failure, [58] and greater than 50 percent of patients have concurrent conditions that warrant other drug therapies. [51, 53, 108, 109] This often creates complex dosing regimens, resulting in decreased adherence rates. [82] Also, considering the average age of patients with heart failure is over 75, and steadily increasing, the presence of other concomitant diseases is also increasing, potentially decreasing the odds of compliance by about one third. [107, 108]

2.6 Summary

Heart failure is a debilitating disease resulting in frequent hospitalizations and an increased risk of death. The prescribing of life-prolonging therapy, such as ACE inhibitors and beta blockers in heart failure patients, along with their continued regular use should provide substantial benefit to these patients. [1, 9, 10] Considering the superior survival advantage observed with beta blocker use in clinical trials, non-adherence to these agents likely results in a significant excess of preventable deaths each year. Although reasonable success has been achieved in promoting greater prescribing of these agents in heart failure patients, it is unknown how many patients actually continue therapy long enough to achieve the benefits. Currently, there is minimal data in terms of adherence rates to beta blockers and the effects that adherence can have on health outcomes.

3. STUDY DESIGN

A population based retrospective cohort study was created using linked administrative databases from the province of Saskatchewan, Canada.

Ethical approval was obtained from the University of Saskatchewan Biomedical Research Ethics Board on August 18, 2006 (ethics number 06-173 - Appendix A).

3.1 Data Source [110]

Saskatchewan has a publicly funded health system where residents of the province enjoy universal health insurance. As a result, the Saskatchewan Department of Health (Sask Health) has accumulated a large amount of medical information over many years in electronic databases. The databases include a population registry, prescription drug database, hospital services database, medical services database and vital statistics database, among others. All data used in this study were obtained from Sask Health. To ensure confidentiality throughout this study, all data were de-identified by Saskatchewan Health personnel. Person-level analysis was possible because Sask Health assigned eligible study subjects a study-specific unique identifier that only pertains to the present study and does not appear in any source database.

From the population registry, information is available on all residents eligible for Saskatchewan Health benefits. This includes over 99 percent of the population, with the only exceptions being members of the Royal Canadian Mounted Police

(RCMP), members of the Canadian Forces, and federal penitentiary inmates. It contains basic information about Saskatchewan beneficiaries such as coverage details, age, sex, place of residence and marital status. For the current study, we were provided with the variables sex, year of birth and certain coverage details.

The prescription drug database includes information about prescription claims submitted by Saskatchewan pharmacies when that drug is on the Saskatchewan Formulary. Approximately 91 percent of Saskatchewan Health beneficiaries are eligible for coverage through the Saskatchewan Drug Plan. Exceptions include registered Indians, and veterans covered under veterans affairs. For each eligible prescription dispensed, the following information was provided: date of fill, the dose of the medication, the number of units dispensed, the dosage form, and an indicator of the type of special support received (if any) on drug costs.

The hospital services database captures information about all hospital visits for Saskatchewan beneficiaries (i.e., includes out-of-province hospitalizations). Information provided for every hospitalization included: the dates of admission and discharge, up to 25 diagnoses from each individual hospital visit, up to 20 procedures performed during the hospital stay, and the attending physician specialty of each hospital visit.

The medical services database captures data from physician service claims. The information provided included the date of physician visit, one diagnosis for that visit, and the specialty of physician seen.

The vital statistics database captures information on all births and deaths throughout Saskatchewan regardless of health coverage. For every death that occurs in

Saskatchewan, information is obtained on the date of death, and the cause of death as recorded on the Medical Certificate of Death form. This information can then be used to examine various reasons for death, and apply them as outcomes for analysis.

4. THE STUDY POPULATION

Subjects included all residents holding a valid Saskatchewan health card that were discharged from hospital alive with a first-ever primary or most-responsible diagnosis of heart failure between the dates of January 1, 1994 and December 31, 2003 and were eligible for prescription drug benefits. Additionally, each subject had to have a minimum of 5 years of continuous coverage prior to the index hospitalization to adequately assess their past history.

Any subject exhibiting the following within five years prior to the index hospitalization were excluded from the study: hospitalization for heart failure or evidence of medical conditions that may have substantially decreased their life expectancy such as HIV/AIDS, solid organ transplant or terminal illness. Evidence of these medical conditions was determined using the hospital services database, physician services database and the drug database (Appendix B).

Patient Follow Up

Information on each eligible subject was collected from the date of discharge for the index hospitalization until the occurrence of one of the following:

a) Death,
b) Coverage termination (e.g., movement out of the province of Saskatchewan)
c) Organ transplantation or initiation of anti-rejection medication,
d) Diagnosis of HIV/AIDS or initiation of anti-retroviral therapy,
e) The end date of the study, Dec 31, 2003.

5. METHODOLOGY

Analyses of the study population were carried out in three separate phases using SPSS version 14.0 for Windows:

Phase 1 Utilization of heart failure medications:

i) Prescribing rates after discharge from index hospitalization, and

ii) Average doses of beta blockers dispensed throughout the study period.

Phase 2 Adherence:

i) Adherence rates of beta blockers and ACE inhibitors, and

ii) Predictors of beta blocker adherence.

Phase 3 Survival analysis:

i) Association between beta-blocker use/adherence and health related outcomes.

5.1 Phase I: Utilization of Heart Failure Medications

The proportion of subjects filling at least one prescription for a guideline recommended heart failure medication (specifically beta blockers and ACE inhibitors/ARBs) within 30 days of discharge from the index hospitalization was calculated in two year intervals starting on January 1, 1994. As such, all subjects were analyzed within a single time interval based on their year of entry into the study.

For the calculation of beta-blocker utilization, only prescriptions for atenolol, metoprolol, bisoprolol or carvedilol were considered eligible. In contrast, all available ACE inhibitors or ARBs on the market at the time of the study were used to determine utilization rates for these drug classes.

5.1.1 Mean Daily Dose of Beta Blockers

All prescriptions for atenolol, bisoprolol, metoprolol and carvedilol were selected, and each drug was analyzed separately. First, it was necessary to identify all prescription fills being dispensed on a monthly basis, because the prescription drug database in Saskatchewan does not capture a "days supply" variable. Therefore, only subjects with fill quantities that were sensibly divisible by 34 days were selected on the assumption that a monthly prescription is intended to last 34 days. This assumption is based on the contract between Sask Health and each Saskatchewan pharmacy that allows pharmacists to claim one dispensing fee for each 34-day supply dispensed (with some exceptions). For example, a fill quantity of 68 is divisible by 34 and would reflect a patient taking two tablets per day for one month. Only beta blocker prescriptions with a fill quantity between 14 and 18, 28 and 35, or 56 and 70 days were used to determine average daily doses.

For each one-month prescription selected, the quantity of tablets dispensed was divided by 34 in order to calculate the number of tablets/capsules taken per day between each fill. To calculate the individual dose of beta blocker taken per day, the strength of the beta blocker dispensed at each fill was multiplied by the number of tablets per day. This daily dose of beta blocker for all patients was then summed and

this number was divided by the total number of beta blocker fills to calculate the average dose of beta blocker per day.

5.2 Phase II: Adherence to ACE inhibitors and Beta Blockers

All subjects filling a prescription for a beta blocker or ACE inhibitor at least 3 times throughout the study period (January 1, 1994 to December 31, 2003) were included in this analysis, providing that the first prescription fill was within three months of discharge from the index hospitalization. Adherence was calculated separately for beta blockers and ACE inhibitors. Although any ACE inhibitor could be included for analysis, only the beta blockers atenolol, metoprolol, bisoprolol and carvedilol were selected. Adherence rates were calculated at yearly intervals from the time of first fill, and eligible subjects had to have available data throughout the entire interval.

Data Analysis

Adherence rates were calculated for each subject by taking the total number of fills in a given time period divided by the total number of months in that time period. This adherence measure is called the "fill frequency" and has been used in previous studies using Saskatchewan prescription drug data. [111] As a one month prescription fill under the Saskatchewan drug plan is for 34 days, to calculate the total number of months in a time period, the number of days in that period was divided by 34. For example, the number of months in one year is calculated to be 10.74.

Because this patient population requires frequent hospitalizations and in-hospital prescription use is not captured in the database, all hospitalized days during the course of the observation period were accounted for in the adherence calculation. Specifically, the number of days that each subject spent in hospital was calculated and subtracted from the overall time in that interval. The fill frequency measure was then calculated using the adjusted time interval. In this way, adherence is adjusted for time spent in hospital on the assumption that subjects received study medications regularly during each hospital stay.

Once the fill frequency was calculated for each subject, the percentage of subjects exhibiting high adherence was then determined for each year. High adherence was defined as having a fill frequency that is greater than or equal to 0.8 (or 80%).

Adherence to beta blockers was also calculated from a more global perspective incorporating subjects who filled their first prescription later than three months after discharge. As such, the global adherence perspective takes into account how long it took for a subject to begin a beta blocker as well as whether or not they continued to take it on a regular basis. To calculate adherence from this perspective the same steps were taken with one exception. Instead of calculating adherence on a yearly basis from the time of first fill of a beta blocker, adherence was determined from the day a subject was discharged at their index hospitalization.

Comparison of Adherence Measures

In an attempt to validate our fill frequency adherence measure, an alternate measure of adherence termed the tablets per day measure was also used to calculate

adherence for subjects taking beta blockers and ACE inhibitors, and these two measures were compared.

Tablets per day was calculated by adding all tablets that a subject had filled throughout a given time period and dividing this by the total number of days in that time period. When performing this calculation one must take into account the fact that some subjects take a medication more than once a day, or perhaps take half a tablet per day. Unfortunately, the Saskatchewan prescription drug database does not capture days supply of a prescription fill. Thus, to accurately compare fills per month and tablets per day, adherence was calculated for medications that are usually only prescribed once a day. For ACE inhibitor adherence lisinopril, ramipril, trandolopril and perindopril were used. For beta blocker adherence bisoprolol and atenolol were used. Furthermore, to ensure greater accuracy of the tablets per day measure, only subjects who had filled prescriptions for 28 to 35 tablets at a time were selected.

For each subject, both adherence measures were calculated over a one year period, and a Pearson's correlation coefficient (r) was calculated to compare these adherence rates.

Predictors of Beta Blocker Adherence

Adherence to beta blockers was calculated using the fill frequency measure of adherence from the time of discharge from index hospitalization until a subject's exit from the study. Subjects must have started a beta blocker within six months of the index hospitalization and survive longer than this period of time. Once calculated, adherence was divided into two cohorts, 80 percent or greater and 50 percent or less,

which was meant to capture subjects that are strictly adherent, and strictly non-adherent.

A binary logistic regression analysis was used to determine predictors of beta blocker adherence, with the dependent variable being beta blocker adherence. All available patient characteristics (see Appendix C for explanation of variables) were entered into one logistic regression model at the same time with the exception of chronic disease score, [112] Deyo comorbidity score, [113, 114] and number of diseases at index. These three characteristics are all predictors of overall general health at baseline and it was felt that co-linearity would be present if they were all inserted within the model. Each of the three characteristics was entered into the model in a stepwise fashion and the variable producing the lowest -2 log likelihood was used. Based on this, the number of diseases at index was used to adjust for overall general health at baseline in the logistic regression model.

5.3 Phase III: Effects of Beta Blockers on Health Related Outcomes

To determine if an association exists between adherence to beta blockers (atenolol, metoprolol, bisoprolol and carvedilol) and major health outcomes, Cox proportional hazards models were constructed. Each of the analyses is described below in detail.

5.3.1 Effects of Beta Blocker Use on All-cause Mortality

<u>The Study Population</u>

To determine if the use of a beta blocker in 'real world' heart failure patients prolonged survival, all study subjects surviving at least six months past the index hospitalization were eligible for inclusion in this analysis so that a reasonable period of exposure to beta blockers could be ensured. Subjects were then split into two cohorts based on whether or not they had filled a prescription for a beta blocker throughout the study period. For those taking a beta blocker, the first fill had to occur within six months of the index hospitalization in order for these patients to be included in the analysis. Patients filling the first prescription later than six months were excluded to minimize the likelihood of survivor treatment selection bias that has been observed in other observational studies of this nature. [115, 116]

Data Analysis

Beta blocker use/adherence and its effect on health related outcomes was assessed using Cox proportional hazards models. The final multivariate Cox model for each endpoint included the following variables that were deemed to be clinically significant: age, sex, prior ischemic heart disease, and a measure of over-all general health at baseline (one of: CDS, Deyo comorbidity score or number of diseases at baseline – selected based on the variable producing the lowest -2 log likelihood in the final model). As well, other clinically important variables were included in each endpoint analysis, and will be discussed within each relevant endpoint section. To find the optimal multivariate model in all subsequent analyses, certain steps were performed. [117]

Step 1. As there were 30 patient variables available (Appendix C) for inclusion into each Cox proportional hazards model, a univariate analysis was run for all non-clinically important variables to determine if a significant effect ($p \leq 0.1$) on survival time was present. Thus, approximately 26 univariate models were constructed for each outcome of interest.

Step 2. Significant variables identified on univariate analysis were included into a multivariate model along with the clinically important variables. As such, each variable in the model was adjusted for by all other included variables. Variables that became non-significant ($p>0.05$) in the multivariate model were deleted from the final analysis, and variables not in the model were re-inserted to check for a significant effect in the presence of the other variables. There were approximately 10 multivariate models constructed during step two for each outcome to determine the most appropriate variables to be included in the final model.

Step 3. Upon determining the best variables for the model, beta blocker use/adherence was inserted into the model and possible interactions between variables were examined. Any significant interactions were added to the model, and this final model was then used for survival analysis.

For the Cox proportional hazards model analyzing the effect of beta blocker use on all-cause mortality, the cohort of patients not taking a beta blocker was used as the reference group. Clinically important variables were deemed to be sex, age, CDS, nitrate use, ACE/ARB use and prior IHD. All other patient variables (see Appendix C for explanation of variables) were analyzed in univariate models to determine significance (Table 5.1). Interactions between age^2 and nitrate use, and age^2 and beta

Table 5.1. Variables Considered for Use in the Final Cox Proportional Hazards Model for Beta Blocker use on All-Cause Mortality

Variables Significant in Univariate Analysis		Clinically Important Variables	Variables added to the Final Model	
Warfarin use	NDP-CCB use	Sex	BB use	Age^2
Digoxin use	Spironolactone use	Age	Sex	CDS
Prior ACE use	Prior BB use	CDS	Prior IHD	ACE/ARB use
Statin use	Prior statin use	Nitrate use	Digoxin use	NDP-CCP use
Renal Failure	Thiazide diuretic use	ACE/ARB use	Prior ACE use	Prior stain
Anti-arrhythmic use		Prior IHD	Renal Failure	Warfarin use
Use of DM medication			Statin use	Nitrate use
Other HTN medication use			Spironolactone use	
Year at index hospitalization			Anti- arrhythmic use	
Number of hospitalizations in the 1st 6 months			Use of DM medication	
Type of doctor seeing patient at index			Other HTN medication use	
Number of hospitalizations in year prior to index			Days spent in hospital at index hospitalization	
Days spent in hospital at index hospitalization			Type of doctor seeing patient at index	
			Number of hospitalizations in the 1st 6 months	

NDP-CCB = non-dihydropyridine calcium channel blocker; ACE = angiotensin converting enzyme inhibitor; BB = beta blocker; DM = diabetes mellitus; HTN = hypertension; CDS = chronic disease score; ARB = angiotensin receptor blocker; IHD = ischemic heart disease. See Appendix C for a more detailed definition of each variable.

blocker use were detected and inserted into the final model. All variables were categorical in nature with the exception of age which was a continuous variable. Of note, the continuous variable age was determined not to be a linear term in regards to survival time, and thus other options were explored to optimize the model. Both age^2 and age as a categorical variable were assessed for fit, and as determined by the -2 log

likelihood, age^2 fit the current model better than the categorical variable of age, and thus was used in the final model.

5.3.2 The Effect of Beta Blocker Adherence on Health Related Outcomes

The Study Population

As a follow up to the previous analysis evaluating the impact of beta blocker use as a dichotomous classification, the following analysis was intended to discriminate between various adherence rates among beta blocker users, and determine any effect this might have upon mortality and hospitalization.

Only those filling a prescription for a beta blocker within the study period were selected for this analysis. Two criteria were imposed upon these subjects taking a beta blocker. First, subjects had to fill a beta blocker prescription within six months of index hospitalization. Second, subjects had to have survived at least six months from the index hospitalization.

Data Analysis

Adherence was calculated using the fill frequency measure of adherence from the time of index hospitalization, until the end of follow-up (i.e., the global perspective). From the calculated adherence measure, each subject was separated into three distinct cohorts as follows:

1. Subjects receiving a beta blocker and who were $\geq$ 80 percent adherent throughout the study. This group of subjects is referred to as the high adherence cohort.

2. Subjects receiving a beta blocker and who were between 50 and 80 percent adherent throughout the study. This group of subjects is referred to as the medium adherence cohort.

3. Subjects receiving a beta blocker and who were ≤ 50 percent adherent throughout the study. This group of subjects is referred to as the low adherence cohort.

All Cause Mortality

Beta blocker adherence and its effect on all-cause mortality was analyzed using a Cox proportional hazards model, with the low adherence cohort used as the reference group. Clinically important variables were deemed to be sex, age, CDS, ACE inhibitor/ARB adherence, anti-arrhythmic drug use, use of diabetic medication and prior IHD. All other patient variables (see Appendix C for explanation of variables) were analyzed in univariate models to determine significance (Table 5.2). An interaction between digoxin and prior ischemic heart disease was found and added to the model. All variables were categorical in nature with the exception of age, which was a continuous variable. When tested, age was a linear predictor of survival time, and thus was included in the model unaltered.

Several subgroups were analyzed separately to evaluate the consistency of the results from the all-cause mortality model:

- Patient age groups, where the continuous variable age was separated into three categories: ≤ 70, 71 to 79, and ≥ 80
- ACE inhibitor or ARB use
- Male or female sex
- History of ischemic heart disease

- Number of conditions at baseline, which was separated into two categories: $\leq$ 3 conditions or >3 conditions
- Patients filling a prescription for a diabetes medication
- Patients with evidence of renal failure
- Medical visits in first 6 months, which was separated into two categories: < 20 visits or $\geq$ 20 visits

Table 5.2. Variables Considered for Use in the Final Cox Proportional Hazards Model for Beta Blocker Adherence on All-Cause Mortality

Variables Significant in Univariate Analysis		**Clinically Important Variables**	**Variables added to the Final Model**	
Warfarin use	Digoxin use	Sex	BB adherence	Age
Prior ACE use	Statin use	Age	Sex	CDS
Loop diuretic use	Renal Failure	CDS	Prior IHD	ACE/ARB adherence
Nitrate use		Prior IHD	Digoxin use	Renal Failure
Number of physician visits in the 1st 6 months		ACE/ARB adherence	Warfarin use	Prior stain
Days spent in hospital at index hospitalization		Anti-arrhythmic use	Statin use	Anti-arrhythmic use
Drug benefits category at index		Use of DM medication	Use of DM medication	
			Other HTN medication use	
			Number of physician visits in the 1st 6 months	
			Days spent in hospital at index hospitalization	

ACE = angiotensin converting enzyme inhibitor; BB = beta blocker; DM = diabetes mellitus; HTN = hypertension; CDS = chronic disease score; ARB = angiotensin receptor blocker; IHD = ischemic heart disease. See Appendix C for a more detailed definition of each variable.

Cardiovascular Mortality and Time to First Hospitalization

The effects of beta blocker adherence on cardiovascular mortality and time to first hospitalization, both considered to be secondary endpoints, were analyzed using a Cox proportional hazards model. In each of these analyses the low adherence cohort was used as the reference group.

For the analysis of cardiovascular death, clinically important variables were deemed to be sex, age, CDS, ACE inhibitor/ARB adherence, use of diabetic medication and prior IHD. All other patient variables (see Appendix C for explanation of variables) were analyzed in univariate models to determine significance (Table 5.3). No interactions were noted. All variables were categorical in nature with the exception of age, which was a continuous variable. When tested, age was a linear predictor of survival time, and thus was included in the model unaltered.

Table 5.3. Variables Considered for Use in the Final Cox Proportional Hazards Model for Beta Blocker Adherence on Cardiovascular Death

Variables Significant in Univariate Analysis		**Clinically Important Variables**	**Variables added to the Final Model**	
Warfarin use	Nitrate use	Sex	BB adherence	Age
Digoxin use	Statin use	Age	Sex	CDS
Prior ACE use	Loop diuretic use	CDS	Prior IHD	ACE/ARB adherence
Renal Failure		Prior IHD	Digoxin use	Statin use
Drug benefits category at index		Use of DM medication	Renal Failure	Warfarin use
Number of hospitalizations in the 1st 6 months		ACE/ARB adherence	Use of DM medication	
Days spent in hospital at index hospitalization			Number of hospitalizations in the 1st 6 months	

ACE = angiotensin converting enzyme inhibitor; BB = beta blocker; DM = diabetes mellitus; CDS = chronic disease score; ARB = angiotensin receptor blocker; IHD = ischemic heart disease. See Appendix C for more a detailed definition of each variable.

For the endpoint of time to first hospitalization, adherence was recalculated from the time of index hospitalization until the date of admission of first hospitalization, and only subjects having a first hospitalization six months after the index hospitalization were included in the analysis. This was to help ensure that there was adequate time for adherent and non-adherent subjects to be distinguished. Subjects were once again separated into three adherence cohorts (high, medium and low adherence) for the purpose of analysis. Clinically important variables were deemed to be sex, age, CDS, prior ACE inhibitor use, prior statin use, prior beta blocker use, prior IHD, and number of physician visits in the first six months. As adherence was re-calculated from index until time to first hospitalization, only patient variables (see Appendix C for explanation of variables) available at baseline or prior were assessed for significance with univariate analysis (Table 5.4). An interaction between sex and prior ischemic heart disease was noted and entered into the model. All variables were categorical in nature with the exception of age, which was a continuous variable. When tested, age was a linear predictor of survival time, and thus was included in the model unaltered.

Table 5.4. Variables Considered for Use in the Final Cox Proportional Hazards Model for Beta Blocker Adherence on Time to First Hospitalization

Variables Significant in Univariate Analysis	Clinically Important Variables	Variables added to the Final Model	
Year at index hospitalization	Sex	BB adherence	Age
Drug benefits category at index	Age	Sex	CDS
Type of doctor seeing patient at index	CDS	Prior IHD	Prior BB use
	Prior ACE use	Prior ACE use	Prior stain
	Prior statin use	Number of physician visits in the 1st 6 months	
	Prior IHD		
	Prior BB use		
	Number of physician visits in the 1st 6 months		

ACE = angiotensin converting enzyme inhibitor; BB = beta blocker; CDS = chronic disease score; IHD = ischemic heart disease. See Appendix C for a more detailed definition of each variable.

6. RESULTS

Of all eligible subjects residing in Saskatchewan between January 1, 1994 and December 31, 2003, there were 14, 445 patients admitted to hospital for a first admission for heart failure meeting the inclusion and exclusion criteria. This population had an average age of 78.5 years (range of 6 to 107) and 51.7 percent were male. The mean survival time of all subjects was 2.4 years with a range of 0 days to 10 years. Approximately 24 percent of subjects did not survive 3 months past the index hospitalization, limiting the number of subjects in subsequent analyses.

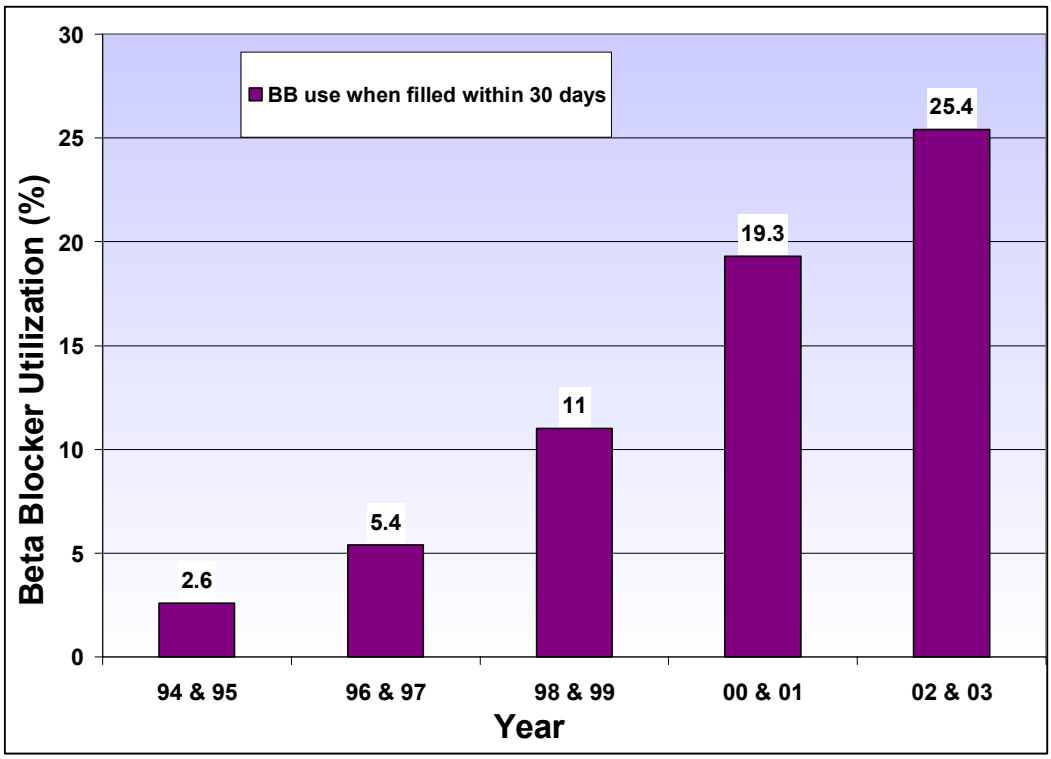
6.1 Phase I: Utilization of Heart Failure Medications

A total of 3324 subjects (23 percent) started a beta blocker and 9796 subjects (67.7 percent) started an ACE inhibitor at some time throughout the study period. Using a t-test it was determined that subjects taking a beta blocker were significantly younger than those not on one (75 versus 80 years of age), as were subjects taking an ACE inhibitor or ARB (77 versus 80 years of age). In addition, initiation of these medications was associated with more frequent physician visits within the first 6 months.

Only 1572 subjects (12 percent) started a beta blocker within 30 days of discharge from the index hospitalization and are included in the analysis for utilization rates. Although the overall utilization rate appears quite low, beta blocker prescribing

in this population has increased dramatically since 1994, reaching 25 percent in subjects discharged in the years 2002 and 2003 (Figure 6.1).

Figure 6.1. Proportion of Subjects Filling at least One Prescription for a Beta Blocker within 30 days of Discharge for Heart Failure



BB = beta blocker

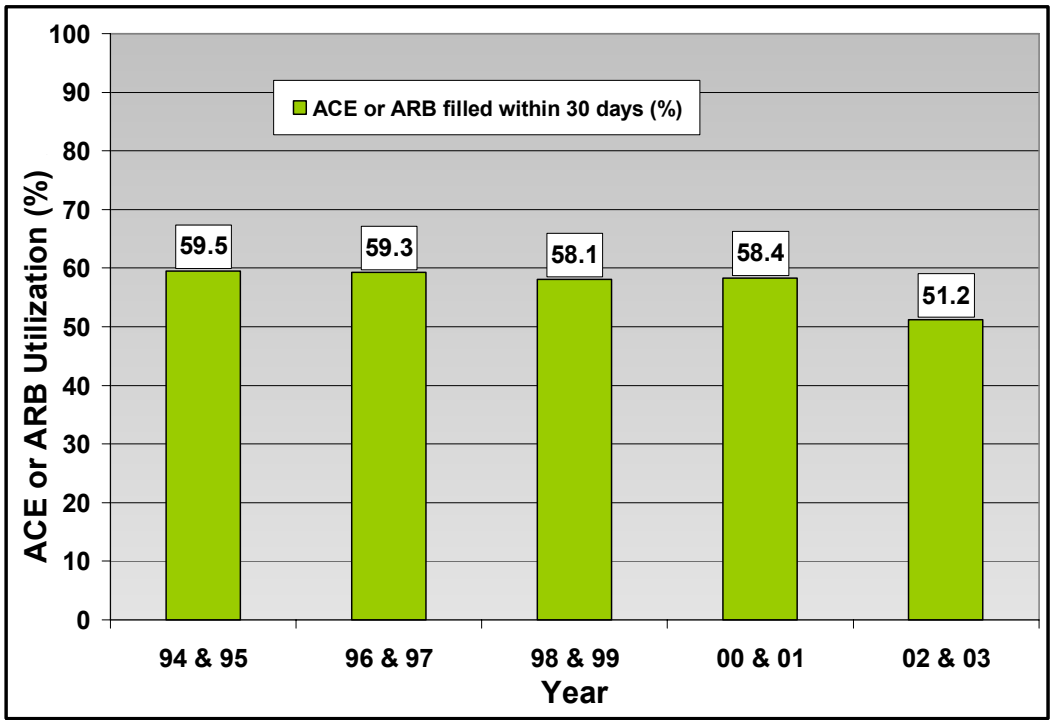
Overall, there were 7111 subjects (57 percent) starting an ACE inhibitor or an ARB within 30 days of discharge from the index hospitalization. When ACE inhibitor and ARB use is broken down into two year time intervals, there is little change over a 10 year period, with utilization rates being between 51 to 60 percent (Figure 6.2)

6.1.1 Mean Daily Dose of Beta Blockers

There were a total of 3324 subjects taking at least one of the four selected beta blockers at some time throughout the study period. The average daily doses being

taken by study subjects receiving one-month prescriptions for atenolol, metoprolol, bisoprolol and carvedilol were calculated to be approximately 44mg, 59mg, 6mg, and 18mg, respectively (Table 6.1).

Figure 6.2. Proportion of Subjects Filling at least One Prescription for an ACE or ARB within 30 days of Discharge for Heart Failure



ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker

Table 6.1. Mean Daily Doses of Beta Blockers used in Saskatchewan Patients

Drug	Mean Dose (mg/day)	Range (mg/day)	Number of Patients Taking	Target Dose (mg/day)
Atenolol	44.16	10.29 – 205.9	1362	Unknown
Metoprolol	59.16	11.03 – 205.9	1470	100 to 200
Bisoprolol	5.66	2.06 – 9.85	26	10
Carvedilol	17.71	2.57 – 50.37	625	50

6.2 Phase II: Adherence to ACE inhibitors and Beta Blockers

There were 1143 subjects filling at least three prescriptions for a beta blocker and 5084 subjects filling at least three prescriptions for an ACE inhibitor within the first year. As per the inclusion criteria described previously, all of these subjects initiated their respective medications within 3 months of the index hospitalization and survived for a minimum of 1 year. As many of these patients did not survive (or were censored) for all subsequent years while calculating adherence, fewer patients were included in each adherence calculation at yearly intervals (Table 6.2).

Table 6.2. Number of Patients Included in Each Year for the Adherence Calculation

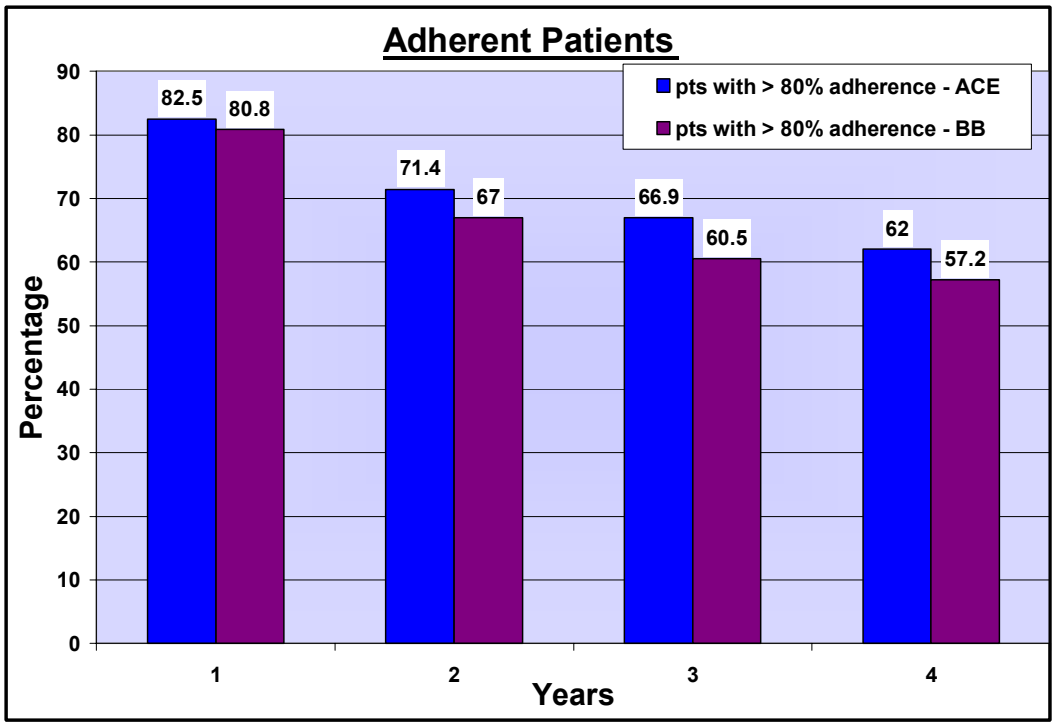
Year Past Index	Number of patients included in ACE inhibitor adherence	Number of patients included in beta blocker adherence
1	5084	1143
2	3853	749
3	2784	501
4	1937	306

Adherence over the first year was excellent for both beta blockers (80.8 percent) and ACE inhibitors (82.5 percent). Thereafter, the proportion of patients remaining adherent slowly decreased to reach approximately 60 percent, for both medication classes, after 4 years (Figure 6.3).

This adherence analysis was also conducted on a broader population including subjects filling only one or two prescriptions over the observation period. In this population, overall adherence to beta blockers and ACE inhibitors is attenuated by approximately 10 percent: 69.8 and 74.2 percent in the first year, 58.6 and 64.3 percent

in the second year, 53.2 and 61.4 percent in the third year and 50.7 and 56.9 percent in the fourth year, respectively.

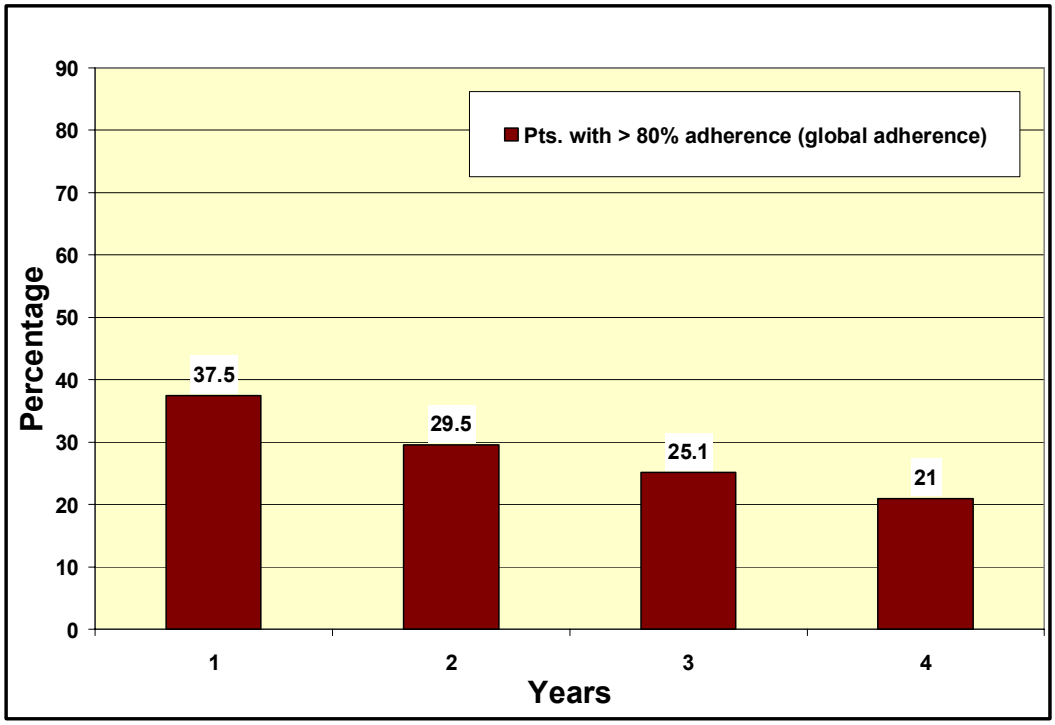
Figure 6.3. Proportion of Patients Achieving 80% Adherence to ACE Inhibitors and Beta Blockers in the Years Following Hospitalization



ACE = angiotensin converting enzyme inhibitor; BB = beta blocker

When examining the global adherence measure, which takes into account subjects who did not receive a beta blocker immediately after discharge, only 37.5 percent of subjects are adherent to a beta blocker in the first year, and this decreases with time to 21 percent in year four (Figure 6.4).

Figure 6.4. Proportion of Patients Achieving 80% Adherence to Beta Blockers when Date of Discharge is used as the Beginning of the Observation Period



Comparison of Adherence Measures

The tablets per day and fill frequency adherence measures were calculated and compared for both beta blocker and ACE inhibitor subjects, with 158 and 1389 subjects included in this calculation, respectively. These adherence measures were strongly correlated for both ACE inhibitors ($r = 0.977$) and beta blockers ($r = 0.972$) and were significant at the 0.01 level (Tables 6.3 and 6.4).

Table 6.3. Correlation of Adherence Measures for ACE Inhibitors

		Fill frequency	Tabs per day
Fill frequency	Pearson Correlation	1	.977(**)
	Sig. (2-tailed)		.000
	N	1389	1389
Tabs per day	Pearson Correlation	.977(**)	1
	Sig. (2-tailed)	.000	
	N	1389	1389

** Correlation is significant at the 0.01 level (2-tailed).

Table 6.4. Correlation of Adherence Measures for Beta Blockers

		Fill frequency	Tabs per day
Fill frequency	Pearson Correlation	1	.972(**)
	Sig. (2-tailed)		.000
	N	158	158
Tabs per day	Pearson Correlation	.972(**)	1
	Sig. (2-tailed)	.000	
	N	158	158

** Correlation is significant at the 0.01 level (2-tailed).

Predictors of Beta Blocker Adherence

There were 1815 subjects starting a beta blocker within 6 months of the index date who survived at least 6 months. Of those, 1013 exhibited high adherence ($\geq$80 percent) and 532 exhibited low adherence ($\leq$ 50 percent). From all of the variables entered into the logistic regression analysis, it appears that the greatest effect on predicting adherence is related to the time of index hospitalization. For example, the odds of being adherent to a beta blocker are 5 times more likely in subjects having a first hospitalization in the years 2002 and 2003 compared to subjects entering the study in 1994. [OR = 5.0 (95% CI: 2.65 – 9.47; $p<0.0001$)]. Subjects who are adherent to ACE inhibitor or ARB medications are also more likely to be adherent to beta blockers [OR = 1.66 (95% CI: 1.12 – 2.46; $p=0.011$)]. Other significant predictors of adherence include female sex [OR = 1.35], use of diabetic medication [OR = 1.33], and filling the

beta blocker prescription within one month of the index hospitalization [OR = 1.5] (Table 6.5).

Conversely, if subjects are taking an antiarrhythmic medication [OR = 0.658 (95% CI: 0.476 – 0.909; p=0.011)], a non-dihydropyridine calcium channel blocker [OR = 0.714 (95% CI: 0.511 – 0.996: p=0.047)], or have more than 34 visits to their physician in the first 6 months [OR = 0.522 (95% CI: 0.347 – 0.785; p = 0.002)], they have a greater likelihood of not being adherent to a beta blocker.

Table 6.5. Positive Predictors of Overall Beta Blocker Adherence

Characteristic	Odds Ratio	p – Value	95% CI
Patients adherent to an ACE inhibitor or ARB	1.66	0.011	1.12 – 2.46
Female gender	1.35	0.019	1.05 – 1.73
Beta blocker filled within 1 month of index	1.50	0.007	1.10 – 1.99
Use of diabetic medication	1.33	0.038	1.02 – 1.75
Index in the years 94 and 95	1.00		
Index in the years 98 and 99	3.06	<0.0001	1.76 – 5.54
Index in the years 00 and 01	3.20	<0.0001	1.74 – 5.86
Index in the years 02 and 03	5.00	<0.0001	2.65 – 9.47

CI = confidence interval; ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker

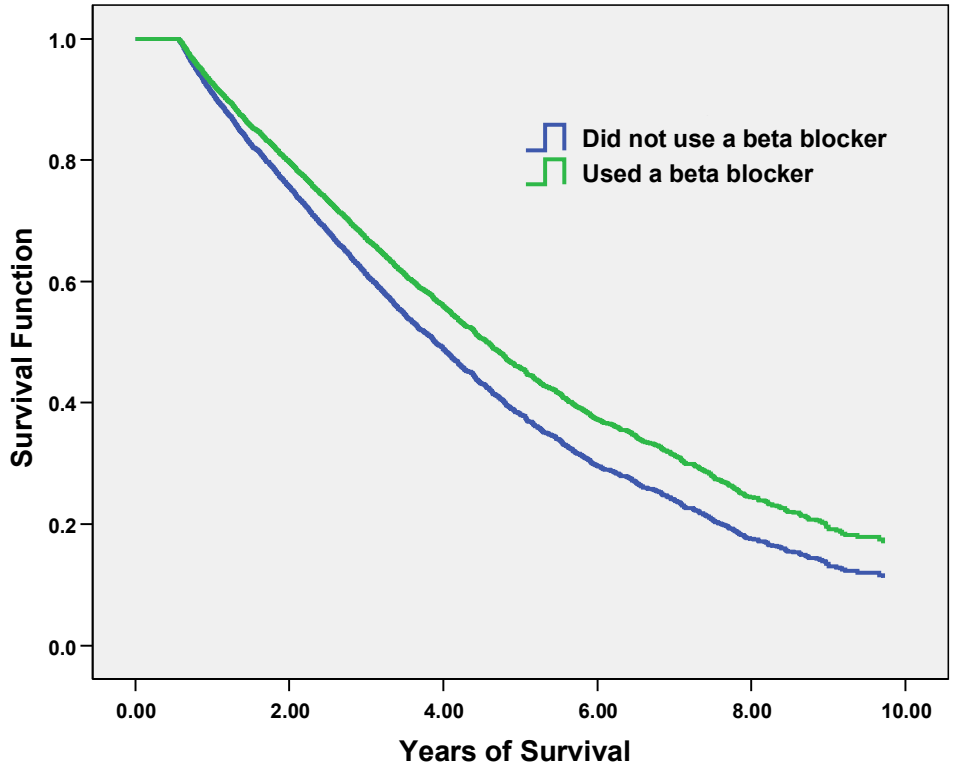
6.3 Phase III: Effects of Beta Blockers on Health Related Outcomes

6.3.1 Effects of Beta Blocker Use on All-cause Mortality

A total of 9272 heart failure subjects were discharged alive and survived at least 6 months. Of these subjects, 1815 used a beta blocker and 7457 never started one throughout the study period. The average survival time for subjects on a beta blocker

was 2.76 years compared to subjects never taking a beta blocker who lived an average of 3.2 years. An unadjusted hazard ratio for the effect of beta blocker use on mortality was calculated to be 0.671 (95% CI: 0.616 – 0.730; p<0.0001). After controlling for several confounding factors, the use of a beta blocker was associated with a 61 percent reduction in the risk of death [HR = 0.39 (95% CI: 0.26 to 0.58; p<0.001)] when compared to patients not taking a beta blocker (Figure 6.5).

Figure 6.5. Adjusted Survival Curves of Beta Blocker Use using a Cox Proportional Hazards Model



6.3.2 The Effect of Beta Blocker Adherence on Health Related Outcomes

Of the subgroup of beta blocker users described previously in the predictors of beta blocker adherence section (Phase II), an overall adherence rate of 74 percent was calculated from the time of index hospitalization until the end of follow up.

Approximately half of these subjects were male and the mean age was around 75, resembling the typical heart failure patients seen in epidemiological studies. Patients in the high adherence group had higher chronic disease scores compared to the other two cohorts, however, the number of medical visits within the first six months is higher in the low adherence group (Table 6.6).

Table 6.6. General Patient Characteristics of Patients using Beta Blockers

Baseline Characteristics (%)	High Adherence (n=1013)	Medium Adherence (n=270)	Low Adherence (n=532)
Mean Follow-up*	**2.5 yrs**	**2.6 yrs**	**3.2 yrs**
Male*	488 **(48.2)**	157 **(58.1)**	286 **(53.8)**
Age [mean + SD]	74.9 [11]	73.9 [12]	75.1 [11]
Numb days at index hosp [mean + SD]	**7.5 [8.8]**	**6.6 [5.9]**	**7.7 [8.0]**
Medical visits in 1st 6 months* [mean + SD]	**22.8 [16]**	**23.3 [17]**	**25.9 [18]**
Chronic Disease Score*			
0 to 3	123 **(12.1)**	42 **(15.6)**	91 **(17.1)**
4 to 5	167 **(16.5)**	48 **(17.8)**	95 **(17.9)**
6 to 7	269 **(26.6)**	69 **(25.6)**	162 **(30.5)**
8 to 9	239 **(23.6)**	53 **(19.6)**	103 **(19.4)**
10 to 22	215 **(21.2)**	58 **(21.5)**	81 **(15.2)**

SD = standard deviation
* indicates a significant ($p \leq 0.05$) difference between groups. Significance was determined using a t-test for continuous variables and a chi-square analysis for categorical variables.

Prior ACE inhibitor, beta blocker and statin use, as well as prior ischemic heart disease is seen more frequently in the high adherence cohort compared to the other groups. The majority of subjects in all three cohorts had less than three hospital admissions in the year prior to the index hospitalization (Table 6.7).

Table 6.7. Patient Characteristics Prior to Study Entry in Patients using Beta Blockers

Baseline Characteristics (%)	High Adherence (n=1013)	Medium Adherence (n=270)	Low Adherence (n=532)
Prior ACE inhibitor use*	534 **(52.7)**	146 **(54.1)**	227 **(42.7)**
Prior beta blocker use*	558 **(55.1)**	139 **(51.5)**	232 **(43.6)**
Prior statin use*	226 **(22.3)**	45 **(16.7)**	63 **(11.8)**
Prior IHD*	518 **(51.1)**	124 **(45.9)**	238 **(44.7)**
Hospitalizations in year prior			
0	470 **(46.4)**	122 **(45.2)**	252 **(47.4)**
1 to 2	389 **(38.4)**	104 **(38.5)**	206 **(38.7)**
3 to 18	154 **(15.2)**	44 **(16.3)**	74 **(13.9)**

ACE = angiotensin converting enzyme; IHD = ischemic heart disease
* indicates a significant ($p \leq 0.05$) difference between groups. Significance was determined using a t-test for continuous variables and a chi-square analysis for categorical variables.

As to be expected in the heart failure population, over 90 percent of subjects taking a beta blocker also used a loop diuretic throughout the study period. Also, over 85 percent of subjects taking a beta blocker filled a prescription for an ACE inhibitor or an ARB. Subjects in the low adherence cohort were less likely to be adherent to an ACE inhibitor or ARB compared to the high beta blocker adherence group. Other medication use was similar between groups with the exception of lower digoxin use and higher statin use in patients exhibiting high adherence (Table 6.8). Overall, there appeared to be few clinically important differences between the adherence cohorts.

Table 6.8. Patient Characteristics: Use of Heart Failure Medication Throughout the Study Period in Patients using Beta Blockers

Baseline Characteristics (%)	High Adherence (n=1013)	Medium Adherence (n=270)	Low Adherence (n=532)
Loop diuretic use	947 **(93.5)**	252 **(93.3)**	499 **(93.8)**
ACE or ARB use			
Not used	109 **(10.8)**	37 **(13.7)**	65 **(12.2)**
< 80% adherence*	214 **(21.1)**	94 **(34.8)**	217 **(40.8)**
> 80% adherence*	690 **(68.1)**	139 **(51.5)**	250 **(47)**
Spironolactone use*	436 **(43)**	133 **(49.3)**	206 **(38.7)**
Digoxin use*	449 **(44.3)**	134 **(49.6)**	290 **(54.5)**
Statin use*	371 **(36.6)**	89 **(33)**	124 **(23.3)**
Hydralazine use	59 **(5.8)**	18 **(6.7)**	28 **(5.3)**
Nitrate use	650 **(64.2)**	171 **(63.3)**	341 **(64.1)**

ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker
* indicates a significant ($p \leq 0.05$) difference between groups. Significance was determined using a t-test for continuous variables and a chi-square analysis for categorical variables.

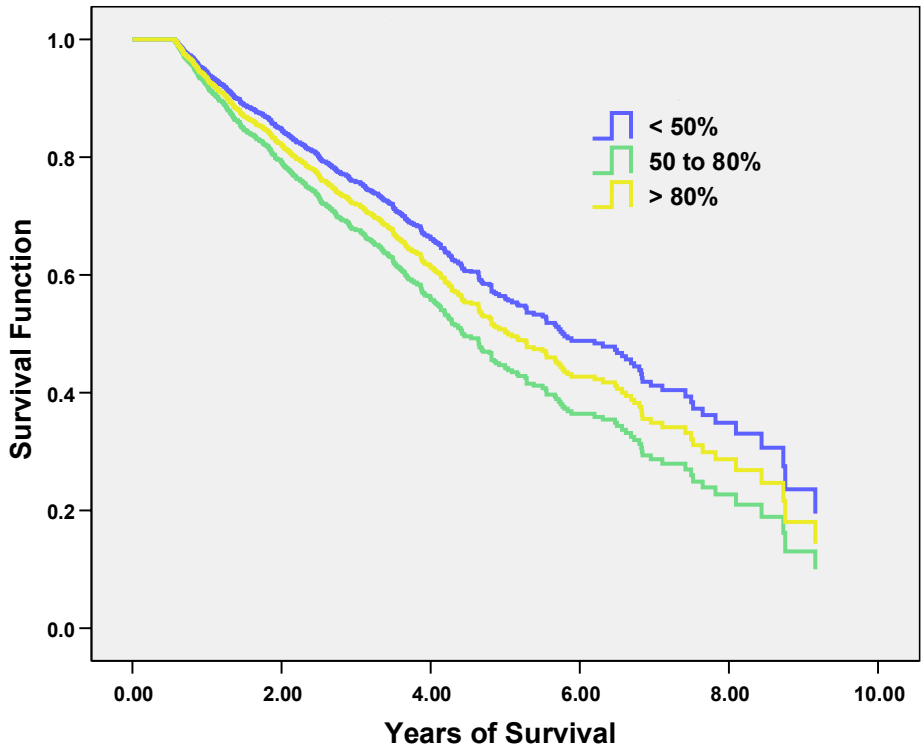
All-cause Mortality

Of the patients in the three adherence cohorts, 202 (38 percent) died in the low adherence, 96 (35.6 percent) died in the medium adherence, and 317 (31.3 percent) died in the high adherence cohort, and the median survival time for all patients dying within these cohorts was 2.2, 1.9 and 1.6 years, respectively. Compared to those exhibiting low adherence, patients in the medium adherence cohort (50 to 80 percent) had significantly shorter survival [HR = 1.41 (95% CI: 1.09 to 1.81; $p<0.01$)]. Although there was no significant difference in survival between the high and low adherence cohorts, there appeared to be a trend towards higher mortality in those who remained adherent [HR = 1.18 (95% CI: 0.98 to 1.43; $p=0.07$) (Figure 6.6 and Table 6.9).

Similar findings were discovered when various subgroups were examined. The low adherence cohort consistently demonstrated the longest survival time, and survival

curves were comparable to the results of all beta blocker users. Any slight differences seen within the survival curves of the subgroups are deemed to be due to chance variation and small sample size.

Figure 6.6. Adjusted Survival Curves for Beta Blocker Adherence with an Outcome of All Cause Mortality using a Cox Proportional Hazards Model



< 50% = the low adherence cohort; 50 to 80% = the medium adherence cohort; > 80% = the high adherence cohort

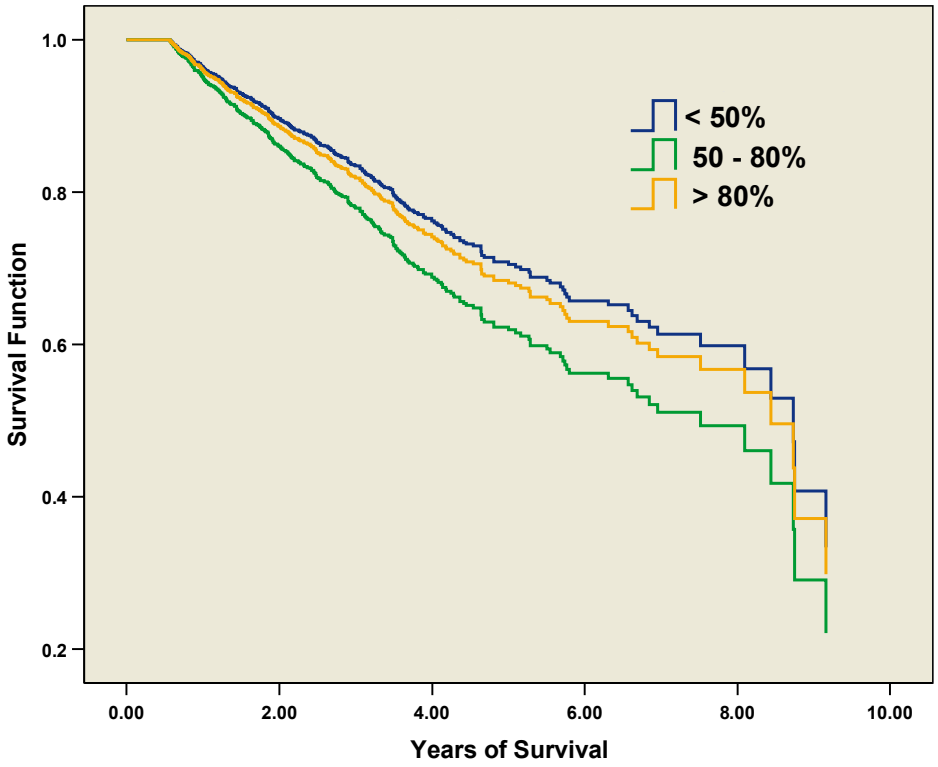
Cardiovascular Mortality and Time to First Hospitalization

There were a total of 375 cardiovascular deaths among the 1815 beta blocker subjects included in this analysis. One hundred and thirty subjects (24.4 percent) died of a cardiovascular cause in the low adherence cohort, 61 (22.6 percent) in the medium adherence and 184 (18.2 percent) in the high adherence cohort. Of those dying of a

cardiovascular cause in the low, medium and high adherence cohorts, the median survival time was 2.1, 1.8 and 1.7 years, respectively.

Compared to the low adherence group, the 50 to 80 percent cohort had a hazard ratio of 1.37 (95% CI: 1.01 to 1.87; p<0.045), thus indicating a significantly decreased survival time. The ≥ 80 percent adherence group, when compared to the low adherence cohort, had a HR of 1.1 (95% CI: 0.87 to 1.39; p=0.42). (Figure 6.7 and Table 6.9).

Figure 6.7. Adjusted Survival Curves for Beta Blocker Adherence with an Outcome of Cardiovascular Mortality using a Cox Proportional Hazards Model



< 50% = the low adherence cohort; 50 to 80% = the medium adherence cohort; > 80% = the high adherence cohort

The sample size in the survival analysis for time to first hospitalization was drastically reduced compared to the analysis of all-cause mortality. The reason for this

is that many of the patients who were initiated on a beta blocker throughout the study period did not start it prior to their first hospitalization, and also because the first hospitalization had to be at least 6 months after index. Thus, only a total of 484 patients were included in the analysis of this secondary endpoint. There were 86 patients in the low adherence, 82 patients in the medium adherence and 316 patients in the high adherence cohorts.

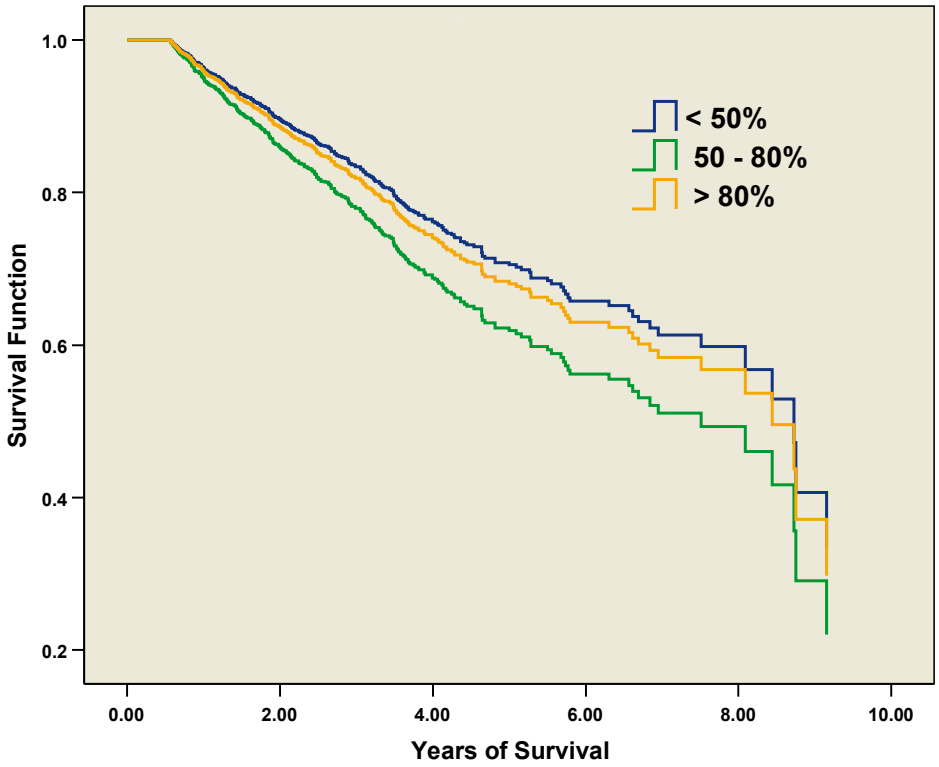
The average time until the first hospitalization was 17 months from the index date. Approximately 50 percent of subjects were hospitalized within the first year of their index hospitalization, with 80 percent of subjects being hospitalized within 2 years.

Compared to the low adherence group, the medium adherence cohort had a significantly greater risk for repeat hospitalization [HR = 1.44 (95% CI: 1.05 to 1.99; p=0.025)]. In the high adherence cohort, although not statistically significant, there appears to be a higher risk for hospitalization compared to the low adherence group [HR = 1.21 (95% CI: 0.94 to 1.55; p=0.15)] (Figure 6.8 and Table 6.9).

Table 6.9. Results of Survival Analyses

	Hazard Ratio (95% Confidence Interval)	
	High vs Low Adherence Cohort	**Medium vs Low Adherence Cohort**
All-cause Mortality	1.18 (0.98 to 1.43)	1.41 (1.09 to 1.81)
Cardiovascular Mortality	1.10 (0.87 to 1.39)	1.37 (1.01 to 1.87)
Time to First Hospitalization	1.21 (0.94 to 1.55)	1.44 (1.05 to 1.99)

Figure 6.8. Adjust Survival Curves for Beta Blocker Adherence with an Outcome of Time to First Hospitalization using a Cox Proportional Hazards Model



< 50% = the low adherence cohort; 50 to 80% = the medium adherence cohort; > 80% = the high adherence cohort

7. DISCUSSION

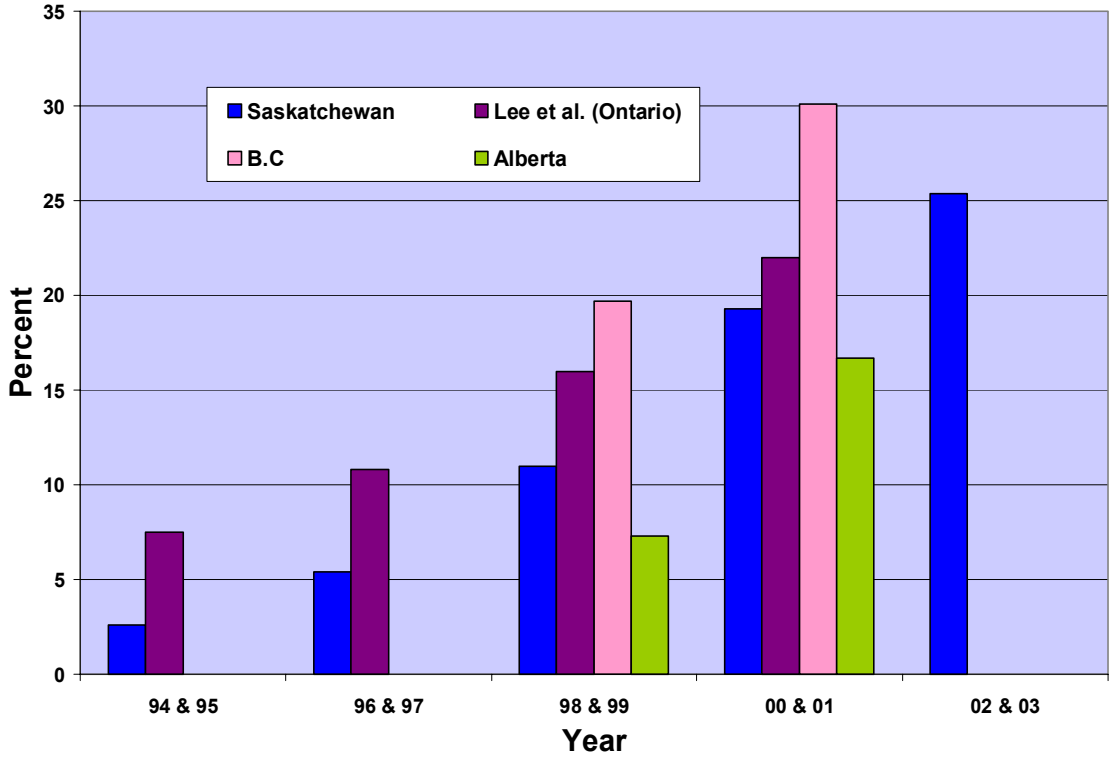
Between 1994 and 2003, over 14,000 subjects were discharged from a Saskatchewan hospital with a first-ever primary or most responsible diagnosis of heart failure. In the Saskatchewan population, the average age of heart failure patients was 78.5 years with 51.7 percent being male. These characteristics are similar to subjects seen in other population based heart failure papers. For example, patients with newly diagnosed heart failure have been reported to have a mean age ranging from 71.3 to 80 years with approximately 53 percent of the patient population being male. [5, 21, 28, 58] de Giuli et al. reports an average survival time of heart failure patients to be approximately two years, which was similar to the Saskatchewan population (2.4 years). [3]

7.1 Phase I: Utilization of Heart Failure Medications

Prior to the publication of landmark trials showing a mortality benefit in heart failure patients, use of beta blockers in Saskatchewan was minimal at 2.6 percent. After the benefit of beta blockers was recognized in 1996, their use almost doubled every two years and by the end of 2003, approximately 25 percent of heart failure patients were receiving a beta blocker (Figure 6.1 in Results section). This increase in use over time in the Saskatchewan heart failure population is comparable to other Canadian provinces (Figure 7.1). [36, 76] Utilization of beta blockers in other countries is also similar, but slightly higher than that seen in Saskatchewan. The EuroHeart

Failure Survey, which includes data from 24 countries belonging to the European Society of Cardiology, reported an average beta blocker utilization rate of 36.9 percent (range of 10 to 66 percent) in 2003. [58]

Figure 7.1. Utilization of Beta Blockers within Canada[36, 76]



Despite the rapidly increasing utilization rate, only 25 percent of patients at the end of 2003 started a beta blocker within 30 days of being discharged from their index hospitalization. Although poor uptake of evidence-based guidelines likely plays a significant role, subtle diagnostic issues may also have contributed to the low rates of beta blocker use. For example, diastolic heart failure may account for 50 percent or more of all heart failure admissions and although beta blockers may provide some benefit, they are not specifically targeted in this group of patients because few clinical

trials are available to guide drug therapy. [1, 9] Using data from Saskatchewan Health databases, it was impossible to distinguish between patients exhibiting heart failure with preserved systolic function (diastolic heart failure) versus those with systolic dysfunction. In addition, it is plausible that certain patients were misdiagnosed with heart failure and did not require a beta blocker after discharge. However, researchers in Ontario have demonstrated their administrative heart failure diagnoses to be very accurate, at least in hospitals with frequent heart failure admissions. [118]

It has been reported that only 15 percent of heart failure patients have a contraindication for beta blocker use. [119] If this is the case, the current use of beta blockers in Saskatchewan, even taking into account the prevalence of diastolic heart failure, indicates a vast underutilization of that drug class in heart failure patients, and the benefits seen in randomized controlled trials are not being realized in the general heart failure population.

In contrast to the increasing use of beta blockers, utilization of ACE inhibitors and ARBs within a 10 year period has remained relatively unchanged in Saskatchewan at approximately 60 percent (Figure 6.2 in Results section). Since landmark ACE inhibitor trials were first published in the late 1980s and early 1990s, it is likely that a trend for increased prescribing was observed prior to our observation period (1994-2003). This appears to be true, as one study in the United States showed an increase in ACE inhibitor use from 24 percent in 1990 to 34 percent in 1992, and then a plateau with a very gradual increase to 38 percent in 2002. [73] Studies within the last seven years have shown similar utilization rates for ACE inhibitors (range of 40 to 85

percent) that were seen in the Saskatchewan population, with utilization rates of ARBs being less than 10 percent. [58, 72, 75-77, 80]

It is recommended that all heart failure patients with systolic dysfunction receive an ACE inhibitor, and ACE inhibitors should also be considered for most patients with preserved systolic function. [9] Only 6.7 to 17 percent of patients were unable to tolerate an ACE inhibitor in clinical trials. [44-46, 61] Although poor tolerance may be slightly higher in a community based heart failure population, utilization of these important classes of medication would also seem to be problematic in Saskatchewan.

7.1.1 Mean Daily Dose of Beta Blockers

Beta blockers prescribed for heart failure patients in Saskatchewan fail to meet target doses by one third to a half. Although, a target dose for atenolol has not been established, it is probable that atenolol would have a target dose of 100mg per day based on its use in other cardiovascular conditions. Of the subjects taking atenolol, there were only 41 (3 percent) with an average daily dose of 100 mg or higher. Metoprolol succinate, which was used in the MERIT-HF [52] trial at a target dose of 200 mg a day, is not available for use in Canada. A target dose for metoprolol tartrate (available in Canada) has not been formally established, however, this formulation was titrated to a target of 100 mg a day in the COMET [51] trial. In the Saskatchewan population, only 157 subjects (10.7 percent) taking metoprolol had an average dose of 100 mg or higher, with only 18 (1 percent) having a mean daily dose of 200 mg or higher. A target dose of 25 mg twice daily for carvedilol in chronic heart failure

patients was seen in the COPERNICUS and COMET trial, along with the US Carvedilol Heart Failure Study. [51, 55, 120] In Saskatchewan, there were only 11 subjects (1.8 percent) taking an average daily dose of carvedilol reaching 50 mg or more per day.

Heart failure guidelines suggest that beta blocker doses should be titrated to target levels in all patients if tolerated. [1, 9] Despite this suggestion, it appears that many patients do not have their doses increased. Interestingly, this problem appears to be prevalent around the world. The EuroHeart Failure survey showed average daily doses that were very similar to the results shown in Saskatchewan (46, 75, 4.7 and 17.6 mg per day (EuroHeart) versus 44, 59, 5.6, and 18mg per day (Saskatchewan) for atenolol, metoprolol, bisoprolol and carvedilol, respectively). [58] Various other population based studies reveal similar results, with prescribed beta blocker doses only reaching up to 50 percent of target. [72, 75, 80, 92] Thus, not only is there a vast underutilization of beta blockers in heart failure, but it appears that target doses are not met in the majority of patients.

Reasons for the low doses seen may include the advanced age of heart failure patients, the inability for a patient to tolerate higher doses due to the severity of the disease, lack of knowledge in regards to heart failure guidelines and/or clinical inertia. Regardless of the reason, it is generally felt that titrating beta blockers to target doses will provide greater benefits. Post-hoc analysis of the CIBIS-II and MERIT-HF trials show that there may be a greater benefit for target doses of beta blockers compared to low doses, but when compared to placebo, both dosage levels had relatively the same benefit on mortality. [121, 122] The MOCHA trial showed that the use of carvedilol at 25

mg twice daily resulted in a mortality of 1.1 percent compared to doses of 12.5 mg or 6.25 mg twice daily, which resulted in a mortality of approximately 6 percent. [123] Unfortunately, this trial was not designed to evaluate the effect of dose on mortality and the number of deaths was small. In a post-hoc analysis of the SENIORS trial, target and medium doses of nebivolol, a beta-1 specific beta blocker with vasodilating properties (not available in Canada), provided greater benefit in terms of all cause mortality or cardiovascular hospitalization then low dose nebivolol when compared to placebo. [124] Although results are conflicting, all of these post-hoc analyses agree that the use of a beta blocker in systolic heart failure patients at any dose will provide some benefit, but that target doses should be strived for if tolerated.

7.2 Phase II: Adherence to ACE inhibitors and Beta Blockers

Unlike most trials of adherence to medication in heart failure, it was the goal of this study to calculate adherence on a yearly basis and observe trends over a four year period. It appears that the majority of heart failure patients in Saskatchewan are adherent with both beta blocker and ACE inhibitor therapy, especially in the first year, as adherence rates reach approximately 80 percent. Unfortunately a decrease in adherence is seen over time, such that approximately only 60 percent of patients are adherent after four years (Figure 6.3 in the Results section). Furthermore, a significant number of individuals stop these life-saving medications after only one or two fills. It is interesting to note that both ACE inhibitor and beta blocker adherence in the Saskatchewan population is almost identical and that this similarity continues over time.

When the adherence measure is calculated from the day of discharge rather than the first prescription fill, only one third of all patients meet the 80 percent requirement for optimal adherence. Subsequently, less than one-quarter are adherent after four years (Figure 6.4 in the Results section). This adherence perspective suggests that many of the patients requiring a beta blocker (evidenced by beta blocker use at some point in time), do not receive this life-saving medication early on in their disease. This is unfortunate, as the benefits of beta blockers have been observed in heart failure patients from the time of diagnosis, and guidelines suggest starting a beta blocker as early as possible after diagnosis of left ventricular dysfunction. [1, 9, 44, 53]

Regardless of the perspective examined, a decrease in adherence is still observed over time. Diminishing adherence rates may be a result of problems with memory, concerns over medication cost, lack of understanding of the benefits of the medication or various other reasons. Perhaps heart failure patients are not reminded of these benefits often enough and have no incentive to continue taking them over the long term.

In contrast to patient-specific issues, it is also possible that physicians are discontinuing the use of these medications for various reasons. A study examining persistence with medication in heart failure patients reported that a common reason for discontinuation with a beta blocker was failure to re-initiate therapy after a hospital admission. [101] Whatever the reason, it is the responsibility of health care professionals to ensure that patients with heart failure are prescribed life-saving medications on an ongoing basis and that they strive to minimize the barriers associated with chronic medication adherence.

Despite the numerous studies examining medication adherence in general, it is unknown which method of measuring adherence is the most appropriate. Using Saskatchewan Health data, it was possible to evaluate a large number of subjects who were unaware that adherence was being examined. As such, their refill habits were likely to be "natural". Furthermore, it has been shown that there is a high correlation between adherence calculated from a prescription claims database and adherence from pill counts. [87] None of the previously published adherence papers in heart failure calculated adherence using the global perspective, and thus do not take into account the time to initiation of heart failure medication from diagnosis.

Our study supports previous findings, showing that adherence to medications in heart failure is relatively high and usually exceeds 70 percent, with many studies reporting adherence rates of over 80 or 90 percent. [84-86, 88-90, 93, 94, 100] van der Wal et al. reported overall medication adherence in heart failure patients to be 98.6 percent. [125] However, this study used a questionnaire on hospitalized patients asking about adherence over the past week, the past month and three months prior to hospitalization, relying on patient memory and self-report. [125] In contrast, the results generated from our present study were based on a more objective measure of adherence.

Adherence to ACE inhibitors has been reported to range from 67 to 92.9 percent, which is similar to rates reported herein.[88-91, 93, 94] Sample sizes varied from 64 to 5259 subjects, and adherence was measured using administrative databases, pharmacy records, and electronic counters (MEMS). Consecutive changes in adherence on a yearly basis had not been examined in any of the previously published ACE inhibitor adherence papers.

Aside from papers examining discontinuation rates or persistence of use, only one study measuring adherence to beta blockers could be found. [91] Cole et al. used a large database from the UnitedHealthcare insurance plan to measure adherence to both beta blockers and ACE inhibitors and examine the effect that various copayment prices have on this adherence rate. Just over 5000 subjects taking a beta blocker were included in the adherence calculation and the median adherence rate was 91.6 percent. As all subjects in this trial had coverage under the UnitedHealthcare insurance plan, subjects were not paying full price for heart failure medications, and this may have resulted in a higher than expected median adherence rate. Also of note, subjects with adherence below 20 percent and over 120 percent were excluded. The results of the study by Cole et al. reflect excellent adherence rates for beta blockers that are higher than, but similar to, rates seen in the Saskatchewan population.

Predictors of Beta Blocker Adherence

In terms of predicting adherence to beta blockers in the Saskatchewan population, the year of entry into the study had the greatest impact. Subjects entering the study within the years of 2002 and 2003 had 5 times better odds of being adherent compared to subjects entering within the years 1994 and 1995. As subjects are more likely to have better adherence rates in the first year or two after diagnosis, the reason for this predictor may be that subjects entering in the latter part of the study period had less time to become non-adherent. Another reason may be better acceptance of beta blocker use in heart failure patients by health care professionals and better adherence with guideline recommendations.

Subjects filling a beta blocker within 1 month of index hospitalization had 1.5 times better odds of being adherent compared to subjects filling a prescription after that time. This may suggest that initiating life-saving drugs early on plays a big role on continued use of these medications and subsequent long term adherence.

Of interest is the fact that adherence to other medications, such as ACE inhibitors or ARBs, increased the likelihood of being adherent to a beta blocker by 1.66 times. Complexity of a patient's drug regimen has been cited in the past as a reason for poor compliance, [82] but results from the Saskatchewan population may imply that polypharmacy does not necessarily have a negative impact on adherence. A recent study supports this, as Gislason et al. found that multiple concomitant medication use was associated with the increased persistence of ACE inhibitors, ARBs, and beta blockers in heart failure patients. [92]

7.3 Phase III: Effects of Beta Blockers on Health Related Outcomes

7.3.1 Effects of Beta Blocker Use on All-cause Mortality

Using a Cox proportional hazards model to analyze the effect of beta blocker use on all-cause mortality resulted in an unadjusted risk reduction of 33 percent. This is similar to most of the landmark beta blocker trials in chronic systolic heart failure which showed an average risk reduction of approximately 35 percent. [52, 54, 56] After controlling for patient variables in our study, the risk reduction with beta blocker use was shown to be 61 percent which is similar to the 65 percent reduction in the risk of death seen in the US Carvedilol Heart Failure study. [55]

A Canadian trial examining the use of beta blockers in a heart failure clinic in Alberta, found that beta blocker use was associated with a 37 percent reduction in mortality risk after adjustment of patient characteristics. [119] Because the trial took place in a heart failure clinic, investigators had access to valuable information such as ejection fraction, type of heart failure, and NYHA class, all of which was included in their Cox proportional hazards model. Although the adjusted risk reduction in this Canadian trial is not the same as that seen in the Saskatchewan population, both show a significant mortality benefit with the use of beta blockers within a real world population.

7.3.2 The Effect of Beta Blocker Adherence on Health Related Outcomes

Patients demonstrating high adherence to beta blockers exhibited a higher chronic disease score and greater frequency of ischemic heart disease compared to non-adherent patients at baseline. In contrast, the number of medical visits within the first six months is higher in the low adherence cohort. A higher prevalence of ACE inhibitor, beta blocker and statin use was seen in the high adherence cohort, whereas digoxin was used more commonly in the low adherence groups. The importance of all observed baseline differences was assessed and adjusted for in Cox proportional hazards models.

A survival advantage could not be demonstrated for subjects who exhibited high adherence compared to the low adherence group (HR = 1.18; p=0.07) in terms of all-cause mortality. Interestingly, the small group of subjects categorized with medium adherence exhibited a statistically significant decrease in survival compared

to the low adherence cohort (HR = 1.41; $p<0.01$). Secondary analysis examining the effect of beta blocker adherence on cardiovascular mortality and all-cause hospitalization shows similar results.

The reason for our inability to detect a survival advantage with increasing levels of adherence remains unclear. All patients included within these survival analyses had a primary or most responsible diagnosis of heart failure, and for each patient there were 30 variables available from our database that could have been used in our Cox model. All variables having a significant effect on survival time and all clinically relevant variables were used within each model. Of course there is the possibility of missed information that was unavailable to us, such as lifestyle factors, smoking status and body mass index. However, it is important to note that rates of obesity, smoking, and other such lifestyle risk factors would be expected to be lower in the adherent cohort due to the healthy adherer effect. [126] Overall, it is felt that the most important variables were included in the model and accounted for.

Selection bias is also an issue that needed to be examined. In terms of the present study, selection bias refers to the unknown characteristics of a patient that may influence adherent behavior to a drug. To both examine and limit selection bias in our data, a basic propensity analysis was performed for the primary endpoint of all-cause mortality. Propensity analysis is a statistical tool that calculates the probability of a subject being assigned to a certain cohort based on known subject characteristics. [127] Once the propensity score is calculated it can be used as part of a multivariate adjustment to account for possible selection bias. [127] Using the beta blocker adherence cohorts, a propensity score was calculated to predict the probability of a subject being

adherent based on each individual's characteristics. The scores were then categorized into quintiles and inserted into the Cox proportional hazards model. No significant effects on survival time were noted, meaning that selection bias was not an issue within our analysis.

Certainly one limitation in our analysis would be the small sample size within each beta blocker cohort. From a total of 1815 subjects in the adherence analysis, division resulted in a limited sample size of 1013, 270, and 532 subjects in the high, medium and low adherence cohorts, respectively. Another limitation is the fact that no clinical evidence exists for the use of atenolol in heart failure. As this drug has a high frequency of use in the heart failure population, and has similar properties to bisoprolol and metoprolol, it was included in our analysis. Post-hoc subgroup analysis, which was conducted separately for carvedilol, metoprolol, and bisoprolol, resulted in no differences compared to patients taking atenolol. Throughout this study we assumed that dispensations from community pharmacies were a direct measure of 'prescribing'. As such, all prescribing rates were estimated solely on the basis of dispensing records. Although there is a distinct difference between prescribing and dispensing, it is felt that this difference is likely to be small and it should be noted that other observational trials making use of administrative databases have made the same assumption. [76] Other limitations that have been stated previously, include our inability to distinguish between types of heart failure, and possible diagnostic issues.

In contrast to our study, Gislason et al. studied the effect of non-persistence with a beta blocker on survival time in Denmark and concluded that patients having a break in beta blocker therapy of at least 90 days have a higher risk of death than

patients without that break in therapy. [92] Interestingly, of all subjects who were classified as non-persistent, almost half of these patients re-initiated a beta blocker after the 90 day break in therapy. The patient population within this study was very similar to that seen in our study, and the only major difference, aside from the adherence measure used, is that there were a total of 107,092 patients with a first hospitalization of heart failure, and 29,084 patients started on a beta blocker and were included in their survival analysis.

Another adherence paper in heart failure patients examined the effect of digoxin non-compliance on hospitalization and mortality. [105] Digoxin compliance was measured using serum drug concentration, and it was found that non-compliance to digoxin resulted in a 2.5 times higher rate of hospitalization and a two times higher mortality rate. Although patients were suffering from chronic heart failure, digoxin was prescribed for treatment of supraventricular tachycardia. As this medication has not been shown to reduce mortality in patients with heart failure[128], the results seen may be due to the control of resting heart rate and not because of any beneficial effect on heart failure.

8. CONCLUSIONS

The data presented herein clearly demonstrates a vast underutilization of both beta blockers and ACE inhibitors or ARBs in heart failure patients. Even in the patients receiving these life-saving medications, a large delay in obtaining the first prescription was observed for many. Clearly, much work is needed by health care professionals to improve the management of heart failure patients in the community setting.

For those patients prescribed beta blockers and ACE inhibitors, it appears that adherence is generally optimal in the first year. Unfortunately, over time, these medications are not filled on a regular basis or are being stopped altogether. It needs to be realized by both patients and health care professionals just how important it is to continue taking these medications for the treatment of heart failure. A most interesting finding, in regards to adherence, was that concomitant medication use increases the likelihood of adherence to a beta blocker.

Similar to the landmark beta blocker trials, we were able to show in this real-world sample, that use of beta blockers was significantly associated with increased survival. In contrast, we were unable to detect a mortality benefit due to optimal adherence. However, the overall rate of adherence was excellent in the vast majority of patients during the first year. It is possible that non-adherence is not responsible for a significant burden of mortality in Saskatchewan heart failure patients and the focus of quality improvement should be optimal prescribing of evidence-based therapies.

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APPENDIX A

Biomedical Ethics Approval

University of Saskatchewan
Biomedical Research Ethics Board (Bio-REB)

18-Aug-2006

Certificate of Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
David Blackburn	Pharmacy	06-173

INSTITUTION (S) WHERE RESEARCH WILL BE CARRIED OUT

University of Saskatchewan

Saskatoon SK

STUDENT RESEARCHER(S)

Darcy Lamb

SPONSORING AGENCIES

UNIVERSITY OF SASKATCHEWAN

TITLE:

Utilization and Adherence Rates of Heart Failure Medications and their Subsequent Effect on Hospitalization and Mortality in Patients with Heart Failure

ORIGINAL APPROVAL DATE	CURRENT EXPIRY DATE	APPROVAL OF
18-Aug-2006	01-Aug-2007	Protocol as submitted

CERTIFICATION

The University of Saskatchewan Biomedical Research Ethics Board has reviewed the above-named research project at a full-board meeting (any research classified as minimal risk is reviewed through the expedited review process). The proposal was found to be acceptable on ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research project, and for ensuring that the authorized research is carried out according to governing law. This Approval is valid for the above time period provided there is no change in experimental protocol or in the consent process.

ONGOING REVIEW REQUIREMENTS/REB ATTESTATION

In order to receive annual renewal, a status report must be submitted to the Chair for Committee consideration within one month of the current expiry date each year the study remains open, and upon study completion. Please refer to the following website for further instructions: http://www.usask.ca/research/ethics.shtml. In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. This approval and the views of this REB have been documented in writing.

APPROVED.

Michel Desautels, Ph.D., Chair
University of Saskatchewan
Biomedical Research Ethics Board

Please send all correspondence to:

Ethics Office
University of Saskatchewan
Room 305 Kirk Hall, 117 Science Place
Saskatoon, SK S7N 5C8
Phone: (306) 966-4053 Fax: (306) 966-2069

APPENDIX B

Administrative Codes and Medications Used to Identify Excluded Subjects

Identification of Exclusion Diagnoses Through Saskatchewan Health Databases

HIV/AIDS	**ICD-9:** • 042 to 44.x, 795.8 **ICD-10:** • B20 to B24.xxx, R75, Z21 **Medication use:** • abacavir, amprenavir, delavirdine, didanosine, efavirenz, indinavir, lamivudine, lopinavir, nelfinavir, nevirapine, rotinavir, saquinavir, stavudine, zalcitabine, zidovudine
Solid organ transplant	**ICD-9:** • V42.0 to V42.8 inclusive **ICD-10:** • Z94.0 to Z94.4xx inclusive **CCP:** • 45.5x, 45.6x, 49.5x, 62.4x, 64.8x, 67.5x **FFS:** • 303R-305R, 307R, 308R, 350D **Medication use:** • cyclosporine, mycophenolate mofetil, sirolimus, tacrolimus
Terminal illness	**ICD-9:** • V58.8 **ICD-10:** • Z51.5 **Medication use:** • Any prescription fill with palliative care coverage

ICD–9: World Health Organization International Classification of Diseases, Ninth Revision codes - diagnoses from hospital services database discharge abstracts
ICD-10: World Health Organization International Classification of Diseases, Tenth Revision codes - diagnoses from hospital services database discharge abstracts
CCP: Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures - codes for procedures performed during hospital stays in the hospital services database discharge abstracts
FFS: Fee for service codes billed through the physician services database

APPENDIX C

Description of Variables used in Analysis of Heart Failure Patients

1. Sex – refers to the gender of the patient. This information was given to us in the subject file database from Saskatchewan Health. For analysis purposes, this was a dichotomous variable: male and female.

2. Age – refers to the age of the subject at the time of index hospitalization. The date of birth is available from the subject file database, and age was calculated based on this information. For analysis purposes, this was a continuous variable.

3. ACE inhibitor or ARB adherence – From the drug database, all fills for an ACE inhibitor and/or an ARB were selected for all patients. From this information, adherence was calculated using the fill frequency measure of adherence (global perspective). These values were adjusted based on hospitalization throughout the study period. This continuous variable was then broken down into three categories for the purpose of analysis: patients with adherence $\geq$ 80 percent, patients with adherence $<$ 80 percent, and patients not taking an ACE inhibitor or an ARB.

4. Anti-arrhythmic drug use – refers to whether or not a subject filled at least one prescription for a medication (with the exception of digoxin, beta blockers and calcium channel blockers) used in the treatment of arrhythmia. An anti-arrhythmic drug was considered to be one of the following: mexiletine, procainamide, propafenone, disopyramide, flecainide, quinidine, amiodarone, tocainide or sotalol. This information was acquired from the drug database, and anyone filling at least one prescription for an anti-arrhythmic agent within the study period was selected. This variable was dichotomous in nature.

5. Digoxin use – refers to whether or not a subject filled at least one prescription of digoxin within the study period, and as such this was a dichotomous variable. This information was obtained through the drug database.

6. Use of diabetes medications – refers to whether or not a subject filled at least one prescription for any type of diabetic medication (oral or injectable) within the

study period, and as such this was a dichotomous variable. A diabetic medication was considered to be one of the following: acarbose, acetohexamide, chlorpropamide, glyburide, insulin, metformin, nateglinide, phenformin, pioglitazone, repaglinide, rosiglitazone or tolbutamide. This information was obtained through the drug database.

7. Hydralazine use – refers to whether or not a subject filled at least one prescription of hydralazine within the study period, and as such this was a dichotomous variable. This information was obtained through the drug database.

8. Loop diuretic use – refers to whether or not a subject filled at least one prescription of a loop diuretic within the study period, and as such this was a dichotomous variable. A loop diuretic was considered to be one of the following: furosemide, bumetanide or ethacrynic acid. This information was obtained through the drug database.

9. Physician caring for patient at index hospitalization – refers to the type of physician caring for the patient during their index hospitalization. Type of physician includes general practitioner, internist, cardiologist or other. This information is given to us in the hospital services database. This variable is categorical in nature.

10. Non-dihydropyridine calcium channel blocker use – refers to whether or not a subject filled at least one prescription of a non-dihydropyridine calcium channel blocker (diltiazem or verapamil) within the study period, and as such this was a dichotomous variable. This information was obtained through the drug database.

11. Nitrate use – refers to whether or not a subject filled at least one prescription of a nitrate within the study period, and as such this was a dichotomous variable. A nitrate was considered to be one of the following: erythrityl tetranitrate, isosorbide dinitrate, isosorbide mononitrate or nitroglycerin. This information was obtained through the drug database.

12. Number of hospitalizations in the year prior to index – refers to the number of times a patient was admitted to hospital (excluding day surgery admissions) in the year prior to the index hospitalization. This variable was calculated using the hospital services database, and was broken down into the following categories: 0 hospitalizations, 1 to 2 hospitalizations, and $\geq$ 3 hospitalizations.

13. Use of other hypertension medications – refers to whether or not a subject filled at least one prescription for a hypertension medication not already included in another variable. The term other hypertension medication was considered to be one of the following: clonidine, doxazosin, guanethidine, methyldopa, minoxidil, nimodipine, prazosin, reserpine, terazosin, amlodipine, felodipine, nicardipine or nifedipine. This information was obtained from the drug database, and the variable was dichotomous in nature.

14. Prior ACE inhibitor use – refers to whether or not a subject filled at least one prescription of an ACE inhibitor in the five years prior to the index hospitalization, and as such this was a dichotomous variable. This information was obtained through the drug database.

15. Prior beta blocker use – refers to whether or not a subject filled at least one prescription of any beta blocker in the five years prior to the index hospitalization, and as such this was a dichotomous variable. This information was obtained through the drug database.

16. Prior statin use – refers to whether or not a subject filled at least one prescription of a statin in the five years prior to the index hospitalization, and as such this was a dichotomous variable. A statin was considered to be one of the following: atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin. This information was obtained through the drug database.

17. Prior ischemic heart disease – refers to whether or not a subject had any evidence of prior ischemic heart disease in the five years prior to the index hospitalization, and as such this was a dichotomous variable. Information for this variable was obtained from the hospital services database, and evidence of prior ischemic heart disease comes from either a diagnosis of myocardial infarction or other ischemic heart disease, or from a surgical admission for PTCA or CABG.

18. Drug benefits category at index – refers to the type of drug coverage benefits (if any) that a subject was receiving at the time of index hospitalization. There are five categories: regular benefits, Saskatchewan assistance plan, family based income security programs, senior based programs, and the palliative care drug program. The majority (95 percent) of patients either had regular coverage or were receiving benefits from the senior based program. As there are five categories, this variable was categorical in nature. Information for this variable was obtained from the drug database.

19. Renal failure – refers to any patient presenting with evidence of renal failure within the study period, and as such this was a dichotomous variable. A diagnosis of renal failure or occurrence of renal dialysis was determined to be evidence of renal failure. This information was taken from both the hospital services and the medical visits database.

20. Spironolactone use – refers to whether or not a subject filled at least one prescription of spironolactone within the study period, and as such this was a dichotomous variable. This information was obtained through the drug database.

21. Statin use – refers to whether or not a subject filled at least one prescription of a statin within the study period, and as such this was a dichotomous variable. A statin was considered to be one of the following: atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin. This information was obtained through the drug database.

22. Thiazide diuretic use – refers to whether or not a subject filled at least one prescription of a thiazide diuretic within the study period, and as such this was a dichotomous variable. A thiazide diuretic was considered to be one of the following: hydrochlorothiazide (HCTZ), metolazone, a combination of amiloride and HCTZ, and a combination of triamterene and HCTZ. This information was obtained through the drug database.

23. Warfarin use – refers to whether or not a subject filled at least one prescription of warfarin within the study period, and as such this was a dichotomous variable. This information was obtained through the drug database.

24. Year at index hospitalization – refers to the year that a subject had their index hospitalization. This variable was broken down into two year periods and as such is a categorical variable as follows: 1994/95, 1996/97, 1998/99, 2000/01, 2002/03. This information was taken from the subjects file database.

25. Days spent in hospital at index hospitalization – refers to the length of time a subject was in the hospital for at their index hospitalization. This information was gathered from the hospital services data base and recorded in days. Number of days was then broken down into the following five separate categories: up to 2 days, 3 to 5 days, 6 to 11 days, 12 to 20 days, and $\geq$ 20 days.

26. Deyo comorbidity score – is a score that reflects the overall health of a patient at baseline, and the higher the score a patient has, the less healthy they are. This score was adapted and developed by Deyo et al. for use in administrative databases.[113, 114] The comorbidity score was calculated by Saskatchewan health based on ICD-9 and ICD-10 codes and given to us in the subject file database. The comorbidity score was broken down into the following four separate categories: 0, 1, 2 and $\geq$ 3.

27. Chronic disease score – is a score that reflects the overall health of a patient at baseline, and the higher the score a patient has, the less healthy they are. This score is created using the number of distinct drug classes being dispensed in the year prior to the index hospitalization. The calculation for this score is based on a paper by Von Korff et al.[112] Saskatchewan Health calculated the chronic disease score for each patient and included it in the subject file database. The score was broken down into the following 5 separate categories: 0 to 3, 4 to 5, 6 to 7, 8 to 9, and $\geq$ 10.

28. Number of diseases at index – refers to the number of disease states that each patient had at the time of index hospitalization. This information was taken from the subjects file database and was calculated based on medication use for various disease states that was given to us from the chronic disease score calculation. This variable was broken down into the following five separate categories: 0, 1, 2, 3, 4, and $\geq$ 5.

29. Number of physician visits within the first six months after index – refers to the number of outpatient physician visits each subject had in the first six months after index hospitalization. The information for this variable was taken from the medical visits database. This variable was broken down into the following five separate categories: 0 to 10, 11 to 16, 17 to 23, 24 to 33, and $\geq$ 34.

30. Number of hospitalizations in the first six months after index – refers to the number of times a subject was hospitalized in the first six months after index hospitalization. The information for this variable was taken from the hospital services database. This variable was broken down into the following 4 separate categories: 0, 1, 2, and $\geq$ 3.