PREDICTING OUTCOMES OF ACUTE MYOCARDIAL INFARCTION USING ADMINISTRATIVE DATA: IS DEPRESSION ASSOCIATED WITH SURVIVAL?

by

GILAT LINN GRUNAU

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Abstract

Study objectives: This dissertation investigated three main issues: Determination of the most appropriate risk-adjustment method to control for comorbidity when predicting mortality following acute myocardial infarction (AMI); whether depression following AMI is associated with important prognostic factors such as comorbidities; and whether early- and late-onset incident depression following AMI affect short- and long-term survival and health services use.

Methods: *Data* The British Columbia (BC) Linked Health Database, which includes all hospitalizations, drug prescriptions, physician visits and deaths in BC. *Participants* A cohort of 4874 individuals aged 66 years and over who had an AMI in 1994 or 1995. *Analysis* Risk-adjustment methods were compared using the C-statistic; Chi-square and Kruskal-Wallis analyses were used for testing associations between depression and prognostic factors; logistic regression analyses were used to measure the relationship between depression and health services use; Kaplan Meier and Cox regression analyses were used for determining the effect of depression on survival following AMI.

Main findings: A risk-adjustment method developed specifically for predicting mortality following AMI (the Ontario AMI predictive rule) was found to be a more appropriate method than more general methods of predicting mortality (e.g., the Charlson Index). Depression following AMI was associated with an increase in comorbidity. Both early- and late-onset incident depression following AMI significantly increased short- and long-term mortality, and is one of the strongest predictors of mortality following AMI in older adults. Depression was not found to be associated with increased health services use.

Conclusions and Significance: This was the first study to investigate the impact of depression following AMI using administrative data. Early- and late-onset depression following AMI significantly affects survival, however it does not affect health services use. In contrast to previous research, in this study incident rather than prevalent depression was measured as well as depression occurring up to 5 years following AMI, and not only at the time of or shortly after the index hospitalization. The relationship between depression and comorbidity was investigated which has not been previously done. Future research should focus on determining effective treatments for individuals with depression following AMI.

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1 CHAPTER I: Introduction

Cardiovascular disease (CVD) includes coronary heart disease (about 50%), stroke (about 25%), and all other diseases of the circulatory system. (1) CVD is the single greatest killer in the province of British Columbia (BC), Canada and accounts for more than 35% of the deaths in BC. (2) Approximately 120,000 British Columbians live with CVD as a part of their daily lives. (2)

Comorbid depression and CVD are frequently encountered (3, 4) with a combined prevalence of major and minor depression estimated in one study to be 45% in people with CVD (5). The primary goal of this dissertation was to assess the impact of early- and late-onset depression occurring after acute myocardial infarction (AMI) on the short- and long-term survival of older adults.

This introductory chapter provides an overview of the burden of illness of cardiovascular disease, the impact of depression in later life, and the relationship between depression and heart disease with regard to its epidemiology and the possible mechanisms through which depression is associated with an increased risk of mortality after an AMI. It also provides a review of the role of administrative data in health services research. Finally, the chapter ends with a discussion of the purpose of each of the chapters of this dissertation.

1.1 Cardiovascular disease

CVD inflicts the highest death toll of all diseases in BC and drains the largest portion of resources from the health care system. Based on the high level of cardiovascular risk factors prevalent among British Columbians today and on the increase

of the aging population, CVD is likely to continue to be the leading and most expensive cause of death in the province. (6)

British Columbians are more likely to die from cardiovascular disease than from any other cause. In BC, the likelihood of dying from cardiovascular disease increases with age, rising to the second leading cause of death between the ages of 45 and 64, and the number one killer after age 65. (6) Ischemic heart disease (IHD), also called coronary heart disease (CHD), is the term for heart-related conditions caused by poor delivery of blood carrying oxygen to the heart. (7) The majority of CVD's patients die from IHD, which accounts for more than one half of the CVD deaths in men and just under one half of those in women. (6)

IHD includes acute myocardial infarction (AMI), which occurs when an area of heart muscle dies or is permanently damaged because of an inadequate supply of oxygen. Most AMIs are caused by a clot that blocks one of the coronary arteries. The clot usually forms in a coronary artery that has been previously narrowed from changes related to atherosclerosis. The atherosclerotic plaque inside the arterial wall sometimes cracks, which triggers the formation of a clot known as a thrombus. A clot in the coronary artery interrupts the flow of blood and oxygen to the heart muscle leading to the death of heart cells in that area. (8) Approximately 10.2% of deaths in Canada are due to myocardial infarction. (6)

1.2 Depression in later life

Major depression according to the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) occurs when an individual exhibits one or both of two core symptoms of

depressed mood and lack of interest, along with four or more of the following symptoms for at least 2 weeks: feeling of worthlessness or inappropriate guilt; diminished ability to concentrate or make decisions; fatigue; reduced psychomotor activity or agitation; insomnia or hypersomnia; significant decrease or increase in weight or appetite; and recurrent thoughts of death or suicidal ideation. (9) Depression is perhaps the most frequent cause of emotional suffering in later life and significantly decreases quality of life in older adults. (10)

Major depression affects 5%-10% of older adults who visit primary care providers (11-13) and approximately 10%-12% of adults hospitalized for medical and surgical services, with an additional 23% experiencing significant depressive symptoms. (14)

1.3 Depression and heart disease

1.3.1 Impact of depression on development of heart disease in individuals with no pre-existing heart disease

There is a vast literature on mortality and mental illness. Findings of an increased risk of early death in individuals suffering from a mental illness were first described in the nineteenth century. A meta-analysis of published studies found that an increased risk is present in a variety of mental disorders and that elevated death rates are due to suicide, accidental causes, or natural causes. (15)

In the 1950s and 1960s, research conducted on the impact of psychiatric illness and increased cardiac risk focused on the putative association between type A personality and cardiac death. Heart disease and its risk beahviours became a major target of epidemiological studies. (16) This led to the hypothesis that affective disorders might

play a significant role in the development of cardiovascular disease. In the majority of these studies, symptoms of depression were independently associated with an increased risk for fatal and non-fatal heart disease, even after controlling for well established cardiovascular risk factors. Usually, these studies did not include patients with pre-existing heart disease. (16) Mendes de Leon et al. (17) followed 2812 elderly individuals (over 65 years of age) to investigate whether depression leads to increased cardiovascular risk, using the Center for Epidemiologic Studies Depression (CES-D) Scale (18) at baseline to measure depressive symptoms. The authors found that among women, depressive symptoms had a significant association with coronary heart disease (CHD) mortality (relative risk (RR)=1.03; 95% CI 1.01, 1.05), after controlling for standard CHD risk factors, however this relative risk is not very large. Such an association was not found for men. Ferketich et al. (19) also investigated depression as an antecedent to heart disease. They followed 5006 women and 2888 men without a history of any heart condition for 10 years, and also used the CES-D scale (18) to measure symptoms of depression. After adjusting for poverty, diabetes, hypertension, smoking and body mass index (BMI), the adjusted RR of nonfatal CHD among women was 1.73 (95% CI 1.11, 2.68). The adjusted RR estimate of an acute event and all cause mortality among depressed women was not significant. For men, the adjusted RR for depression for a nonfatal CHD event was 1.71 (95% CI 1.14, 2.56) (adjusted for poverty, race, hypertension, BMI, smoking and smoking*log time). All cause mortality was higher among depressed men than men who were not depressed, with an adjusted RR of 2.34 (95% CI 1.54, 3.56), adjusted for poverty, BMI, race, diabetes, hypertension, and nonfatal events. Cohen et al. (20) followed 5564 individuals with hypertension for

approximately 5 years. Using a Cox regression model, the authors found that a history of treatment for depression was a significant risk factor for myocardial infarction (RR=2.10; 95% CI 1.04, 4.23), after controlling for age, total cholesterol, race, history of diabetes, sex, smoking and left ventricular hypertrophy. An interesting finding of this study was that depression was not a significant predictor of non-CVD events. Barefoot et al. (21) followed 409 men and 321 women for up to 27 years. They measured depression using the Minnesota Multiphasic Personality Inventory (MMPI) (22) and found that depressive symptoms had a significant impact on IHD mortality and all cause mortality, with a relative risk of 1.62 and 1.57, respectively, even after controlling for other risk factors (including age, sex, blood pressure, triglycerides, smoking, sedentary work and leisure). Ford et al. (23) conducted a study to determine if clinical depression is an independent risk factor for incident coronary artery disease. They followed 1190 males for 40 years. Depression was measured using a mailed survey with direct questions concerning the occurrence of depression and associated treatment. In a multivariate model controlling for age, baseline cholesterol level, premature parental myocardial infarction, physical activity, time-dependent smoking, incident hypertension and incident diabetes, depression was found to be significantly associated with AMI (RR 2.2; 95% CI 1.11, 4.06) and CHD (RR=2.12; 1.24, 3.63). Pratt et al. (24) followed 1897 individuals for 13 years. At baseline they measured depression using the Diagnostic Interview Schedule (DIS). (25) In a logistic regression model adjusting for coronary risk factors, sex, age, marital status, and history of hypertension, depression was found to increase the risk for AMI (RR =4.5; 95% CI 1.65-12.44).

A large multi-country case control study, called the INTERHEART study (26) compared individuals who had their first myocardial infarction with age and sex-matched controls from 262 centers in Asia, Europe, the Middle East, Africa, Australia, and North and South America. They found that consistently across regions, different ethnic groups and men and women, cases had more depression than controls with an odds ratio of 1.55 (CI 1.42-1.69) in the year prior to the AMI.

The studies described above show that there is considerable evidence that depression (as measured in several ways) is consistently a risk factor for the development of CHD. The next section focuses on whether depression affects outcomes in individuals with pre-existing heart disease, specifically those who have had an AMI.

1.3.2 Impact of depression on individuals with pre-existing heart disease

There is evidence of an association between depression and increased morbidity or mortality in patients with various physical illnesses. (27) Considerable recent research has been concerned with the prognostic implications of depression in patients with CVD. (28) In many studies, depression following AMI has been found to increase cardiac mortality (29-35) as well as all cause mortality. (35) In one study, even minimal symptoms of depression following AMI were found to increase the risk of mortality, after controlling for independent predictors of mortality including left ventricular ejection fraction. (36) In this study, 271 individuals hospitalized with an AMI were followed for 4 months following hospitalization. Patients were evaluated soon after their AMI for mood disorder syndrome (major depression, dysthymia, and bipolar psychiatric disorder) using the Structured Clinical Interview for DSM-III-R (37) and for symptoms of depression using the Beck Depression Inventory (BDI). (38) This study showed that among patients

65 years old or over with left ventricular ejection fraction under 35%, four month mortality was 12% whereas in the same group those who had a BDI score of 10 or over (which is the threshold for symptoms of mild clinical depression) had a 4-month mortality of 50%. Frasure-Smith et al. (31) followed 222 individuals for 6 months following AMI. Depression was measured at admission for AMI using the National Institute of Mental Health Diagnostic Interview Schedule (DIS) (26) and the BDI. (38) They found that after controlling for previous AMI and Killip class [1] (known as significant independent predictors of mortality) and baseline differences between the depressed and not depressed patients (warfarin use and lack of close friends), depression had a significant impact on mortality at 6 months (Odds Ratio (OR)=3.44; 95% CI 2.25, 4.63). Frasure-Smith et al. (32) followed the same individuals for 18 months. Multivariate logistic regression was used to identify the most parsimonious group of predictors for 18-month cardiac mortality. The final model included previous AMI, premature ventricular contractions (PVCs), and Killip class. The impact of depression was assessed by forcing it into the model. The authors found that while the DIS based diagnosis of depression did not significantly improve the predictive ability of the standard risk factors, the dichotomized (at a score of 10) BDI score produced a significant improvement over the model based on previous AMI, PVCs and Killip class with an odds ratio of 6.64 (95% CI 1.76, 25.09). The continuous scores based on the BDI also improved the predictive power of the model. The interaction of PVCs and dichotomized BDI scores marginally improved the model; Thus individuals with symptoms of

[1] Killip Class is a clinical measure of left ventricular dysfunction which provides a clinical estimate of the severity of the myocardial derangement. (39) Class I includes individuals who have no heart failure, Class II includes individuals with heart failure, Class III includes individuals with severe heart failure and show frank pulmonary edema, and class IV have cardiogenic shock including signs of hypotension, and evidence of peripheral vasoconstriction.

depression who had frequent PVCs had elevated mortality risk, but the risk in those with frequent PVCs who did not have symptoms of depression was similar to those without frequent PVCs. Frasure-Smith et al. (30) followed 887 individuals who had an AMI for 1 year. They measured depression symptoms at admission for AMI using the BDI. (38) After controlling for confounders such as age and Killip class, they found that the depressed individuals were at significantly greater risk of 1-year cardiac mortality (OR=3.36; 95% CI=1.68, 6.70). Lesperance et al. (35) followed 896 individuals who had an AMI for 5 years and investigated the impact of depression (also measured using BDI) on cardiac mortality. They found that individuals with depressive symptoms (BDI score above 19) had an OR of 3.13 (95% CI=1.56, 6.27) compared to those with few depressive symptoms (a score lower than 5 on the BDI). Welin et al. (33) followed 275 individuals who had an AMI for a period of 10 years. They measured depression at admission and at 1 and 3 months using the Zung Self-Rating Depression Scale. (40) In multivariate Cox analysis, high depression scores were found to predict fatal coronary disease (Hazard Ratio=2.16; 95% CI 1.38, 5.89) after controlling for sex, left ventricular ejection fraction, and ventricular dysrhythmia.

There is evidence of the impact of depression on mortality and on the course of heart disease in individuals who have had angina. Lesperance et al. (41) evaluated the impact of depression on 1-year cardiac prognosis following hospitalization for an episode of unstable angina. Depression was measured using the BDI approximately 5 days after admission. In a multivariate model predicting cardiac events, controlling for electrocardiographic evidence of ischemia, left ventricular ejection fraction, and number of diseased vessels, depression was found to have an OR of 6.73 (95% CI 2.43, 18.64).

In contrast to the evidence presented above, other researchers have not found depression to be a risk factor for mortality after a cardiac event when controlling for other predictors of mortality. (42, 43)

1.3.3 Does depression following AMI affect health services use?

Research has shown that, compared with individuals who are not depressed, individuals with depression had higher use of services in all categories of medical care, including inpatient admissions, outpatient visits, laboratory tests, emergency department visits, number of prescriptions, and number of ancillary visits. (44-46) There is however limited evidence of the impact of depression on health services utilization specifically in individuals who have had a cardiac event. Allison et al. (47) followed patients with CHD who participated in a cardiac rehabilitation program for 6 months and investigated the effect of psychological distress on morbidity and hospitalization. Psychological distress was measured during the second week of the rehabilitation program using the Symptom Checklist – 90 Revised, (48) a psychological screening instrument. Each cardiac hospitalization within 6 months after discharge from the index hospitalization was obtained through medical records, personal interviews, mail-in questionnaires and telephone interviews with nonrespondents. Psychological distress remained the strongest predictor of both early cardiovascular rehospitalization and recurrent cardiac events in a multivariate model controlling for confounders such as ejection fraction and smoking. Frasure-Smith et al. (49) followed AMI patients for 1 year to investigate the impact of depression measured 5-15 days after admission, using the BDI, (38) on health services utilization. Medical data were obtained from charts and Medicare data records. They found that individuals who were depressed were more likely to be readmitted on more

than one occasion and spent more total days in hospital during the year than individuals who were not depressed. (49) However, this study used multivariate analysis to control for confounding factors only when investigating health care costs, and not for number of readmission and visits.

1.4 Possible mechanisms linking depression following AMI and increased mortality and morbidity

The mechanisms through which depression affects outcomes in cardiac disease are far from clear (3, 50), though several plausible mechanisms, both biological and behavioural, have been proposed. One suggested mechanism relates to alterations in parasympathetic and sympathetic nervous system activity, as demonstrated by reduced heart rate variability (HRV). (28) HRV is defined as the standard deviation of successive R to R intervals in sinus rhythm and is thought to reflect the balance between sympathetic and parasympathetic affect on the heart. (51) HRV sometimes decreases in patients with heart failure or severe coronary artery disease and the risk of sudden death after AMI is higher in patients with decreased HRV. Reduced HRV has been found to be significantly more prevalent in depressed patients with cardiac disease than in those who were not depressed. (52-54) Also, HRV has been shown to increase in depressed patients following treatment with antidepressants. (55) However, it is still uncertain if the changes in heart rate variability in treated depressed patients are of clinical significance. (56)

Another suggested mechanism through which depression may affect cardiovascular morbidity and mortality is an abnormality in platelet reactivity, which is thought to play a central role in the development of atherosclerosis, thrombosis and acute

coronary syndromes. (28, 57) There is evidence of a significant tendency for enhanced platelet activation in depressed patients compared to normal subjects with and without cardiac disease.(58) Hyperactivity of the sympatho-adrenal (SA) system, comprised of the adrenal medulla and the sympathetic nervous system, observed in many patients with major depression may also contribute to the development of heart disease through the effects of catecholamines on cardiac and platelet function. (28) Stimulation of adrenergic receptors increases the circulation of catecholamines which potentiate the effects of other agonists, and initiate platelet responses including secretion and aggregation. (28) Thus heightened activity of the SA system may be held responsible (directly or indirectly through effects on platelet activity), for the rise in cardiovascular risk and probability of thrombus formation in depressed persons. (59, 60)

Depression following AMI might be linked to mortality and morbidity through behavioural pathways such as non-compliance with medication. (61, 62). Carney et al. (61) followed patients following a coronary anteriography. Depression was assessed using the DIS. (25) Aspirin medication adherence (a key intervention for both the prevention and management of acute cardiac disease) was measured using an electronic medication monitor. Adherence was defined as the percentage of days on which the patient removed two pills from the monitor, regardless of the time of day and interval between doses. The patients who were not depressed adhered to the prescribed regimen, on average, 69% of the days, as compared with an average of 45% for the depressed patients, a statistically significant difference. The authors also found that the depressed group had greater dropout rates from cardiac rehabilitation programs.(63) Another possibility is that the increased risk in depressed patients is due to the association

between depression and smoking and severity of illness. Some researchers have found that distress in individuals with a cardiac event is associated with previous cardiac event, severity of cardiac illness, and smoking (36, 47), whereas others have not found such associations. (5, 43, 64) For example, Watkins et al. (65) found that depression was associated with moderate to severely impaired left ventricular function. However, they found that this relationship was primarily limited to the subset of patients with an AMI history. In patients who did not have an AMI history, there was no significant relationship between depression and left ventricular dysfunction or between depression and size or severity of current AMI, estimated from the peak changes in cardiac enzymes. Also, depressed individuals may take poorer care of themselves, pay less attention to diet, and drink more alcohol. (66) It is important to note, however, that in studies where depression was found to be associated with mortality, it had an independent effect after controlling for variables such as smoking and severity of illness. (29, 32,36)

1.5 Rationale for study

The main goal of this dissertation was to use population based administrative data to assess the impact of early- and late-onset depression that occurs following an acute myocardial infarction (AMI) on short- and long-term survival. The question of the effect of depression following AMI on survival has not been investigated using administrative data, yet there are many advantages for using such data.

The use of administrative data has increased recently as a result of developments in information system technologies, which make administrative databases more readily available to health researchers. Analyses of linked administrative databases have great potential to advance health services and population health research. These databases were

originally developed to supply information to administrators and financial officers about service volumes, expenditures and other aspects of resource management. However, administrative databases were found to offer outstanding potential in exploring a wide range of health research questions. With increased ability to link various administrative datasets, exceptional opportunities emerged to obtain valuable data regarding patterns and trends in health services delivery, healthcare resource utilization, and other important issues.

The use of administrative data is particularly advanced in Canada as a result of its publicly funded healthcare system. The Canadian healthcare system provides universal access and thus administrative data capture information describing very close to the entire population of large geographical areas. The British Columbia Linked Health Dataset (BCLHD) is an anonymized person-specific research data set, which tracks a range of health-related data over time for BC residents including vital events, hospitalizations, physician utilization and pharmaceutical prescriptions. (67)

When compared to other data sources, linked administrative datasets such as those available through the BCLHD, offer several benefits for research addressing health services. These databases can easily be used to undertake longitudinal analyses, because patient information is available over multiple periods. Because the data are usually gathered at a population level, they are typically demographically and geographically diverse. (68) Utilization of these databases also enables researchers to examine large cohorts of subjects, with high statistical power, therefore permitting the study of rare diseases and very specific population subgroups. (68, 69) Compared to primary data

collection, obtaining administrative data is much less expensive, quicker and less likely to be influenced by selection bias.

The use of administrative data to investigate the impact of depression on survival following AMI has many benefits and methodological strengths compared to the studies completed to date; For example, a methodological limitation of these studies is relatively short follow-up periods (i.e., no more than 18 months). Only a few studies followed patients for longer (e.g., 5 years (35) and 10 years (33)). Thus it is impossible to conclude whether depression following AMI has an impact on long term mortality. Second, these studies measured depression symptomatology near the time of admission for the cardiac event. (29, 31, 32, 36, 47, 64, 70) Measurement of depression symptomatology during this period is not a very good measure of major depression because it could very likely capture situational symptomatology of depression, as opposed to long lasting major depression, a more permanent state. Thus it is important to examine how major depression, as opposed to depressive symtomatology affects mortality. Moreover, because past research measured depression close to the time of admission for the cardiac event, it is impossible to distinguish between prevalent and incident depression. Individuals with chronic depression may be different from those who become depressed following their AMI. Another shortcoming of the evidence to date is that most of the studies did not investigate the impact of late-onset depression, which occurs months or years after AMI, even though a fair number of individuals become depressed within one-year following their AMI (14.7% (30); 6% (43); 20.6% (71)). There is no evidence of the impact on survival of depression that occurs later in the course of recovery from AMI. Only some studies measured depression at admission and at 1 year following AMI (30,

35, 43) but only one (35) investigated the impact of depression occurring within 1 year following AMI on mortality. Finally, with regard to the impact of depression on health services use, it is important to conduct multivariate analyses to delineate whether depression has an impact on increased health-services use independent of other confounding factors such as increased comorbidity.

This study addressed these limitations by utilizing administrative data that enabled long follow up (i.e., the cohort was followed for up to 8 years with regard to mortality). Also, it was possible to exclude individuals who had prevalent depression before AMI, because health related data for the years prior to the AMI were available. Furthermore, this study was not limited to individuals with depressive symtomatology, but individuals who more likely had major depression. Depression was measured not only at admission but rather for up to 5 years following AMI. Finally, multivariate analyses were employed to determine whether any differences in their use of health services that were seen between the individuals who were depressed and not depressed were due to confounding factors.

1.6 Conceptual framework

The main question of this dissertation is whether incident depression following AMI affects survival. The approach and conceptual framework used to answer this question is based on two main fields of research: epidemiology and health services research.

Epidemiology is the study of the distribution and determinants of disease frequency in human populations. (72) Another definition of epidemiology is the study of the

distribution and determinants of health related states and events in populations, and the application of this study to the control of health problems. (73)

Health services research is a multidisciplinary field of scientific research which focuses on how social factors, financing systems, organizational structures and processes, health technologies, and personal behaviour affect access to health care, the quality and cost of health care, and ultimately our health and well-being. Its research domains are individuals, families, organizations, institutions, communities, and populations. (74)

This dissertation was written in the context of these two disciplines. With regard to the epidemiological perspective, the incidence of depression following AMI was explored at a population level, potential prognostic factors associated with depression following AMI were investigated. In addition, the association between depression and survival was the main issue investigated in this dissertation. With regard to the health services aspect, this dissertation utilized an administrative dataset frequently used by health services researchers to develop different methods of risk-adjustment and their relative strengths, as well as long term health services utilization outcomes were investigated such as number of readmissions after the AMI.

1.7 Description of chapters

Chapter 2 includes the general methods used in this dissertation. Each chapter includes further detail with regard to chapter-specific methods.

Chapter 3 focuses on comparing different approaches to control for comorbidities using administrative data in a population of individuals who have had an AMI. This was a necessary preliminary step before investigating the impact of depression on survival following AMI because a method of risk-adjustment was required to control for

confounding due to increased comorbidity in the depressed population. Results from this section will be of interest to researchers using administrative data to investigate other outcomes of AMI patients. In addition to describing the prevalence of depression following AMI and the use of antidepressants by the cohort, Chapter 4 shows which important prognostic factors are associated with depression following AMI. Chapter 5 addresses the primary question of this dissertation, assessing the effect of early- and late-onset depression following AMI on survival.

Chapter 6 discusses the results presented in the dissertation, the limitations of the study and the clinical and methodological implications.

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2 Chapter II: General Methods

This chapter includes a description of the general methods used in this dissertation. This chapter also describes the basic characteristics of the main cohorts used in the study. Chapters 3, 4 and 5 describe additional methodological components relevant to the specific analyses described in each chapter.

2.1 General Methods

2.1.1 Data sources

This study used the British Columbia Linked Health Database (BCLHD) (1) to identify the study population and to construct the variables. The BCLHD is a population-based data resource for applied health services and population heath research developed and maintained by the Centre for Health Services and Policy Research (CHSPR). CHSPR acts as the custodian of and access point for the various data holdings of the BCLHD, which remain under the stewardship of the agency that originally collected them (e.g., the British Columbia government). CHSPR prepares data for analysis for approved research projects. The responsibility for the use and interpretation of these data is entirely that of the author. The BCLHD is one of only a small number of data resources in the world where longitudinal research on an entire population can be carried out because it covers the entire population of British Columbia (BC), Canada, a population of about 3,900,000 people. The BCLHD includes administrative data files from various program areas from the BC Ministries of Health and other agencies containing individual-level information on health care service use; claims made to the BC Workers' Compensation Board; basic information about the location and background of select health-care service providers;

surveys that provide a deeper level of understanding for small groups of BC residents who agreed to share and link their data; and descriptive information about neighbourhoods and communities, derived from census data.

The databases linked in this study are:

1. **The Medical Services Plan (MSP) Payment Information Masterfile** (hereafter referred to as MSP): The MSP insures medically required services provided by physicians and other health care practitioners, laboratory services and diagnostic procedures. The MSP files include annual, fiscal-year files of services provided to MSP-covered individuals by practitioners, billed to MSP, and paid by MSP.
2. **Hospital Separation File** (hereafter referred to as HSF): The Hospital Separation Files include records of admissions and separations (discharges, transfers, and deaths) with up to 16 diagnostic codes per record for in-patients and day surgery patients from acute care hospitals in BC.
3. **PharmaCare**: PharmaCare subsidizes eligible prescription drugs and designated medical supplies; the files include records of prescriptions paid by the plan. All seniors 65 years and over are covered by PharmaCare.
4. **Vital Statistics Deaths File**: This file includes all deaths that occurred in BC or in a hospital elsewhere in Canada.
5. **The registry file**: The registry file reflects the work CHSPR has done to clean and consolidate the information on the Registration & Premium Billing file. The registry file contains demographic information on the individuals including age, sex, socioeconomic status and Local Health Authority).

All aspects of the study design and data use were reviewed by the University of British Columbia's Research Ethics Board and the BC Ministry of Health's Data Access Committee (which must approve access to linkable BC data). A person-level analytic file was constructed to link all data relevant to the patient. Patient identifiers were removed from the data file to maintain patient and provider anonymity.

2.1.2 Study design and selection of the main cohort

This study employed an historical inception cohort design. Individuals were selected from the entire BC population if they had a diagnosis of AMI (not necessarily their first AMI) in 1994 or 1995. This included any hospital admission with a principal diagnosis ICD-9 code of 410 and its derivatives (410.0, 410.00, 410.1, etc). Patients discharged with a total length of stay of less than 3 days, including days at a receiving hospital if they were transferred, were excluded under the assumption, given current practice, that these patients had AMIs "ruled-out" rather than confirmed AMIs. (2) Only individuals who were 66 years of age or older at the time of AMI were included. These criteria were met by 5559 individuals (i.e., AMI in 1994 or 1995, with admission for 3 days or longer and 66 years of age or older). Inclusion of individuals 66 and over was done because data on prescription drugs, which was necessary to determine evidence of prior depression, were available only from the age of 65 years. Because the aim of this study was to focus only on individuals who had incident depression that occurred after the index AMI, rather than prevalent depression, individuals with evidence of depression one year prior to the index AMI were excluded. Using a population of 66 years and older allowed for the exclusion of those individuals as described below.

Only individuals with incident rather than prevalent depression following the admission for AMI were of interest. As mentioned previously, individuals with chronic depression may be different from those who become depressed following their AMI, both physiologically and psychologically. As the interest of this dissertation is to investigate the impact of depression which occurs following AMI on mortality and not the impact of chronic depression on mortality, prevalent cases were excluded. Prevalent cases were defined as individuals who had evidence of depression in the year prior to their AMI. One criterion of prevalent depression was any prescription for antidepressants in the year prior to the index AMI. Four hundred and seventy one individuals met this criterion and were excluded, leaving a cohort of 5088. Depression in the year prior to the AMI as indicated in MSP or HSF datasets was also used as a criterion of prevalent depression. Individuals with 2 or more pre-AMI diagnoses (not necessarily principal diagnosis) of ICD9 300 (Neurotic disorders including neurotic depression), 296 (Affective psychoses), 311 (Depressive disorder, not elsewhere classified) or 50B (Anxiety/Depression, only in MSP files) were excluded. Two diagnoses were required to minimize the exclusion of individuals who had depression coded as an error. One hundred and ninety nine individuals met this criterion and were thus excluded, leaving a cohort of 4889. By excluding these individuals it is likely that the cohort did not include individuals who had significant depression prior to the AMI.

Eight individuals were excluded because they did not appear in the registry file. Seven individuals were excluded because they were not residents of British Columbia (they had their AMI in BC and thus were initially selected). Because they were from a different province, follow up data were not readily available for this small number of

individuals, and thus it was appropriate to exclude them. This left a final cohort of 4874 individuals. See Table 2.1 for a complete description of the selection of the cohort.

TABLE 2.1 Construction of the cohort

Cohort selection criteria	Number of individuals excluded	Number of individuals remaining in cohort
The initial cohort selection through the Hospital Separations File. Chosen based on 1. Principal diagnosis of 410 (AMI) and its derivatives 410.0, 410.00, 410.1, etc (all the 410 codes with/without fourth or fifth digits) in 1994 or 1995 2. Length of stay equal or more than 3 days. 3. Individuals were 66 years old or older at time of AMI	None	5559
Excluded because had any prescription of antidepressants within 1 year before index AMI	471	5088
Excluded because had 2 or more codes for depression either in MSP files or HSF files within 1 year before index AMI	199	4889
Excluded because not in registry file	8	4881
Excluded because from out of province	7	4874

2.1.3 Divisions of main cohort into sub-cohorts

Six sub-cohorts were selected from this main cohort. These cohorts were:

1. Cohort 1 which included individuals who survived at least 6 months after their AMI (3945 individuals)
2. Cohort 2 which included individuals who survived at least 1 year after their AMI (3708 individuals)
3. Cohort 3 which included individuals who survived at least 2 years after their AMI (3397 individuals)
4. Cohort 4 which included individuals who survived at least 3 years after their AMI (3096 individuals)

5. Cohort 5 which included individuals who survived at least 4 year after their AMI (2835 individuals)
6. Cohort 6 which included individuals who survived at least 5 years after their AMI (2587 individuals)

The reason for the creation of these sub-cohorts was that all individuals in a certain cohort had to have an equal 'opportunity' to develop depression and to be prescribed antidepressants following the AMI. That is, if an individual died shortly after his or her AMI, they were less likely (had less time) to develop depression than an individual who lived for 5 years past AMI. Thus, to eliminate this bias, each cohort was assessed for depression only during the time of 'equal opportunity'. For example, in Cohort 1, all individuals were examined to determine whether they could be classified as depressed using only data from the 6 months following their AMI.

2.1.4 Variables

2.1.4.1 Demographic variables (age, sex, SES, rural residency)

Demographic variables, including age, sex, and rural residency were obtained from the registry file. Rural residency was determined using the first 3 digits of the postal code for each individual which was included in the registry file. If an individual lived in an area with a postal code in which the second digit was 0, they were classified as 'rural', all others were classified as 'urban'. Socioeconomic status (SES), also obtained from the registry file, was determined using SES quintiles, which were constructed based on Neighbourhood Income Per Person Equivalent (IPPE). IPPE is a household size-adjusted measure of household income, based on 1996 census summary data at the enumeration area (EA, defined as the basic area for which data are collected and the building block of

all standard census geographic area levels). Within each Census Metropolitan Area (CMA, defined as main labour market areas of urban areas of at least 100,000 population, based on previous census), Census Agglomerations (CA, defined as labour market areas with an urbanized core of at least 10,000 population, based on the previous census) or provincial residual area not in any CMA or CA, the population was divided into approximated fifths, creating community-specific income quintiles based on IPPE. The quintiles were defined within each area in order to better reflect the relative nature of this measure, to minimize the effect on household welfare of large differences in housing costs, and to ensure that each CMA or CA would have about an equal percentage of the population in each income quintile. For example, the Vancouver CMA would be one 'area', whose quintile classes would be different than those found within the Quesnel CA. If a household from the Quesnel CA had an income of $50,000, they may be listed in the top quintile, whereas a household in the Vancouver CMA with the same income might be in the middle quintile. This type of classification is beneficial in that it corrects for the differences in relative costs of living between different areas.

2.1.4.2 Definition of Depression

Individuals were categorized as 'depressed', 'possibly depressed' and 'not depressed'. The only method to determine whether an individual is depressed using administrative data is to detect whether they are pharmacologically treated for depression with antidepressants or have a diagnosis of depression during a visit to the hospital, to ambulatory care, or to a physician. It is assumed that individuals who are treated or diagnosed for depression are likely to be depressed, whereas those who are not treated or

diagnosed for depression are less likely to be depressed, or at least their depression was not detected by the medical system.

A relatively specific rather than sensitive definition of depression was used. The reason for this is that it was important to compare individuals who were very likely to be depressed to those who were not. Any individual who was misclassified either by coding error or misdiagnosis, would bias the results to the null, thus it was preferable to err on the side of caution.

In order for an individual to be categorized as 'depressed' they met at least one of two criteria:

1. At least 4 visits to a physician or hospital (recorded in MSP or HSF files) that included one of the following codes (not necessarily a principal diagnosis): 300 (Neurotic disorders including neurotic depression), 296 (Affective psychoses), 311 (Depressive disorder, not elsewhere classified) or 50B (Anxiety/Depression in MSP). or
2. At least 2 unique prescriptions days for antidepressants. Unique prescription days were the number of unique dates in which an individual filled a prescription for antidepressants as shown in the PhamaCare files. The reason that number of unique prescriptions days was used rather than the total number of prescriptions was that an individual could have more than one prescription filled on a given date. In order to show stability of use of antidepressants over time, the number of unique days, rather than the number of prescriptions was used.

At least 4 visits for depression was used as a definition because such individuals would less likely be categorized as depressed due to coding error or misdiagnosis. The

reason that at least 2 prescriptions days of antidepressants was used as a criterion and not just one day was to create a relatively specific criterion indicative of stability of use of antidepressants over time rather than a one time event. Individuals with no prescription days or visits for depression were categorized as 'not depressed'. Individuals with 1-3 visits for depression or 1 prescription day for antidepressants were categorized as 'possibly depressed'.

As described above, the main cohort was divided into 6 separate sub cohorts. The depression criteria were assessed during the common survival period for each cohort. For example, in Cohort 1 in which all individuals survived at least 6 months, the criteria for depression had to be met within those first 6 months after AMI. For Cohort 2 where all individuals survived at least 1 year, the criteria for depression had to be met within the first year after AMI.

See Table 2.2 for description of how depression was defined in the cohorts.

TABLE 2.2 Definition of depression

	0 prescriptions days	*1 prescription days*	*2+ prescription days*
0 visits	Not depressed	Possibly depressed	Depressed
1 visit	Possibly depressed	Possibly depressed	Depressed
2 visits	Possibly depressed	Possibly depressed	Depressed
3 visits	Possibly depressed	Possibly depressed	Depressed
4+ visits	Depressed	Depressed	Depressed

2.1.4.3 Previous AMI and cardiac-related procedures at the time of the index AMI

A binary variable for previous AMI was positive for individuals who had any number of AMIs in the three years prior to the index AMI and negative for individuals who had no AMIs in the three years prior to the index AMI. Cardiac-related procedures completed during the hospitalization for the index AMI were categorized into 2 classes: 'Operations on vessels of the heart' and 'Other operations on the heart and pericardium',

a division based on the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP). These variables were also categorized into Positive/Negative. See Table 2.3 for classification of procedures.

TABLE 2.3 Classification of procedures

OPERATIONS ON VESSELS OF HEART
Removal Of Coronary Artery Obstruction
Removal Of Coronary Artery Obstruction, Unqualified
Percutaneous Transluminal Coronary Angioplasty (PTCA) Without Mention Of Thrombolytic Agent
Percutaneous Transluminal Coronary Angioplasty (PTCA) With Thrombolytic Agent
Open Chest Coronary Artery Angioplasty
Intracoronary Artery Thrombolytic Infusion
Other Removal Of Coronary Artery Obstruction
Bypass Anastomosis For Heart Revascularization
Aortocoronary Bypass For Heart Revascularization, Unqualified
Aortocoronary Bypass Of One Coronary Artery
Aortocoronary Bypass Of Two Coronary Arteries
Aortocoronary Bypass Of Three Coronary Arteries
Aortocoronary Bypass Of Four Or More Coronary Arteries
Single (Internal) Mammary-Coronary Artery Bypass
Double (Internal) Mammary-Coronary Artery Bypass
Other Bypass Anastomosis For Heart Revascularization
Heart Revascularization By Arterial Implant
Other Heart Revascularization
Other Operations On Vessels Of Heart
Repair Of Aneurysm Of Coronary Vessel
Angiocardiography, Unqualified
Angiocardiography Of Right Heart Structures
Angiocardiography Of Left Heart Structures
Combined Right And Left Heart Angiocardiography
Coronary Arteriography Using A Single Catheter
Coronary Arteriography Using Two Catheters
Other Coronary Arteriography
Other Operations On Vessels Of Heart Not else classified

TABLE 2.3 cont.

OTHER OPERATIONS ON HEART AND PERICARDIUM
Pericardiocentesis
Cardiotomy And Pericardiotomy
Incision Of Heart, Unqualified
Cardiotomy
Pericardiotomy
Pericardiectomy
Excision Of Lesion Of Heart
Excision Of Aneurysm Of Heart
Excision Of Other Lesion Of Heart
Repair Of Heart And Pericardium
Heart Transplantation
Implantation Of Heart Assist System
Implant Of Pulsation Balloon
Implant Of Other Heart Assist System
Replacement And Repair Of Heart Assist System
Removal Of Heart Assist System
Implantation Of Cardiac Pacemaker System
Pacemaker Implantation Not otherwise specified
Implantation Of Myocardial Electrodes
Implantation Of Endocardial Electrodes
Implantation Of Automatic Cardioverter/Defibrillator
Removal Or Replacement Of Implanted Cardiac Pacemaker
Replacement Of Myocardial Electrodes
Replacement Of Endocardial Electrodes
Replacement Of Pulse Generator
Replacement Of Battery
Removal Of Myocardial Electrodes
Removal Of Endocardial Electrodes
Removal Of Cardiac Pacemaker System Without Replacement
Replacement Or Removal Of Automatic Cardioverter/Defibrillator Leads
Or Pulse Generator
Other Operations On Heart And Pericardium
Open Chest Cardiac Massage
Injection Of Therapeutic Substance Into Heart Or Pericardium
Biopsy Of Heart
Biopsy Of Pericardium
Right Cardiac Catheterization
Left Cardiac Catheterization
Combined Right And Left Cardiac Catheterization
Other Invasive Diagnostic Procedures On Heart And Pericardium
Other Operations On Heart And Pericardium Not else classified

2.1.4.4 Follow up

Follow up data until 2001 were available, which provided a maximum of 8 years of follow up.

2.2 Description of Cohorts

2.2.1 Description of main cohort

The main cohort included 4874 individuals. The mean age of the cohort was 76.5 (SD=6.55) years, the median was 76 and the mode was 74. The minimum age was 66 years (by definition) and the maximum was 98. Of the main cohort, 38.4% were female, 60.3% were male, and the remaining individuals (1.3%) had no gender information on their records. The individuals lived in various regions of the province with the largest percentages located in Vancouver (11.6%), Victoria (7%), Surrey (8%), Burnaby (4.4%) and Richmond (2.9%). About 24% of the cohort were from the lowest quintile of SES, while 15% were from the highest quintile. SES information was missing on 7.8% of the cohort.

Of the entire cohort, 3.8% of the individuals had one AMI in the 3 years prior to the index AMI, 0.5% of the individuals had two previous AMIs, four individuals had three previous AMIs, and one individual had four previous AMIs.

2.2.2 Description of the subcohorts 1-6

The number of individuals in each cohort and the percentage of those who died by the end of the follow up are shown in Table 2.4.

TABLE 2.4 The cohorts and percentage that died (all causes) by the end of follow up

Cohort	*N (% that died)*
Cohort 1 (6 months common survival period)	3945 (45.3)
Cohort 2 (1 year common survival period)	3708 (41.8)
Cohort 3 (2 years common survival period)	3397 (36.4)
Cohort 4 (3 years common survival period)	3096 (30.3)
Cohort 5 (4 years common survival period)	2835 (23.8)
Cohort 6 (5 years common survival period)	2587 (15.3)

The age and sex distributions for each cohort were similar. The percentage of females ranged between 37.5% and 38.0%. The percentage of males ranged between 61.0% and 61.6%. The mean age ranged between 74.5 (Cohort 6) and 76.0 (Cohort 1). For a description of the distribution of SES in each cohort see Table 2.5.

TABLE 2.5 Distribution of SES in each cohort (percentages)

Cohort	*Quintile 1 (Lowest)*	*Quintile 2*	*Quintile 3*	*Quintile 4*	*Quintile 5 (Highest)*	*Missing*
Cohort 1 (n=3945)	23.3	19.2	17.2	17.7	14.9	7.7
Cohort 2 (n=3708)	23.2	19.3	16.9	17.9	15.2	7.6
Cohort 3 (n=3397)	23.3	19.1	17.4	17.4	15.2	7.4
Cohort 4 (n=3096)	22.6	19.4	17.3	17.5	15.6	7.5
Cohort 5 (n=2835)	22.6	19.3	17.5	17.5	15.7	7.4
Cohort 6 (n=2587)	22.2	19.2	17.7	17.8	15.9	7.2

The number and percentage of individuals with previous AMIs and procedures are shown in Table 2.6. Most of the individuals had no previous AMIs or operations during the hospitalization for their index AMI.

TABLE 2.6 Distribution of previous AMI and procedures

Cohort	*No previous AMI (%)*	*At least 1 previous AMI (%)*	*No operations of vessels of the heart (%)*	*At least 1 operation of vessels of the heart (%)*	*No 'other' operations of the heart and pericardium (%)*	*At least 1 'other' operation of the heart and pericardium (%)*
Cohort 1 (n=3945)	3777 (95.7)	168 (4.3)	3427 (86.9)	518 (13.1)	3419 (86.7)	526 (13.3)
Cohort 2 (n=3708)	3560 (96.0)	148 (4.0)	3199 (86.3)	509 (13.7)	3196 (86.2)	512 (13.8)
Cohort 3 (n=3397)	3274 (96.4)	123 (3.6)	2905 (85.5)	492 (14.5)	2905 (85.5)	492 (14.5)
Cohort 4 (n=3096)	2990 (96.6)	106 (3.4)	2629 (84.9)	467(15.1)	2633 (85.0)	463 (15.0)
Cohort 5 (n=2835)	2750 (97.0)	85 (3.0)	2389 (84.3)	446 (15.7)	2400 (84.7)	435 (15.3)
Cohort 6 (n=2587)	2510 (97.0)	77 (3.0)	2157 (83.4)	430 (16.6)	2175 (84.1)	412 (15.9)

2.3 Bibliography

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3 CHAPTER III: A comparison of risk adjustment methods in a population of AMI patients using administrative data[1]

3.1 Background

An important variable that researchers measure when studying the outcomes of AMI patients is severity of illness. However, there are limitations when using administrative data to assess severity of illness because important indicators of severity such as electrocardiographic changes, elevation of creatinine phosphokinase (CPK) and other physiological indices are not available. However, while short-term mortality is most likely to be related to the physiological severity of AMI, as measured by these indicators, long-term mortality, which is the primary outcome of this study, is more likely related to concurrent or underlying comorbidity (1), which are readily identified in administrative data. For example, controlling for comorbidities would be helpful when trying to answer the following question: Does depression following AMI have an impact on survival? Because depression may be associated with greater comorbidity, it is important to assess whether its effect on survival is independent of comorbidity. Consequently, a method of risk-adjustment is necessary to isolate the independent effect of depression.

The purpose of this study was to determine the best way to adjust for comorbidities when investigating mortality after AMI using administrative data. The main interest was to compare a risk-adjustment method which was developed using an AMI patient population with more general risk adjustment methods.

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[1] A version of this chapter has been accepted for publication. Grunau GL, Sheps S, Goldner E, Ratner PA Specific co-morbidity risk adjustment was a better predictor of 5-year acute myocardial infarction than general methods. J Clin Epidemiol.

The literature on risk-adjustment methods was consulted to identify the range of methods available. Researchers have developed indices for risk-adjustment in AMI patients and AMI "report cards" using hospital discharge databases. (1, 2) However, these models are limited for several reasons. One developed by Normand et al., (1) a 40-variable prediction rule using US medicare data, is very large and complicated and thus unappealing and impracticable to health services researchers. The methods developed in the United States (1, 3, 4) used variables with American-specific response options such as race (black versus white). This approach is not relevant for studies done in BC because the demographics of this province are different than those in the US, and such variables are not available in the database. More importantly, the prediction rules developed by Pennsylvanian and Californian researchers focused only on predicting in-hospital and 30-day mortality (3, 4) and not longer term mortality, which was the outcome of interest in this present study. They also required separate models for direct admission or transferred-in patients (3) and separate models for individuals with no prior hospital admission and those previously hospitalized, which further complicates the analyses. (4) In contrast to these complicated or inappropriate models, a simple Ontario AMI prediction rule (OAMIPR) was developed in Ontario by Tu et al. (5) This model is probably more applicable to the BC population because the BC and Ontario populations are more similar to each other than to the US population. Thus, this method was chosen as one of the methods of risk-adjustment. The validated model predicts 30-day and 1-year mortality and consists of nine comorbidities in addition to age and sex. It is a simple model that has been shown to perform better in short term follow up of AMI patients than the Charlson Index, (6) a very common method of risk-adjustment, albeit not specific for

individuals with AMI. Whether it remains useful past short term follow up is a key question.

The Charlson Index was the second method of risk-adjustment chosen for this study. This is a validated comorbidity measure based on the relative risks of mortality for 19 conditions observed during a longitudinal study of 559 internal medicine cases. (6) In the development of the index any disease generating a relative risk of at least 1.2 and smaller than 1.5 was retained and weighted as 1, a weight of 2 was given for a relative risk between 1.5 and 2.5 including 1.5, a weight of 3 was given for a relative risk between 2.5 and 3.5 including 2.5 and a weight of 6 was given for 2 conditions with relative risks greater or equal to 6 (no conditions had relative risks between 3.5 and 6.0). The sum of the weights for each individual is calculated. For the purpose of this study the D'Hoore adaptation to the Charlson Index was used (7) because the D'Hoore adaptation uses ICD9 codes of 3 digits. Data available from the BCLHD have higher validity when only the first three digits are used (8) because MSP diagnoses are often relatively vague compared to HSF diagnoses, as MSP payments are based on procedures rather than diagnoses.

The comorbidities, their ICD9 codes, and their weights used in the D'Hoore adaptation are shown in Table 3.1.

TABLE 3.1 D'Hoore adaptation of the Charlson Index

Weight	*Condition*	*ICD9 code*
1	Myocardial infarction	410,411
1	Congestive heart failure	398,402,428
1	Peripheral vascular disease	440-447
1	Dementia	290,291,294
1	Cerebovascular disease	430-433,435
1	Chronic pulmonary disease	491-493
1	Connective tissue disease	710,714,725
1	Ulcer disease	531-534
1	Mild liver disease	571,573
2	Hemiplegia	342,434,436,437
2	Moderate or severe renal disease	403,404,580-586
2	Diabetes	250
2	Any tumor	140-195
2	Leukemia	204-205
2	Lymphoma	200,202,203
3	Moderate or severe liver disease	070,570,572
6	Metastatic solid tumor	196-199
6	AIDS	042-044

A third risk-adjustment method chosen for this study was a measure of the total number of distinct comorbidities. Schneeweiss et al. (9) used administrative data from British Columbia for a population of individuals 65 years of age or more who had filled at least one prescription for an angiotensin-converting enzyme inhibitor or calcium channel blocker. Schneeweiss et al. (9) compared the use of the number of distinct comorbidities as a risk adjustment measure to other common methods of controlling for comorbidities (including the Charlson Index and other scores based on it, as well as scores based on outpatient drug utilization data). They found that the number of distinct comorbidities performed just as well as other risk adjustment methods in predicting 1-year mortality. This is a unique method in that it does not give weights to illnesses that have stronger effects on survival, as the Charlson Index does, and it is very general and not disease specific, such as the OAMIPR. (5) Due to its relative simplicity, it was

considered noteworthy to determine how well it performed compared to other methods described.

In summary, this study compared three approaches to risk adjustment to predict mortality post-AMI: OAMIPR (5), the Charlson Index with the D'Hoore adaptation (6), and the number of distinct comorbidities. (9)

3.2 Methods

The general methods are described in section 2.1. Below is a description of the methods applied specifically in this Chapter.

3.2.1 Cohorts

This study used Cohorts 1 to Cohort 5 described in section 2.1.

3.2.2 Variables

The variables used in this study include age, sex, SES, previous AMI and procedures at the time of the index AMI, described in section 2.1. In addition, 3 methods of risk-adjustment were used as described below.

3.2.2.1 Ontario AMI Prediction Rule (OAMIPR)

Tu et al. (5) developed the Ontario AMI prediction rule which is a model that includes 9 comorbidities, in addition to age and sex, present at the time of the index AMI which were found to be the best predictors of 1 year mortality after AMI. These comorbidities include shock, diabetes, congestive heart failure, cancer, cerebovascular disease, pulmonary edema, acute renal failure, chronic renal failure, and cardiac

dysrhythmia. In this study, the comorbidities were measured at the time of the index AMI as well as throughout the time of common survival (i.e., in Cohort 1, which had a common survival time of 6 months, individuals were identified as having heart failure if they had it on their list of comorbidities during the index AMI and also if they had it at anytime in the first 6 months following the AMI).

As mentioned above, the data from the BCLHD are generally most valid when using only the 3 first digits of the ICD9 codes and thus most of the comorbidities in the OAMIPR (5) were defined using only 3 digits. However, some were defined using more than 3 digits when it was expected that 3 digits would not be sufficiently precise. Those comorbidities for which more than 3 digits were used were only assessed with the HSF and not the MSP data, which are relatively less valid when using more than 3 digits. The rest of the codes were extracted from both the MSP and HSF data. See Table 3.2 for details of the ICD9 codes used.

TABLE 3.2 ICD9 Codes used to define the OAMIPR comorbidities

Comorbidity	*ICD9 code*	*Codes used (Data source)*	
Shock	785.5	785.5	(HSF)
Diabetes with complications	250.1-250.9	250	(MSP+HSF)
Congestive heart failure	428.x	428	(MSP+HSF)
Cancer	140.0-208.9	140-208	(MSP+HSF)
Cerebovascular disease	430.0-438.x	430-438	(MSP+HSF)
Pulmonary edema	518.4,514.x	518,514	(MSP+HSF)
Acute renal failure	584.x,586.x,788.5	584,586,788	(MSP+HSF)
Chronic renal failure	585.x,403.x,404.x,996.7,v451	585	(MSP+HSF)
		403	(MSP+HSF)
		404	(MSP+HSF)
		996.7	(HSF)
		v451	(HSF)
Cardiac dysrhythmias	427.x	427	(MSP+HSF)

3.2.2.2 Charlson Index

MSP and HSF data were used to construct the D'Hoore adaptation of the Charlson index. It was measured over the common survival period for each cohort.

3.2.2.3 Number of distinct comorbidities

Only hospitalization data were used for the number of distinct comorbidities because this approach was found to have higher predictive value to other risk-adjustment methods, including the use of both hospitalization and physician visit data. (9)

As this method has not been frequently used, it was of interest to measure this at various periods. The number of distinct comorbidities was determined in four intervals of time: the index hospitalization for the AMI only; 1 year before the index AMI; 1 year before the index AMI and including the index AMI; and during the common survival time including the index AMI.

3.2.3 Outcomes

The outcome investigated was all-cause mortality. See Table 3.3 for details. Data on cardiac mortality were not available due to lack of funding which was necessary to obtain the cause of death from Vital Statistics.

TABLE 3.3 Outcomes investigated in Chapter III

Cohort	*Cohort common survival time*	*Outcomes*
Cohort 1	Survived at least 6 months	Death by 1 year, 2 years, 3 years, 4 years, and 5 years
Cohort 2	Survived at least 1 year	Death by 2 years, 3 years, 4 years, and 5 years
Cohort 3	Survived at least 2 years	Death by 3 years, 4 years, and 5 years
Cohort 4	Survived at least 3 years	Death by 4 years and 5 years
Cohort 5	Survived at least 4 years	Death by 5 years

3.2.4 Analysis

The purpose of the analysis was to determine which of the methods of risk-adjustment described above was predictive of mortality post-AMI. Logistic regression analysis was used and the C statistic and Nagelkerke's R-square were estimated for each model.

The C statistic, is a measure of the area under the receiver operating characteristic (ROC) curve, which ranges from 0 to 1 with 0.5 indicating chance prediction and 1 indicating perfect prediction. For example, the model designed by the Framingham Heart Study which predicted coronary heart disease based on clinical variables including age, blood pressure, smoking, diabetes and low density and high-density lipoprotein cholesterol levels had a C statistic of 0.77. (10) A C statistics of 0.7-0.8 is considered adequate and a C statistic of 0.8-0.9 is regarded as very good. (11) Therefore, the best risk adjustment method was determined by the highest C statistic, and a risk adjustment method with a C statistic over 0.7 was considered acceptable.

The Nagelkerke's R square shows how much variation the model accounts for. It is a useful measure of the success of prediction of the dependent variable by the independent variables. (12) It is a is a modification of the Cox and Snell coefficient and is calculated by dividing the Cox and Snell's R^2 by its maximum in order to achieve a measure that ranges from 0 to 1. The Nagelkerke's R-square is the most frequently reported R-square estimate in logistic regression analysis. The approach with the highest R square was considered the best.

Data were entered stepwise in three blocks variables for each method of risk-adjustment. In the first block, age, sex and SES were entered into the model. In the

second block, previous AMI and procedures at index AMI were added. In the third block, the different methods of risk-adjustment were added. The reasoning behind this approach was that it was of interest to investigate whether the risk adjustment methods improved the model above and beyond a model consisting of those variables which have previously been shown to affect mortality post-AMI. (5, 13-16)

In summary, for each of the five cohorts, nine models were constructed:

Model 1: Age, sex, and SES

Model 2: Age, sex, SES, previous AMI and procedures at the index AMI episode.

Model 3: Age, sex, SES, previous AMI, procedures at the index AMI episode, and OAMIPR comorbidities measured over the common survival period.

Model 4: Age, sex, SES, previous AMI, procedures at the index AMI episode, and OAMIPR comorbidities measured at index admission.

Model 5: Age, sex, SES, previous AMI, procedures at the index AMI episode, and D'Hoore's adaptation of the Charlson Index measured over the common survival period

Model 6: Age, sex, SES, previous AMI, procedures at the index AMI episode, and distinct number of comorbidities over the common survival period

Model 7: Age, sex, SES, previous AMI, procedures at the index AMI episode, and distinct number of comorbidities at index admission.

Model 8: Age, sex, SES, previous AMI, procedures at the index AMI episode, and distinct number of comorbidities 1 year before index including index admission.

Model 9: Age, sex, SES, previous AMI, procedures at the index AMI episode, and distinct number of comorbidities 1 year before index excluding index admission.

Logistic regression analysis assumes a linear relationship between the logit of the independent variables and the dependent variable. Thus, the linearity assumption was tested for continuous variables (age, SES, D'Hoore's adaptation of Charlson Index, and number of distinct comorbidities). The assumption was tested using the Box-Tidwell transformation which adds variable interaction terms that are the cross-products of each independent variable and its natural logarithm [(X)ln(X)]. If these terms are significant, then there is nonlinearity in the logit. SES and age met the linearity assumption. D'Hoore's adaptation of the Charlson Index did not and thus was transformed to an ordinal variable with 5 categories: 0, 1-2, 3-4, 5-6, >6, which then met the linearity assumption. However the number of distinct comorbidities did not meet the linearity assumption even after it was categorized into an ordinal variable with 4 groups (quartiles) and thus was entered into the logistic regression model as a categorical variable with 4 categories (divided by the quartiles).

The Hosmer and Lemeshow Test table, which provides a formal test for whether the predicted probabilities for a covariate match the observed probabilities, was examined for each model. A large p-value indicates a good match, whereas a small p-value indicates a poor match.

Residuals were plotted against predicted values to assess the fit of the model. Specifically, delta chi-squared, delta deviance and delta B (standardized) were calculated and plotted against the predicted values. All of these statistics show the effect of removing each case from the model. If a case is not well fitted by the model, removing it will result in a large change in the delta chi-square and delta deviance values. Hosmer and Lemeshow (11) suggest that values of delta chi-square and delta deviance greater

than four should be considered significant (because asymptotically these quantities would be distributed approximately as the chi-square distribution with one degree of freedom, and under the null hypothesis the critical 5% value is 3.84). Delta beta is a measure of the effect that deleting all subjects with a particular covariate pattern has on the value of the estimated coefficients and the overall summary measures of fit. (11) If the case has a large influence on the values of the fitted parameters, it will be reflected in a large value of delta beta.

3.3 Results

For a description of the demographic characteristics of the main cohorts and the subcohorts, see section 2.1.

All but 9 of the 135 models had non-significant Hosmer-Lemeshow goodness-of-fit statistics. This was of no particular concern because the correlates included in the model were determined a priori, and especially because there was not an obvious pattern associated with the very few models that demonstrated poor overall model fit. For values of the Hosmer-Lemeshow goodness-of-fit statistics see Appendix B.

More than 95% of the delta chi-square and delta deviance were values under 4. It was found that the delta beta values were generally small. For example, for Cohort 1, in Model 5, when the outcome was mortality within 1 year, 93% of the delta betas had values of 0, and the remaining 7% were small numbers such as 0.1 or 0.2. When cases with delta betas of over 0.1 were excluded there was little substantial change in the parameter estimates. When the outcome was mortality within 2 years no delta betas were over 0.09. When the outcome was mortality within 3 years, none of the delta beta values was over 0.05. Thus, the models had evidence of satisfactory fit.

The C statistic and confidence intervals for each of the five cohorts are shown in Table 3.4. In this table, the performance of the 9 models can be compared by their C values. The model with the highest C statistic is highlighted.

TABLE 3.4 C Statistic results

Cohort	*Model*	*Outcome: Died by 1 year (95% CI)*	*Outcome: Died by 2 years(95% CI)*	*Outcome: Died by 3 years(95% CI)*	*Outcome: Died by 4 years(95% CI)*	*Outcome: Died by 5 years(95% CI)*
1	1	0.641 (0.602,0.679)	0.656 (0.630,0.682)	0.663 (0.641,0.685)	0.678 (0.659,0.698)	0.689 (0.670,0.707)
	2	0.664 (0.627,0.700)	0.674 (0.649,0.700)	0.675 (0.654,0.657)	0.691 (0.672,0.710)	0.701 (0.683,0.719)
	3	0.736 (0.704,0.769)	0.764 (0.743,0.786)	0.762 (0.743,0.780)	0.765 (0.747,0.782)	0.771 (0.755,0.787)
	4	0.729 (0.695,0.762)	0.747 (0.724,0.770)	0.737 (0.718,0.757)	0.739 (0.721,0.757)	0.749 (0.732,0.765)
	5	0.732 (0.698,0.766)	0.751 (0.728,0.774)	0.747 (0.727,0.766)	0.750 (0.732,0.767)	0.756 (0.740,0.773)
	6	0.730 (0.697,0.764)	0.740 (0.717,0.763)	0.744 (0.724,0.763)	0.744 (0.726,0.761)	0.747 (0.730,0.764)
	7	0.701 (0.667,0.734)	0.720 (0.697,0.743)	0.724 (0.704,0.743)	0.729 (0.711,0.747)	0.739 (0.722,0.756)
	8	0.717 (0.684,0.751)	0.730 (0.707,0.753)	0.730 (0.711,0.750)	0.735 (0.718,0.753)	0.744 (0.727,0.761)
	9	0.709 (0.676,0.743)	0.701 (0.676,0.725)	0.698 (0.678,0.719)	0.711 (0.692,0.730)	0.718 (0.701,0.736)
2	1		0.660 (0.625,0.694)	0.662 (0.637,0.687)	0.678 (0.657,0.699)	0.687 (0.668,0.707)
	2		0.674 (0.640,0.708)	0.671 (0.647,0.696)	0.688 (0.667,0.709)	0.698 (0.679,0.717)
	3		0.796 (0.770,0.823)	0.768 (0.746,0.789)	0.766 (0.748,0.785)	0.771 (0.754,0.788)
	4		0.749 (0.718,0.779)	0.728 (0.705,0.751)	0.735 (0.715,0.755)	0.740 (0.722,0.759
	5		0.777 (0.749,0.806)	0.755 (0.733,0.777)	0.753 (0.733,0.772)	0.757 (0.739,0.774)
	6		0.763 (0.733,0.794)	0.744 (0.721,0.767)	0.742 (0.722,0.761)	0.743 (0.725,0.761)
	7		0.722 (0.692,0.753)	0.720 (0.697,0.743)	0.724 (0.704,0.744)	0.734 (0.716,0.752)
	8		0.724 (0.694,0.755)	0.720 (0.698,0.742)	0.726 (0.706,0.746)	0.734 (0.715,0.752)
	9		0.689 (0.656,0.723)	0.687 (0.663,0.711)	0.703 (0.683,0.724)	0.710 (0.691,0.729)

TABLE 3.4 C statistic results cont.

Cohort	*Model*	*Outcome: Died by 1 year (95% CI)*	*Outcome: Died by 2 years(95% CI)*	*Outcome: Died by 3 years(95% CI)*	*Outcome: Died by 4 years(95% CI)*	*Outcome: Died by 5 years(95% CI)*
3	1			0.655 (0.621,0.689)	0.673 (0.648,0.699)	0.682 (0.660,0.705)
	2			0.660 (0.627,0.694)	0.682 (0.657,0.707)	0.692 (0.670,0.713)
	3			0.764 (0.737,0.792)	0.762 (0.740,0.784)	0.767 (0.748,0.786)
	4			0.704 (0.673,0.735)	0.711 (0.687,0.735)	0.725 (0.704,0.746)
	5			0.757 (0.729,0.785)	0.749 (0.727,0.771)	0.754 (0.734,0.773)
	6			0.746 (0.716,0.775)	0.733 (0.710,0.756)	0.737 (0.716,0.757)
	7			0.702 (0.672,0.733)	0.709 (0.685,0.732)	0.722 (0.701,0.722)
	8			0.701 (0.671,0.732)	0.709 (0.686,0.733)	0.719 (0.699,0.740)
	9			0.676 (0.643,0.710)	0.696 (0.672,0.721)	0.703 (0.681,0.724)
4	1				0.681 (0.645,0.717)	0.682 (0.655,0.710)
	2				0.694 (0.660,0.728)	0.693 (0.667,0.720)
	3				0.760 (0.729,0.792)	0.757 (0.733,0.780)
	4				0.710 (0.676,0.744)	0.719 (0.694,0.744)
	5				0.744 (0.713,0.776)	0.746 (0.722,0.770)
	6				0.757 (0.725,0.788)	0.740 (0.715,0.765)
	7				0.706 (0.673,0.740)	0.716 (0.690,0.741)
	8				0.708 (0.675,0.740)	0.713 (0.688,0.738)
	9				0.704 (0.670,0.738)	0.702 (0.676,0.728)
5	1					0.673 (0.634,0.711)
	2					0.682 (0.645,0.719)
	3					0.750 (0.719,0.782)
	4					0.726 (0.692,0.761)
	5					0.741 (0.709,0.774)
	6					0.742 (0.709,0.776)
	7					0.717 (0.682,0.752)
	8					0.707 (0.672,0.742)
	9					0.688 (0.652,0.725)

There were consistent results over all six cohorts. The model based on the OAMIPR comorbidities (5) measured over the common survival period (Model 3) was superior to the model that measured the OAMIPR comorbidities (5) at the time of the index admission (Model 4). Model 3 was also superior to the models that included D'Hoore's adaptation to the Charlson Index (Model 5), which was also measured over the common survival period. This adds to the findings of Tu et al. (5) who found that the OAMIPR was a better predictor of all cause mortality than the Charlson Index, when both are measured at the time of index admission. The number of distinct comorbidities measured over the course of the common survival period performed similarly to D'Hoore's adaptation of the Charlson Index, however in most cases D'Hoore's adaptation of the Charlson Index was superior.

Tu et al. (5) assessed the relevant comorbidities measured only at the time of the index AMI. From the results of this analysis, it is shown that a measure of comorbidities over the common survival period is a better predictor than those recorded only at the index admission. The same conclusion can be applied to the risk-adjustment method using the number of distinct comorbidities: when the number was determined over the common survival period, it was a better predictor than when it was determined at the index AMI or in the year prior to the index AMI.

Table 3.9 provides the Nagelkerke's R-square for the 6 month survival cohort, with the highest R-square value for each outcome highlighted. Similar patterns were found for the other cohorts. These data support the results of the C-statistic. Adding comorbidities improves the R-square of the models that include only demographics, previous AMI and procedures at AMI. In most cases, adding the OAMIPR comorbidities

(5) measured over the common survival period, increased the R-square more substantially than the other methods used to control for comorbidities. It also improved the R-square more than when the comorbidities were measured only at the index AMI, as done by Tu et al. (5)

TABLE 3.5 Nagelkerke's R-square for 6 months survival cohort

Model	*Outcome: Died by 1 year*	*Outcome: Died by2 years*	*Outcome: Died by 3 years*	*Outcome: Died by 4 years*	*Outcome: Died by 5 years*
1	0.038	0.067	0.086	0.115	0.136
2	0.052	0.082	0.099	0.130	0.152
3	0.113	0.193	0.219	0.247	0.273
4	0.107	0.172	0.182	0.205	0.228
5	0.114	0.179	0.199	0.223	0.246
6	0.104	0.155	0.187	0.209	0.228
7	0.078	0.125	0.155	0.182	0.212
8	0.092	0.142	0.167	0.194	0.221
9	0.080	0.107	0.125	0.156	0.178

The fact that the results were consistent across all cohorts shows that the risk-adjustment methods can be used when investigating both short and long term mortality.

In summary, of the methods compared, using the OAMIPR (5) measured throughout the common survival period (Model 3), was the best method for risk adjustment when predicting all-cause mortality post-AMI for this population.

3.4 Discussion

This study compared three approaches to risk-adjustment that can be used as methods of controlling for confounding in epidemiological studies using administrative data. The results show that the OAMIPR developed as a risk adjustment method predicting mortality specifically in AMI patients (5), was the method with the highest C statistic and R square, compared to more general methods of risk-adjustment such as

D'Hoore's adaptation of the Charlson Index (7) or the number of distinct diagnoses. Moreover, it was found that the assessment of the comorbidities in the OAMIPR (5) during a longer period after the index AMI was superior to using only those comorbidities recorded at the time of the index admission for AMI, as done by Tu et al. (5) This is consistent with findings by Elmore et al. (17) who found that risk stratification after an AMI is improved by the addition of post-hospitalization data.

It is logical that a risk adjustment method that was developed specifically using data from individuals with AMI would perform better than general methods in predicting mortality following AMI. However, it is important to note that the general methods for risk-adjustment, which measured comorbidities over the common survival period (Models 5 and 6), although not as good as the method developed using AMI patients, were still satisfactory (C statistic above 0.7). This is interesting because it demonstrates that general methods of risk-adjustment can be used with some confidence that they are relatively good approaches. Thus, simpler approaches to risk adjustment are potentially efficient in administrative data based research.

It is also interesting that the basic model that includes age, sex, and SES had an unacceptable range for the C-statistic, which demonstrates that the addition of risk-adjustment methods using comorbidities is critical.

As seen by the comparison of the Nagelkerke's R-square for each of the risk-adjustment methods, the model using the OAMIPR comorbidities (5), measured during the common survival period had the largest R-square for most outcomes. However it is interesting that even the model that included these comorbidities in addition to the demographic variables, previous AMI and procedures at AMI, did not explain more than

27% of the variance. This clearly shows that such a model does not explain much of the variance in mortality. There are other factors that determine mortality, many of them either not measurable, in general, or not measurable due to the limited data available in administrative datasets. Thus, although the addition of such comorbidity measures and scores is useful, particularly because they are readily available, they are limited in their ability to explain more than about a quarter of the variance when predicting mortality. However, because the goal is to control for confounding the best way the data permit, these methods can still be considered useful in epidemiological and health services research.

An important issue when dealing with administrative data is accuracy. The accuracy of diagnostic data varies among databases. To deal with this potential problem, this study mostly used only 3 digits of the ICD9 codes because they have been shown to be more valid in the database used. (8)

Developments in data collection in the medical field in general and in the field of cardiovascular health specifically will likely improve the ability for risk-adjustment methods. For example, in BC, a cardiac registry, initiated in the 1990s, includes important clinical variables not found in the administrative dataset. (18) The British Columbia Provincial Cardiac Registry collects demographic and clinical data on all patients who undergo cardiac procedures in the province. This registry annually adds information for about approximately 3,000 individuals who have had open-heart procedures. Since 1994, individuals who have had pacemaker or angiography procedures have been added. The database is unique in that it is comprehensive and population based. It contains variables such as an operative report, hospital discharge summary,

demographic information, and information on risk factors. Such datasets could be linked to the provincial administrative databases, and as such registries become more widespread they will be extremely useful for studies of the outcomes of cardiovascular patients.

In summary, this study supports the findings by Tu et al. (5) who found that their risk-adjustment method performed well in Ontario AMI patients as well as in patients from California and Manitoba. This study showed that it performed well in British Columbia and adds to these findings by showing that it performs better that the Charlson Index when both risk-adjustment methods are measured over the common survival period. It also adds the critical observation that, not surprisingly, the longer the follow up data used, the better the model performs.

Although outcomes research using clinical data is ultimately the "gold standard", use of administrative data has its advantages with regard to time, expense and the provision of a population-based perspective. A risk-adjustment model that is easily generated using administrative data is very useful because it allows researchers to conduct risk-adjusted outcome analyses simply and efficiently. (5)

3.5 Bibliography

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4 CHAPTER IV: A Population-Based Analysis of Factors Associated With Depression Following AMI

4.1 Background

4.1.1 How common is depression following AMI?

The comorbid association of depression with cardiac disease is frequently encountered. (1, 2) Because depression following acute myocardial infarction (AMI) has been shown to influence cardiac mortality, (3-9) as well as all cause mortality, (9) it is important to know its rate of occurrence.

It is unclear how many individuals develop depression following AMI, or over what time frame incident depression arises. Some authors have reported that the combined prevalence of major and minor depression in cardiac patients is estimated to be 45% (10). Other researchers have shown that 16% of individuals who have had an AMI meet the DSM-II-R criteria for major depressive disorder at the time of interview during hospitalization for AMI. (6) Others have found that approximately 50% of women and 25% of men were at least mildly to moderately depressed, during hospitalization as measured by the Beck Depression Inventory (BDI). (3) Mayou et al. (11) found that during hospital admission for AMI, 7.6% were probable cases of depression and 9.9% were borderline cases as measured by the Anxiety and Depression questionnaire.

Other than the expected inconsistency in rates of depression post-AMI from differing clinical sites and different assessment tools, the two main shortcomings of the available evidence are that researchers to date have measured only short-term manifestations of depression after AMI and have not distinguished between prevalent and

incident depression. It is important to determine the rate of incident depression occurring not only at the time of the index admission for AMI but also in the months and years after AMI because there is evidence that a fair number of individuals are diagnosed as depressed during the first year following their AMI (14.7% (4); 6% (11), 20.6% (12)).

4.1.2 Antidepressant use by individuals who have had an AMI

The treatment of individuals with depression following AMI is complex because it is challenging to find treatments that are safe and effective. Tricyclic antidepressants (TCAs) are known to have adverse cardiovascular effects compared to other types of antidepressants. (13) At therapeutic levels in individuals with a healthy heart, little cardiovascular difficulty is associated with TCAs; greater difficulty is seen in the healthy elderly, and severe problems emerge in people who have heart disease (including delay of cardiac conduction, increased heart rate, and reduced heart rate variability presumably because of TCA's anticholinergic side effects). (14-16) Consequently, although TCAs are an effective treatment for depression in patients with heart disease, their potential for harm is problematic, particularly in the elderly. (13, 17) In general, Selective Serotonin Reuptake Inhibitors (SSRIs) have demonstrated benefits in treating depression, and currently are considered a better alternative to TCAs for depressed patients with cardiac disease. However, systematic studies of the cardiovascular effects of SSRIs are scarce. (18) Little is known about the efficacy of SSRIs in elderly patients, and even less is known about their efficacy in elderly individuals with cardiac disease. (2) Evidence from a few randomized clinical trials shows that treatment with SSRIs in people with comorbid cardiovascular disease is found to be safe and effective for the treatment of depression. (19-21) However most of these studies were funded by pharmaceutical companies

manufacturing SSRIs. Moreover, case reports of patients with pre-existing cardiac disease receiving usual doses of SSRIs, as well as patients without known cardiac disease who have overdosed with these agents, suggest that SSRIs may also produce dysrrhythmias, including atrial fibrillation and flutter, bradycardia, supraventricular tachycardia, and heart block. (2, 22) SSRIs also have been suspected to be associated with bleeding, which certainly could be a serious problem in patients following an AMI who receive anticoagulants or antiplatelet medications. (23, 24) Recently, the Food and Drug Administration (FDA) requested manufacturers of SSRIs to include a warning statement to alert health-care providers to an increased risk of suicidality (suicidal thinking and behaviour) in children and adolescents treated with these agents. (25)

In contrast to this evidence regarding the determental effect of antidepressants on individual with a history of cardiovascular disease, one study (26) found that among persons with cardiovascular disease, antidepressants was associated with decreased risk of hospitalization for myocardial infarction compared to age- and sex-matched population-based controls, althought the differences between different classes of antidepressants were uncertain. Also, no such difference was found among individuals without a history of cardiovascular disease. The authors hypothesize that perhaps antidepressants lower the risk in patients with depression, through their common effect of alleviating depressive symptoms or through a direct protective effect of antidepressants on myocardial infarction. However, the lack of data on depression itself in the sample, including no reference group of patients with untreated depression limits the ability to draw strong conclusions about this hypothesis.

Finally, there are no systematic studies of the cardiovascular effects of most other classes of antidepressants (i.e., venlafaxine, mirtazapine, nefazodone), thus it is not possible to comment on their safety in individuals who have had an AMI.(1) It is important to determine which antidepressants individuals post-AMI are prescribed to determine the potential risks posed by anti-depressant therapy and to guide future research.

4.1.3 Is severity of illness associated with depression following AMI?

It is important to assess the association between depression following AMI and variables that could be potential confounders in any investigation of the effect of depression following AMI on mortality. One such variable is severity of illness, which is associated with mortality, and, which if found to be associated with depression, can be a major confounder in any analysis of the impact of depression following AMI on survival. Although some researchers have found that distress in individuals who had a cardiac event is associated with a previous cardiac event, severity of the cardiac illness, and smoking, (27, 28) others have not found such associations. (10, 11, 29). The association between depression and medical comorbidity has rarely been studied. One study (30) found that depression (both somatic and cognitive) was significantly related to medical comorbidity as measured by a version of the Charlson Index which was slightly revised by the authors to fit the study sample. Moreover, the percentage of nondepressed patients in each comorbidty category decreased as the level of medical comorbidity increased, and found that compared to the nondepressed patients, a significantly higher proportion of patients with major depression had rheumatologic disease, pulmonary disease, congestive heart failure, diabetes or peripheral vascular disease.

4.1.4 Rationale for the study

There were three goals for this study, which was part of a larger research project that aimed to investigate the impact of depression following AMI on long-term all-cause mortality. The first objective of this study was to utilize a population-based approach to describe the incidence of depression post-AMI. The analysis of health-related administrative data to determine the incidence of depression post-AMI has not been previously done and is extremely useful because these data capture the entire population of individuals who had an AMI, as opposed to a clinical sample. Such an analysis allows a thorough assessment of the burden of depression in the population of individuals who have had an AMI. In addition, because administrative data are routinely collected, long-term follow up data are readily available and accessible. Thus, administrative data allow for the assessment of depression occurring not only close to the time of hospitalization for the index AMI, as measured in most studies, but also depression occurring months and even years after the index AMI, which has rarely been examined. Furthermore, it allows for the selection of individuals with incident rather than prevalent depression because information on the period prior to the AMI is readily available.

The second goal of this study was to use administrative data to describe trends in antidepressant prescriptions for individuals who have had an AMI. Administrative data are a useful tool that can be used to describe a comprehensive pattern of antidepressant prescriptions for this population because the data used in this study captured all prescriptions filled by the participants.

The third goal of this study was to use administrative data to determine whether depression is associated with increased comorbidity. Measuring the severity of AMI is

difficult when using administrative data because important indicators of severity, such as electrocardiographic changes, elevation of CPK and other physiological indices are not available. Yet, data on comorbidity are available in administrative datasets. Although short-term mortality is likely to be more strongly related to the clinical severity of AMI, longer-term mortality will be more strongly related to comorbidity. (31) Thus, because the interest of the study was to assess whether depression is associated with factors that are important for longer-term mortality, the association between depression and comorbidity was investigated and considered valuable. The relationship between depression and increased medical comorbidity has been shown previously (30), however in contrast to that study which measured depression only shortly after hospitalization for AMI, this study included individuals with depression which was diagnosed months or even years following AMI, as well as comorbidities which existed not only around the time of the index admission for AMI, but also months and years post-AMI.

4.2 Methods

The general methods are described in section 2.1. Below is a description of the methods applied specifically in this chapter.

4.2.1 Cohorts

This study used Cohorts 1 to Cohort 6 described in section 2.1.

4.2.2 Variables

The variables used in this study include the demographic variables, previous AMI and procedures at the time of the index AMI described in section 2.1. Each individual was assessed for depression as described in section 2.1. Comorbidity was measured using two

methods of measurement of comorbidity in administrative data: The Ontario AMI prediction rule (OAMIPR) developed by Tu et al. (32) and the D'Hoore's adaptation to the Charlson index (33). Both of these measures were determined during the common survival period and are described in more detail in section 3.2.2.

All prescriptions filled for antidepressants as indicated in the PhamaCare files were extracted. For each individual, the number of prescription days was calculated (see section 2.1 for description of this approach).

Antidepressants were categorized into 4 groups: Selective Serotonin Reuptake Inhibitors (SSRI), Tricyclic Antidepressants (TCA), Monoamine Oxidase Inhibitors (MAOI) and 'Other'. For details on how antidepressants were categorized, see Table 4.1.

TABLE 4.1 Classification of Antidepressants

Antidepressant	*Category*
Isocarboxazid	MAOI
Moclobemide	MAOI
Phenelzine	MAOI
Tranylcypromine	MAOI
Amitriptyline	TCA
Amoxapine	TCA
Clomipramine	TCA
Desipramine	TCA
Doxepin	TCA
Imipramine	TCA
Maprotiline	TCA
Nortriptyline	TCA
Protriptyline	TCA
Trimipramine	TCA
Citalopram hydrobromide	SSRI
Fluoxetine	SSRI
Fluvoxamine	SSRI
Paroxetine	SSRI
Sertraline	SSRI
Bupropion	OTHER
Mirtazapine	OTHER
Nefazodone	OTHER
Nomifensine	OTHER
Tryptophan	OTHER
Trazodone	OTHER
Venlafaxine	OTHER

All individuals were assessed as to whether they had at least 2 prescription days of any antidepressants. Of those who had at least 2 prescription days, those who used only 1 category of antidepressant (e.g., SSRIs only) throughout the common survival period, were categorized as 'stable users'. If an individual used more than one class, either simultaneously or not, they were categorized as 'not stable'.

4.2.3 Follow up

Data were available for up to 8 years of follow up post index AMI, which was used when determining the trends of antidepressant prescriptions over time. The rest of the analysis focused on variables which were determined during the common survival period of each cohort, which was a maximum of 5 years.

4.2.4 Analysis

Frequencies were used to describe the characteristics of the cohorts. To identify any associations between the variables, Chi square analysis was used for the categorical variables. ANOVA was used for the continuous variables unless the homogeneity assumption was not met and then Kruskal-Wallis was used. A significance level of 0.05 was used.

The total number of prescriptions recoded in the PharmaCare files for each of the antidepressant categories in each year from 1994-2001 was summed, and the percentage of the total number of prescriptions for each antidepressant category per year was calculated.

4.3 Results

For a description of the main cohort as well as the subcohorts see section 2.1

4.3.1 Number of visits and prescription days

The percentage of individuals with no physician or hospital visits indicating a recorded diagnosis of depression ranged between 90.7% when the visits were assessed within 6 months post-AMI, and 64.6% when the visits were assessed within 5 years post-AMI. The percentage of individuals who had 4 or more physician or hospital visits with a recorded diagnosis of depression ranged between 0.9% within 6 months post-AMI and 8.4% within 5 years post-AMI. The maximum number of visits with a recorded diagnosis of depression ranged from 27 when measured during the first 6 months post-AMI to 79 when measured within the 5 years post-AMI.

The percentage of individuals who had 0 antidepressant prescription days ranged between 96.4% when measured within the first 6 months post-AMI and 84.4% when measured within the first 5 years post-AMI. The percentage of individuals who had 2 or more prescription days ranged between 2% when measured within the first 6 months post-AMI and 10.3% when measured within the first 5 years post-AMI. The maximum number of prescription days ranged between 7 in the first 6 months post-AMI and 78 within the first 5 years post-AMI.

4.3.2 Depression following AMI

The frequency of depression following AMI is described in Table 4.2. As expected, as the 'opportunity' to become depressed increased (i.e. the common survival time in which depression was measured increased), more individuals were classified as depressed.

Table 4.3 shows that approximately 25% (in Cohort 1) to 33% (in Cohort 6) of the individuals who were recognized as depressed by a physician (as indicated by 4 or more physician or hospital visits with a diagnosis of depression), received zero to one prescriptions for antidepressants. Thus, if the definition of depression were based exclusively on the basis of 2 or more prescriptions of antidepressants, these depressed individuals would have been missed.

TABLE 4.2 Depression following AMI

Cohort	*Depressed (%)*	*Possibly depressed (%)*	*Not depressed (%)*	*Total*
Cohort 1: (Depression within 6 months)	108 (2.7)	352 (8.9)	3485 (88.3)	3945
Cohort 2: (Depression within 1 year)	173 (4.7)	430 (11.6)	3105 (83.7)	3708
Cohort 3: (Depression within 2 years)	261 (7.7)	556 (16.4)	2580 (75.9)	3397
Cohort 4: (Depression within 3 years)	331 (10.7)	623 (20.1)	2143 (69.2)	3096
Cohort 5: (Depression within 4 years)	363 (12.8)	655 (23.1)	1817 (64.1)	2835
Cohort 6: (Depression within 5 years)	400 (15.5)	672 (26.0)	1515 (58.5)	2587

TABLE 4.3 Visits and prescriptions in the depressed group

Cohort	No Visits And 2 Or More Prescription Days (%)	1-3 Visits And 2 Or More Prescription Days (%)	4 Or More Visits And No Prescription Days (%)	4 Or More Visits And 1 Prescription Day (%)	4 Or More Visits And 2 Or More Prescription Days (%)
1 (n=108 depressed)	45.4	21.3	23.1	2.8	7.4
2 (n=173 depressed)	35.8	25.4	24.9	3.5	10.4
3 (n=261 depressed)	27.2	26.8	24.5	7.7	13.8
4 (n=331 depressed)	21.8	29.1	27.0	5.8	16.4
5 (n=363 depressed)	20.7	25.9	25.3	7.7	20.4
6 (n=400 depressed)	19.0	26.3	27.0	6.0	21.8

4.3.3 Antidepressant use post AMI

Tables 4.4 and 4.5 describe the use of antidepressants in the cohorts. Most of the individuals who were prescribed antidepressants used only 1 class (i.e., 'stable users') throughout the common survival period. Of those who only used 1 class, most used SSRIs, however a substantial percentage of individuals used TCAs as well.

As seen in Table 4.6, the prescription of TCAs decreased dramatically from 1994 to 2001 while prescriptions of the category 'Other', which includes the drugs Bupropion, Mirtazapine, Nefazodone, Nomifensine, Tryptophan, Trazodone, and Venlafaxine, increased considerably.

TABLE 4.4 Distribution of number of antidepressant classes used in each cohort among those who had at least 2 prescription days

Cohort (number of individuals who had at least 2 prescription days)	*Used 1 class – Stable users (% of total with at least 2 prescriptions)*	*Used 2 classes (% of total with at least 2 prescriptions)*	*Used 3 classes (% of total with at least 2 prescriptions)*	*Used 4 classes (% of total with at least 2 prescriptions)*
Cohort 1 (n=79)	73 (92.4)	6 (7.6)	0	0
Cohort 2 (n=121)	105 (86.8)	16 (13.2)	0	0
Cohort 3 (n=184)	141 (76.6)	38 (20.7)	5 (2.7)	0
Cohort 4 (n=233)	174 (74.7)	50 (21.5)	7 (3.0)	2 (0.9)
Cohort 5 (n=267)	180 (67.4)	54 (20.2)	31 (11.6)	2 (0.7)
Cohort 6 (n=296)	199 (67.2)	69 (23.3)	28 (9.5)	0

TABLE 4.5 Classification of antidepressant category among stable users

Cohort (number of individuals who were stable users in each cohort)	*TCA (% of total stable users)*	*SSRI (% of total stable users)*	*MAOI (% of total stable users)*	*OTHER (% of total stable users)*
Cohort 1 stable users (n=73)	25 (34.2)	38 (52.1)	2 (2.7)	8 (11.0)
Cohort 2 stable users (n=105)	33 (31.4)	57 (54.3)	3 (2.9)	12 (11.4)
Cohort 3 stable users (n=141)	48 (34)	77 (54.6)	3 (2.1)	13 (9.2)
Cohort 4 stable users (n=174)	61 (35.1)	95 (54.6)	1 (0.6)	17 (9.8)
Cohort 5 stable users (n=180)	61 (33.9)	100 (55.6)	1 (0.6)	18 (10.0)
Cohort 6 stable users (n=199)	61 (30.7)	117 (58.8)	2 (1.0)	19 (9.5)

TABLE 4.6 Percentage of prescriptions for each antidepressant category in each year

	SSRI	*TCA*	*MAOI*	*OTHER*
1994	53.7	38.4	2.8	5.1
1995	53.2	36.0	3.1	7.7
1996	53.5	30.5	1.0	15.0
1997	62.8	23.8	1.1	12.4
1998	56.8	27.7	0.6	15.0
1999	58.0	23.6	2.0	16.5
2000	61.6	15.8	1.2	21.4
2001	55.1	14.0	0.9	29.9

4.3.4 Variables by depression

Table 4.7 shows whether depression was associated with various variables. As expected, females were more likely to be depressed. There were no other significant associations with the other demographic factors.

Determination of whether individuals who were depressed, possibly depressed or not depressed differed with regard to their comorbidity (as measured by the D'Hoore's adaptation of the Charlson Index) was explored via a Kruskal-Wallis test. The depressed group had the highest rank of the index, the possibly depressed had a lower ranking than the depressed, and the non-depressed had the lowest mean rank. Thus, it was possible to conclude that depression is associated with increased comorbidity and thus worse health status. It is important to note that there is no method of determining the temporal relationship between the severity of comorbidities and depression. It is impossible to know which came first, however all individuals in the cohorts had no evidence of depression during the year prior to their index AMI. In some cohorts depression was associated with previous AMI or cardiac-related operations, however no consistent pattern across cohorts was found. When a difference was found between the depressed, possibly depressed and not depressed group, the manner in which they differed was that there were more than the expected number of depressed individuals who had previous AMIs or operations.

TABLE 4.7 Association between depression and other variables

Cohort	*Age*	*Sex*	*SES quintiles*	*Rural Residence Vs. Urban*	*Previous AMI*	*Operation of vessels*	*Other operation*	*D'Hoore over common survival period*
6 months	N	Y	N	N	Y	Y	Y	Y
1 year	N	Y	N	N	Y	N	N	Y
2 year	N	Y	N	N	N	N	N	Y
3 year	N	Y	N	N	N	N	N	Y
4 year	N	Y	N	N	N	N	N	Y
5 year	N	Y	N	N	N	N	N	Y

Y $p <= 0.05$
N $p > 0.05$

In general, most of the OAMIPR comorbidities (32) found to be predictive of mortality post-AMI were associated with depression. When a difference was found between the depressed, possibly depressed and not depressed group, the manner in which they differed was that there were more than the expected number of depressed individuals who had the comorbidity. See Table 4.8.

TABLE 4.8 Association between depression and comorbidities measured over the common survival period

Cohorts of survival	*Shock*	*Diabetes*	*Congestive heart failure*	*Canc-er*	*Cerebo-vascular*	*Pulmonary edema*	*Acute renal failure*	*Chronic renal failure*	*Cardiac dysrhythmias*
6 month	Y	Y	Y	N	Y	Y	N	N	Y
1 year	Y	N	Y	N	Y	N	N	N	Y
2 years	N	N	Y	N	Y	Y	Y	Y	Y
3 years	N	N	Y	N	Y	Y	Y	Y	Y
4 years	N	Y	Y	N	Y	Y	Y	Y	Y
5 years	N	Y	Y	Y	Y	Y	Y	Y	Y

Y $p<=0.05$
N $p>0.05$

4.4 Discussion

This study utilized an administrative dataset to describe a population of individuals who had an AMI, and followed them for 5 years. An important contribution of this study is that it was based on the entire population and not a sample, thus it is a very good description of the burden of illness of depression following AMI in the general population of older adults in BC. Also, depression was measured up to 5 years post-AMI, which has not been previously studied, as most studies measure depression close to the time of the index AMI.

As expected, depression was found to occur among individuals following AMI, however the rate of depression found in this study is generally smaller than that found in studies that relied on self-reports. This could be due to the fact that those studies measured prevalent depression and that depression was measured using more sensitive tools such as the Depression Inventory (BDI). (34) Tools such as the BDI which measure psychological distress may not always be appropriate for a population with a medical condition such as heart disease because they were developed mainly for mental health populations and thus may overestimate the prevalence of depression by including items (such as somatic items found in the BDI which measure sleep disturbance, fatigue) that are confounded with the medical conditions causing the same symptoms. (35)

There are several other reasons why the rate of depression based on physician diagnoses and treatment may be lower than that based on a scale such as the BDI. First, depression may be unrecognized by a physician. Coyne et al. (36) compared patients' diagnoses according to the Center for Epidemiological Studies – Depression (CES-D) scale and the Structured Clinical Interview with physician ratings and found that physicians detected 34.9% of the cases of major depression and 27.9% of patients with depressive disorders. Similar results were found by Perez-Stable et al. (37) who compared physicians' recognition of depression (defined by chart notation or prescription of antidepressants) with diagnoses generated by the Diagnostic Interview Schedule (DIS). They found that physicians recognized only 35.7% of the individuals who were categorized as depressed by the DIS. Other researchers (38-41) have found that about 50%-60% of patients with major depression in a primary care setting were recognized. Wells et al. (42) found that 78.2% to 86.9% of depressed patients who visited mental

health specialists had their depression detected, compared with 45.9% to 51.2% of depressed patients who visited general medical clinicians.

In addition to the general difficulty of detecting depression, recognizing depression after a coronary event is even more difficult, for both patient and physician. One problem in making the diagnosis is that there is considerable overlap between the symptoms of depression and those of coronary heart disease. (43) Fatigue and insomnia, for example, are common symptoms of both. Another important barrier to proper diagnosis and treatment of depression in these patients may be the common misconception that depression in such a situation is an expected, normative reaction (i.e., situational), rather than a serious disorder. (44)

Even if the physician recognizes depression, because of the potential for stigma associated with mental illness in general, physicians or patients may try to keep a diagnosis of depression from appearing in the medical records. (45) Therefore due to the under recognition, under treatment and undercoding of depression, the percentage of individuals identified as depressed in this study may be an underestimate.

It is likely that those who were defined as depressed in this study probably had an episode of major depression rather than being a false positive or having mild depression. Patients with unrecognized depression have been found to be less severely ill and less functionally impaired, compared to those who were recognized by their physician. (36, 46, 47) Also, physicians are less likely to treat individuals with antidepressants who are mildly depressed because there is no substantial evidence showing that the treatment of mild depression with antidepressants is more beneficial than placebo treatment. (48)

Another interesting finding in this study was that it was important to include individuals who did not receive any prescriptions for antidepressants, however did have evidence of depression based on their physician or hospital visits. This subgroup included a substantial percentage of the depressed group.

The analysis of the prescription patterns for antidepressants over the years of the study showed that there is an increase in the prescription of the category of drugs that includes Bupropion, Mirtazapine, Nefazodone, Nomifensine, Tryptophan, Trazodone and Venlafaxine. This is a particular concern because there are few systematic studies of the cardiovascular effects of most of these antidepressants; it is difficult to comment on their safety in this context.(1) More research on the efficacy and safety of these drugs in individuals who have had an AMI should be conducted in light of their increasing use.

Depression was found to be associated with increased comorbidity measured using the OAMIPR, (32) or using an adaptation of the Charlson Index. (33) This is a unique finding because most researchers have investigated the association between severity of AMI rather than comorbidity and depression. This is also a crucial finding because it indicates that when investigating the impact of depression on mortality following AMI, it is essential to control for comorbidity; given that it is an important potential confounder. This finding is supported by Scheliefer et al. (10) who found that depression following AMI was not associated with severity of the cardiac illness, however it was associated with the presence of non cardiac medical illnesses. The literature shows that individuals who are depressed following their AMI are not necessarily more severely ill with regard to their AMI, but the measurement and assessment of comorbidity are usually ignored. This finding, however, must be

interpreted with caution because increased comorbidity may lead to increases in detection of depression but not necessarily increases of depression incidence. Because individuals have more contact with the healthcare system due to their increase comorbidity, their depression is more likely to be detected by a physician than an individual who is depressed however does not have as many comorbidities. On the other hand, increases of depression incidence may lead to increases in contact with the healthcare system and thus lead to increased of detection of comorbidities. This potential bias is especially a concern in this study because the dataset used to determine depression status is the same as the dataset used to determine comorbidity. The association between depression following AMI and increased comorbidity following AMI should be tested in further research with depression assessed independently (i.e., not through data derived from administrative data if is also the source for determining comorbidity). In addition, this shows the importance of multivariate analysis when investigating the impact of depression following AMI, especially when using administrative data as the source for determination of depression. In the following chapter such an analysis is presented.

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5 CHAPTER V: Early- and late-onset depression following AMI: Does it affect short- and long-term survival and health services use?

5.1 Background

Depression occurring shortly following AMI has been shown to influence cardiac mortality (1-7) as well as all cause mortality. (7) The effect of depression on survival can be as high as threefold, as shown in Frasure-Smith et al. (1) who found that high depression scores were related to cardiac mortality with an odds ratio of 3.29 (95%CI 1.02,10.59) for women and 3.05 (95%CI 1.29,7.17) for men. One study showed that even minimal symptoms of depression increased the risk for mortality post-AMI. (8) However, other researchers have not found an association between depression and survival (9, 10). There is some evidence that depression following AMI also affects health services use with depressed patients having greater use of services in all categories of medical care, including inpatient admissions, outpatient visits, laboratory tests, emergency department visits, number of prescriptions, and number of ancillary visits. (11-13)

There are several important limitations in the studies investigating the impact of depression on survival. First, the follow up of most of these studies is short (i.e., no more than 18 months). Thus, it is not known whether depression post-AMI has an impact on longer term mortality. Second, most of the studies to date assessed depression symptomatology only shortly after admission for the cardiac event, (1, 3, 4, 8, 14-16) which may not be an optimal or relevant measure of major depression because it may capture only transient (situational) states occurring after a traumatic cardiac event, rather than actual episodes of major depression. Moreover, because no data were available in

these studies on the period prior to admission with regard to depression symptoms, it is impossible to distinguish between prevalent and incident depression. Individuals with chronic depression may be different than those who become depressed following their AMI. Finally, most of the studies did not investigate the impact of depression occurring later in the course of recovery from AMI, even though a significant number of individuals become depressed throughout the first year post-AMI, with estimates ranging between 6% and 20%. (2, 10,17) While some researchers have measured depression at 1 year following AMI (2, 7, 10), only one study (7) investigated the impact of 1-year depression on mortality. Therefore, little is known about the impact of late onset depression post-AMI on survival. The main limitation of studies investigating the association between depression and health services use is that they used only univariate analyses when investigating readmissions and visits, thus they were unable to conclude whether the association found is due to confounding factors such as increased comorbidity.

This chapter describes the results of the analysis of the main questions of this dissertation – whether depression following AMI has an effect on survival and health services use. This study investigated the impact of early- and late-onset depression following AMI on short- and long-term survival using administrative data, a data source that has not been previously used to investigate this question. Administrative data, gathered at a population level (18), can expand current knowledge because they provide information about an entire population rather than a clinical sample, increasing the generalizability of the findings, and reducing the possibility of selection bias. The administrative data used in this study also allow explicit identification of incident

depression and exclusion of individuals with prevalent depression, and permits long term follow up.

5.2 Methods

For a description of the general methods of data acquisition, cohort selection, and the variables used see section 2.1. The section below describes the additional chapter specific methods.

5.2.1 Cohorts

Cohorts 1-6 were used for the investigation of the impact of depression on survival. Another cohort (Cohort 7) was constructed which included 2311 individuals who survived at least 5 years after the index AMI, and were not categorized as depressed or possibly depressed within the first 6 months post-AMI. This cohort was used to assess the impact of late-onset depression (depression incidence occurring between 6 months and 5 years post-AMI) on survival. For analysis of the impact of depression on readmissions, a cohort of individuals who survived at least 4 years was used.

5.2.2 Variables

The variables examined included age, sex, SES, previous AMI and procedures at time of index AMI as described in section 2.1. Two methods to assess the comorbidities were used and are described in detail in Chapter 3:

1. Comorbidities found in the OAMIPR (19) were measured over the course of the common survival period of each cohort. These included: shock, diabetes, congestive heart failure, cancer, cerebovascular disease, pulmonary edema, acute renal failure, chronic renal failure, and cardiac dysrhythmia.

2. D'Hoore's adaptation of the Charlson Index (20) was also measured over the common survival period of each cohort.

Both of these were found in Chapter 3 to be predictive of mortality, and, as described in Chapter 4, they are associated with depression, thus it was important to control for them.

5.2.2.1 Measurement of depression

For the analysis of the impact of depression on survival, each individual was categorized as 'Depressed', 'Possibly depressed' or 'Non-depressed' as described in section 2.1, assessed during the common survival periods. Only for the analysis of the impact of depression on readmissions, each individual was assessed as to whether they were 'Depressed' , 'Possibly depressed' or 'Non-depressed' during the first year following AMI. The reason this was used rather than depression which occurred throughout the 4 years of the common survival period was that readmissions were counted between 1 year post-AMI and 4 years post-AMI. In order to guarantee the temporal relationship between depression and readmissions, depression was assessed in the first year post-AMI while the readmissions were only assessed after the first year.

5.2.3 Outcomes and follow up

The main outcome investigated was all cause mortality. Follow up data through 2001 were available, which is a maximum of 8 years of follow up. Information on cardiac mortality was not available due to lack of funding required in order to obtain data on cause of death from Vital Statistics.

A secondary outcome was health services use as measured by readmissions to hospital. Three measures of readmission were used: the total number of readmissions excluding readmissions for depression as the primary diagnosis; the number of readmissions for circulatory system problems as primary diagnoses; and the number of emergency readmissions. These outcomes were measured during the second to fourth years post-AMI.

5.2.4 Analysis

5.2.4.1 Outcome: death

Univariate analysis using Chi-Square was conducted for sex by death by the first year, second year, third year, fourth year and fifth year, excluding individuals who did not have data on sex.

For Cohort 1, relative risks and their 95% confidence intervals were calculated for death by the first, second, third, fourth, fifth and sixth years following the index AMI. For Cohort 7 a relative risk and 95% confidence interval was calculated for death by the sixth year.

Kaplan Meier (KM) (21) survival curves were used to compare the survival of the different groups. Specifically, KM curves were used to compare:

1. Individuals who were depressed, possibly depressed and not depressed
2. Individuals who were depressed versus those who were not depressed
3. Individuals who were depressed versus those who were possibly depressed
4. Individuals who were possibly depressed versus not depressed

To determine whether there were differences within the individuals with depression with regard to survival due to the various ways of defining depression Kaplan Meier survival curves were used to compare the following groups:

1. Individuals in the depressed group who had 4 or more physician visits with an indication of depression however no prescription for antidepressants, compared to the rest of the individuals in the depressed group
2. Individuals in the depressed group who had 2 or more prescriptions for antidepressants however no physician visits with an indication for depression compared to the rest of the individuals in the depressed group
3. Individuals in the depressed group who had 2 or more prescriptions for antidepressant and 4 or more physician visits with an indication for depression compared to the rest of the individuals in the depressed group (i.e. those who had either only 2 or more prescriptions for antidepressants or those who had only 4 or more physician visits with an indication for depression)

The log-rank test was used to determine whether the survival curves were significantly different.

Cox regression analysis (22) was used to determine whether depression was independently associated with mortality after controlling for confounding factors (including age, sex, SES, previous AMI, operations at time of index AMI and comorbidities). The proportional hazards assumption was tested using log-minus-log graphs. Four blocks of variables were used. The first block included age, sex (with males being the reference category), and SES (with the lowest SES quintile being the reference

category). The second block added previous AMI and procedures at index hospitalization. The third block added the risk-adjustment method (either the OAMIPR (19) or the D'Hoore's adaptation of the Charlson Index (20), both measured over common survival period). The fourth block added the depression variable used as a categorical variable with the reference category being the 'Not depressed' group.

A significance level of 0.05 was applied.

5.2.4.2 Outcome: Readmissions

Univariate analysis was used to determine whether there was a difference between the individuals who were depressed, possibly depressed and not depressed on the number of readmissions. As the homogeneity assumption was not met, ANOVA could not be used and a Kruskal–Wallis test was used.

For the multivariate analysis, dichotomized variables for total number of admissions, circulatory admissions and emergency admissions were constructed with 0 indicating 0 admissions and 1 indicating 1 or more admissions. This outcome was used in a logistic regression analysis with the same variables used in the Cox regression analysis. The reason for using a binary outcome rather than number of admissions was that 65% had no admissions for circulatory reasons and 34% had no admission for any reason (excluding depression as the main reason for admission) between year 2 and year 4 following the index AMI. It was of interest to investigate the difference between those who were readmitted and those who were not.

Logistic regression analysis assumes a linear relationship between the logit of the independent variables and the dependent variable. Thus, the linearity assumption was tested for continuous variables (age, SES, and D'Hoore's adaptation of Charlson Index).

The assumption was tested using the Box-Tidwell transformation which adds variable interaction terms that are the cross-products of each independent variable and its natural logarithm [(X)ln(X)]. If these terms are significant, then there is nonlinearity in the logit. All the continuous variables met the linearity assumption. Standardized residuals, used to check for outliers in the data, were calculated and observed to determine whether there were any residuals below -3 or above 3. If the standardized residual value is above 3 or below -3, the observation is a potential outlier.

5.3 Results

5.3.1 Outcome: All cause mortality

For a description of Cohorts 1-6 see section 2.1. In the univariate analysis of sex by death, no significant differences were found.

The distribution of mortality by depression status for Cohort 1 and Cohort 7 is shown in Table 5.1. The relative risks of annual mortality post index AMI for the depressed group versus the not depressed group and their 95% confidence intervals are shown in Table 5.2. Early-onset depression occurring within the first 6 months post-AMI (Cohort 1) was associated with short- and long-term all-cause mortality. Early-onset depression had the strongest effect on short-term mortality, however, the effect, even though decreased, was still significant up to 6 years post-AMI. Late-onset depression occurring after the first 6 months post-AMI (Cohort 7) was also significantly associated with long-term mortality.

TABLE 5.1 Mortality by depression status for Cohort 1 and 7

Cohort	Outcome	Depressed	Possibly depressed	Not depressed
Cohort 1		***n=108***	***n=352***	***n=3485***
	Died by end of year 1	12.0%	8.2%	5.6%
	Died by end of year 2	22.2%	19.9%	13.0%
	Died by end of year 3	32.4%	27.3%	20.6%
	Died by end of year 4	38.9%	34.4%	27.2%
	Died by end of year 5	44.4%	38.6%	33.7%
	Died by end of year 6	49.1%	42.3%	39.2%
Cohort 7		***n=274***	***n=522***	***n=1515***
	Died by end of year 6	13.9%	10.3%	6.7%

TABLE 5.2 Relative risks for the depressed group versus the not depressed group

Cohort	Outcome	Relative risk (95% confidence interval
Cohort 1	Died by the first year	2.15 (1.26, 3.56)
	Died by the second year	1.71 (1.17, 2.40)
	Died by the third year	1.57 (1.17, 2.04)
	Died by the fourth year	1.43 (1.11, 1.79)
	Died by the fifth year	1.32 (1.05, 1.61)
	Died by the sixth year	1.25 (1.03, 1.52)
Cohort 7	Died by the sixth year	2.06 (1.45, 2.92)

5.3.1.1 Kaplan Meier (KM) Curves

The proportional hazards assumption was valid for all the models. Figures 5.1 through 5.7 show the Kaplan Meier curves for each of the cohorts comparing all depression groups. The log-rank tests on all 7 curves were significant. Figures 5.8 through 5.14 show the KM curves for only the depressed versus the not depressed group. The survival curves were significantly different when tested with the log rank test.

FIGURE 5.1 Kaplan Meier curve for Cohort 1 for all depression groups

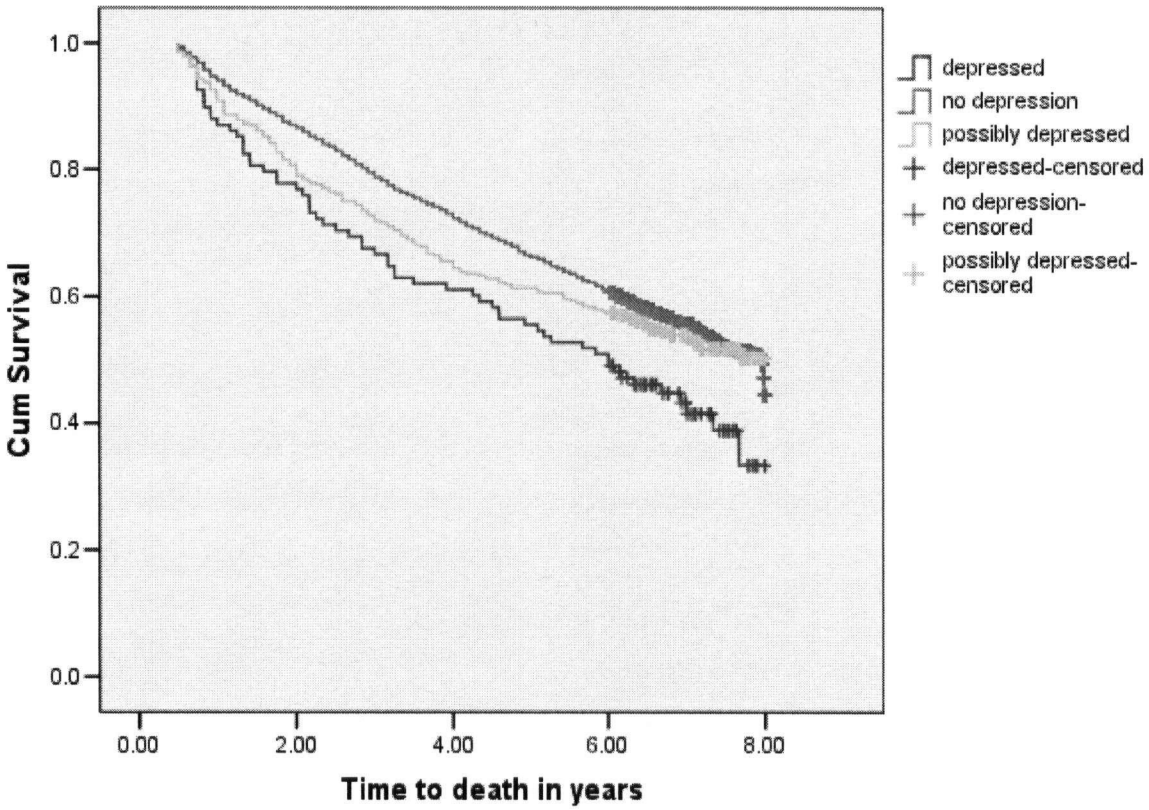


FIGURE 5.2 Kaplan Meier curve for Cohort 2 for all depression groups

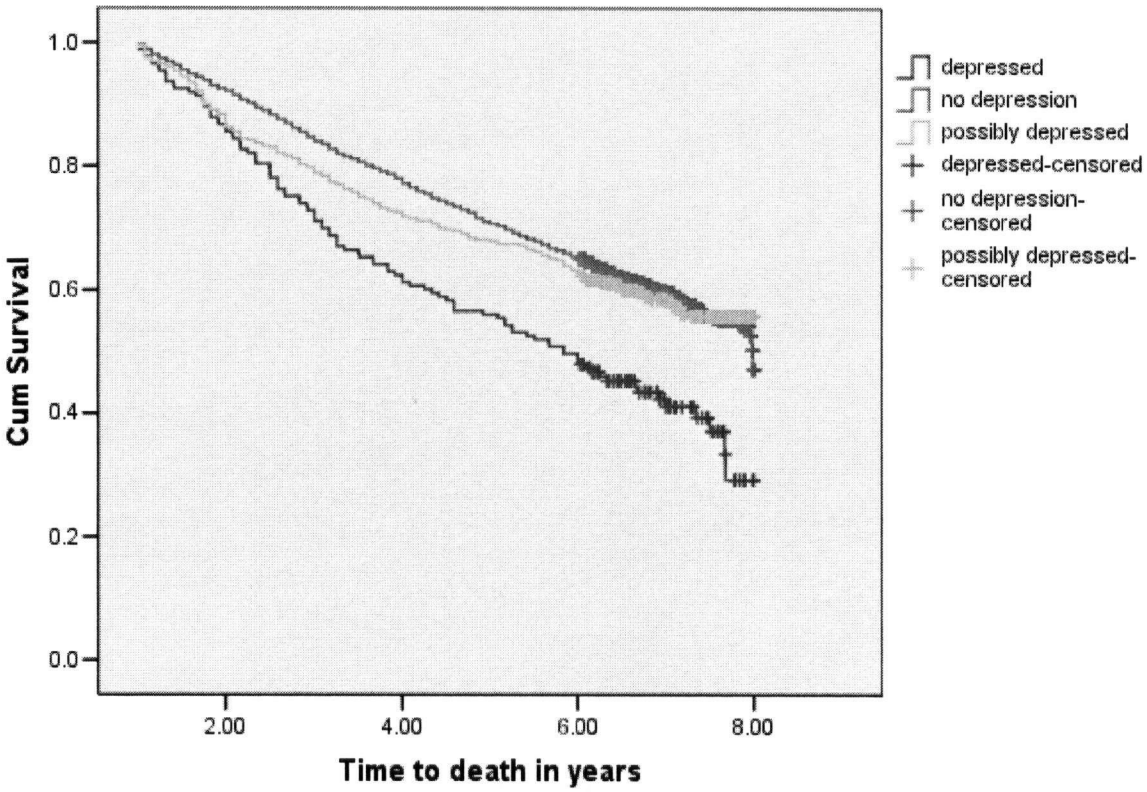


FIGURE 5.3 Kaplan Meier curve for Cohort 3 for all depression groups

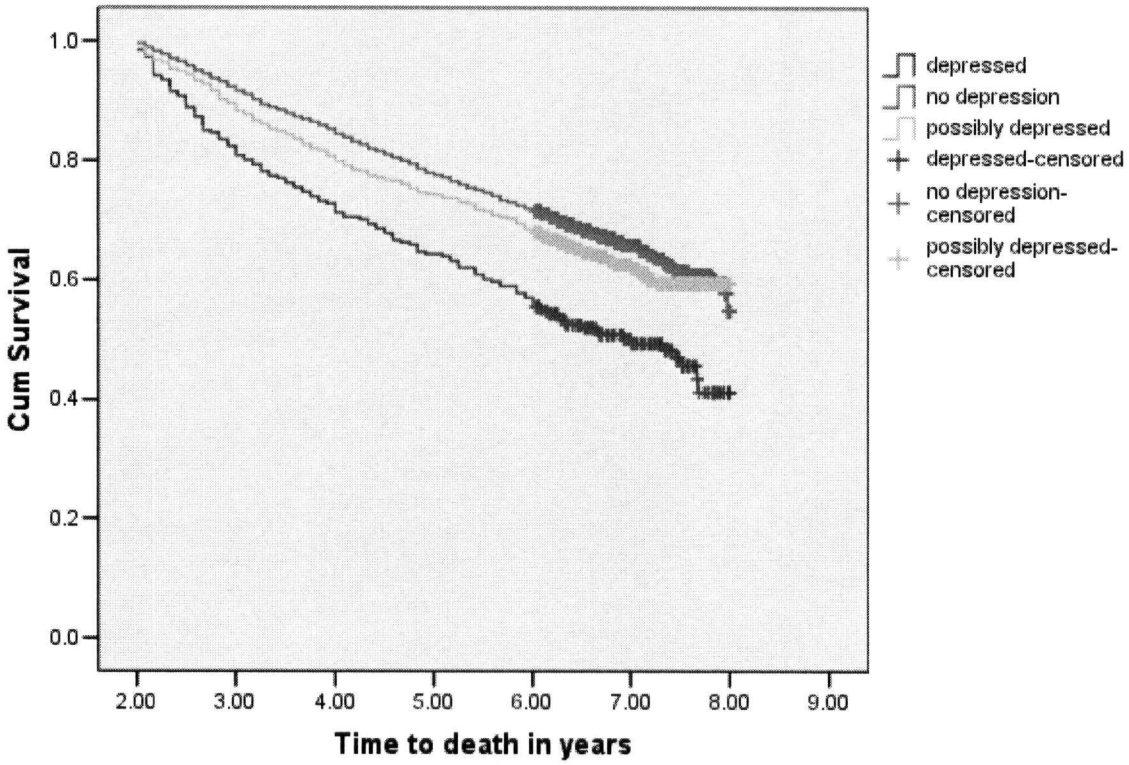


FIGURE 5.4 Kaplan Meier curve for Cohort 4 for all depression groups

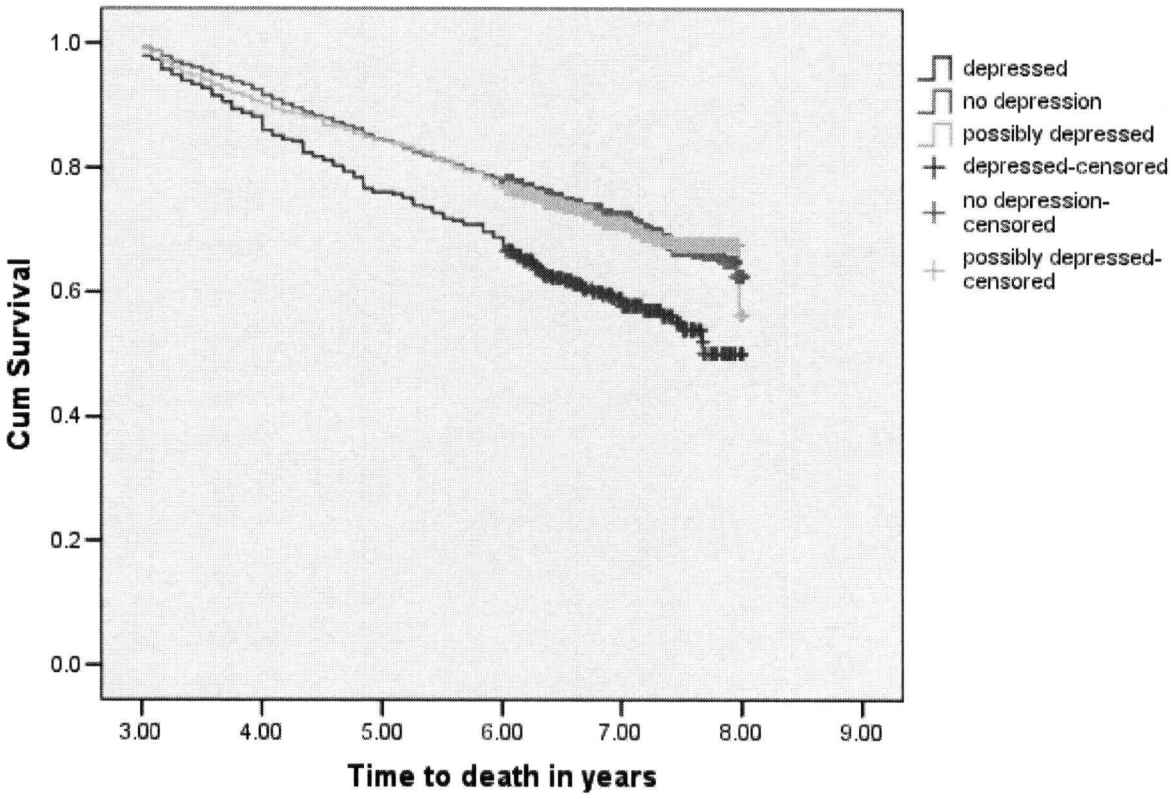


FIGURE 5.5 Kaplan Meier curve for cohort 5 for all depression groups

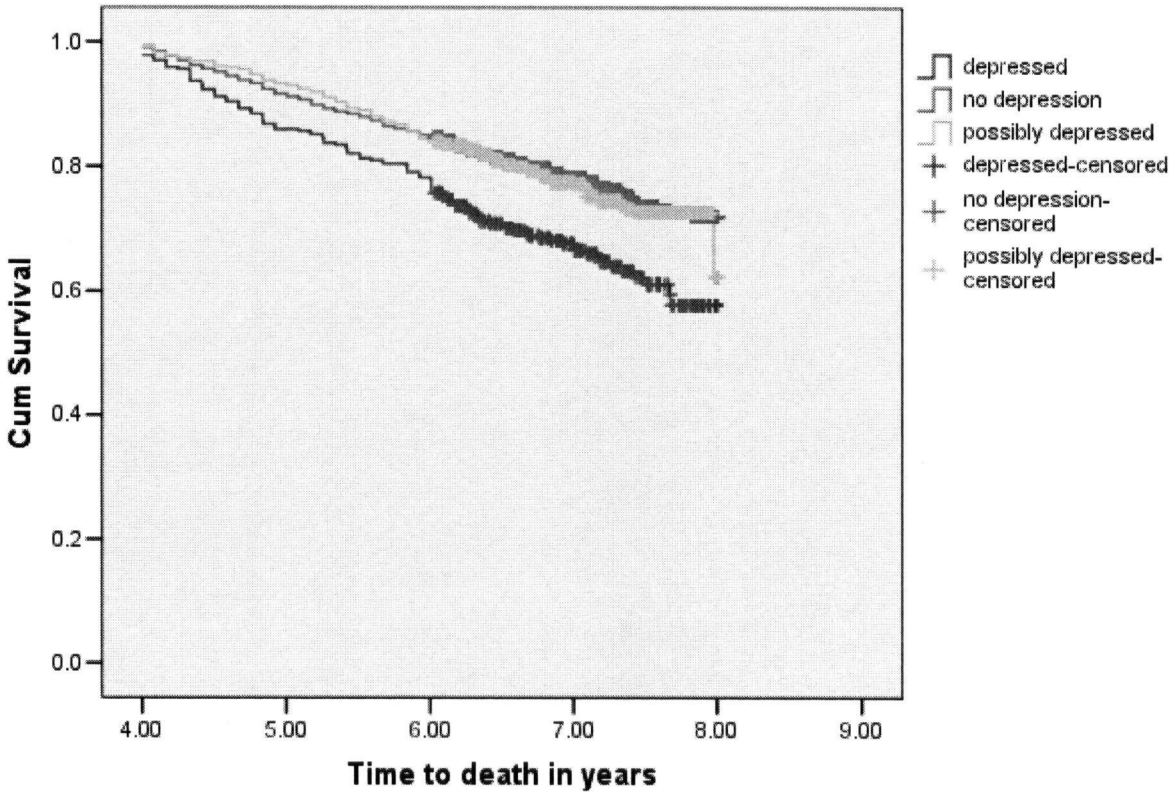


FIGURE 5.6 Kaplan Meier curve for Cohort 6 for all depression groups

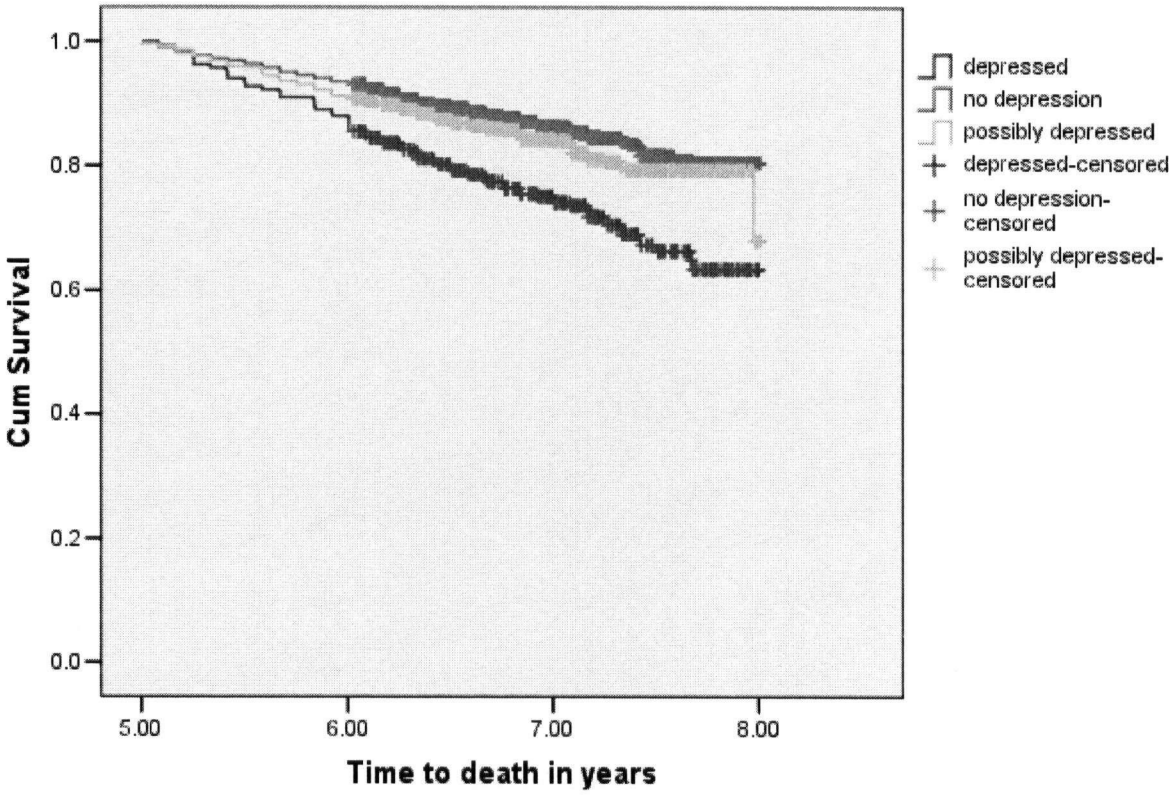


FIGURE 5.7 Kaplan Meier curve for Cohort 7 for all depression groups

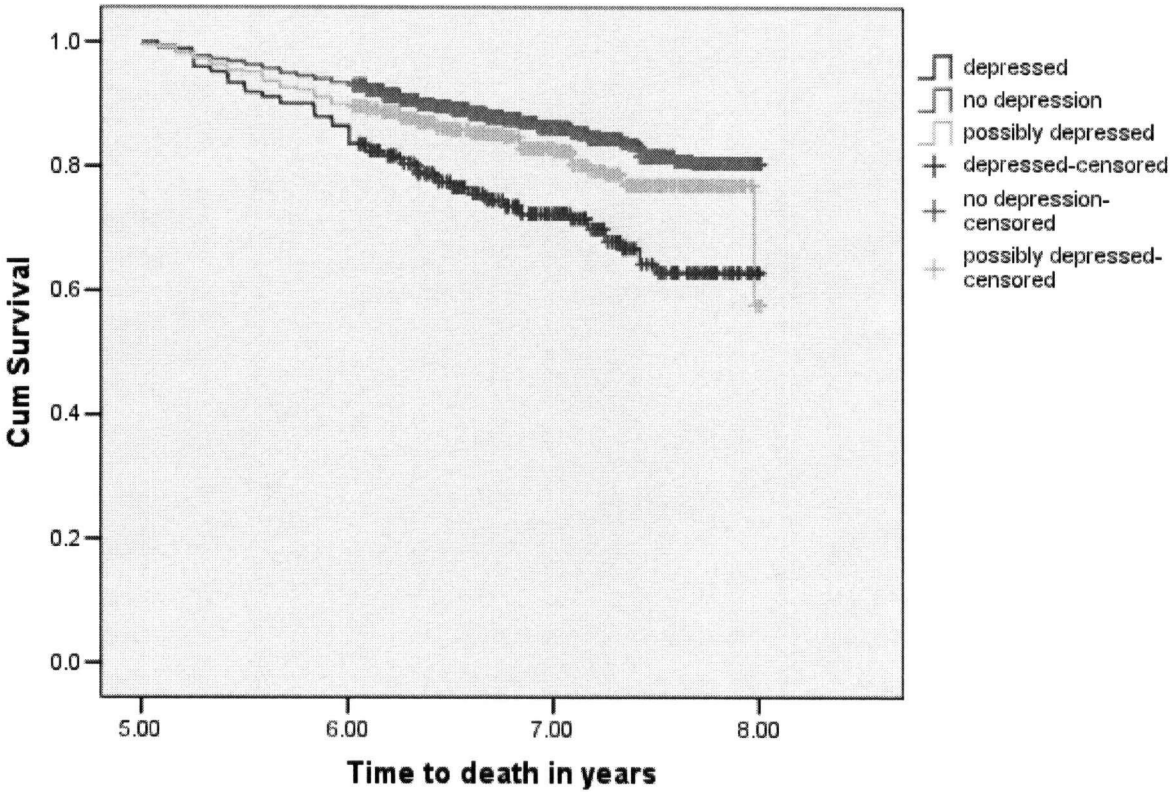


FIGURE 5.8 Kaplan Meier curve for Cohort 1 for depressed vs not depressed

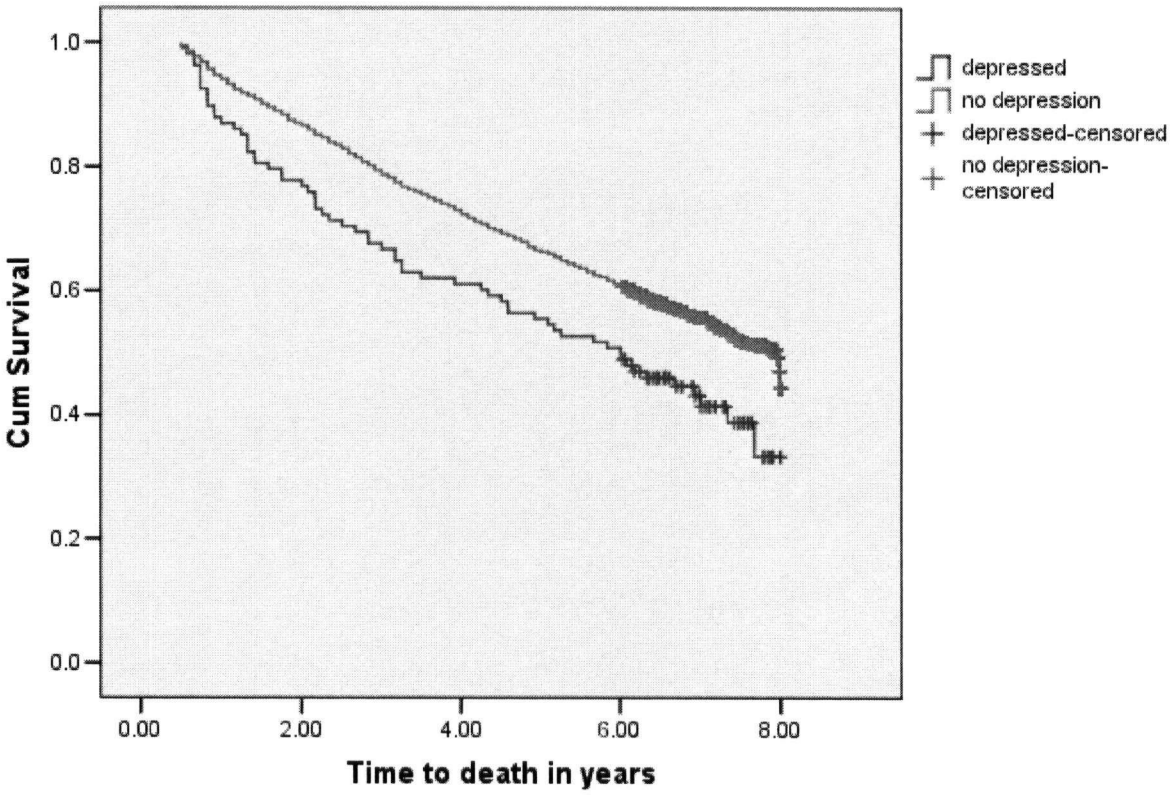


FIGURE 5.9 Kaplan Meier curve for Cohort 2 for depressed vs not depressed

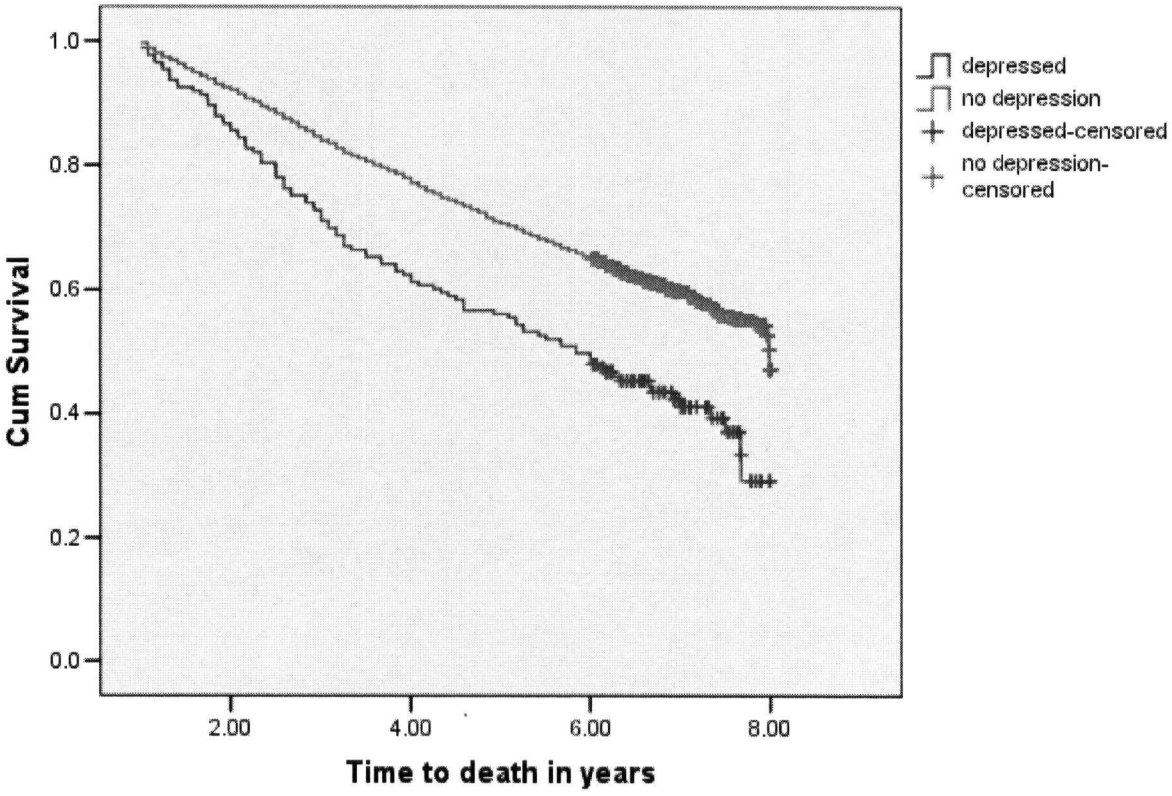


FIGURE 5.10 Kaplan Meier curve for Cohort 3 for depressed vs not depressed

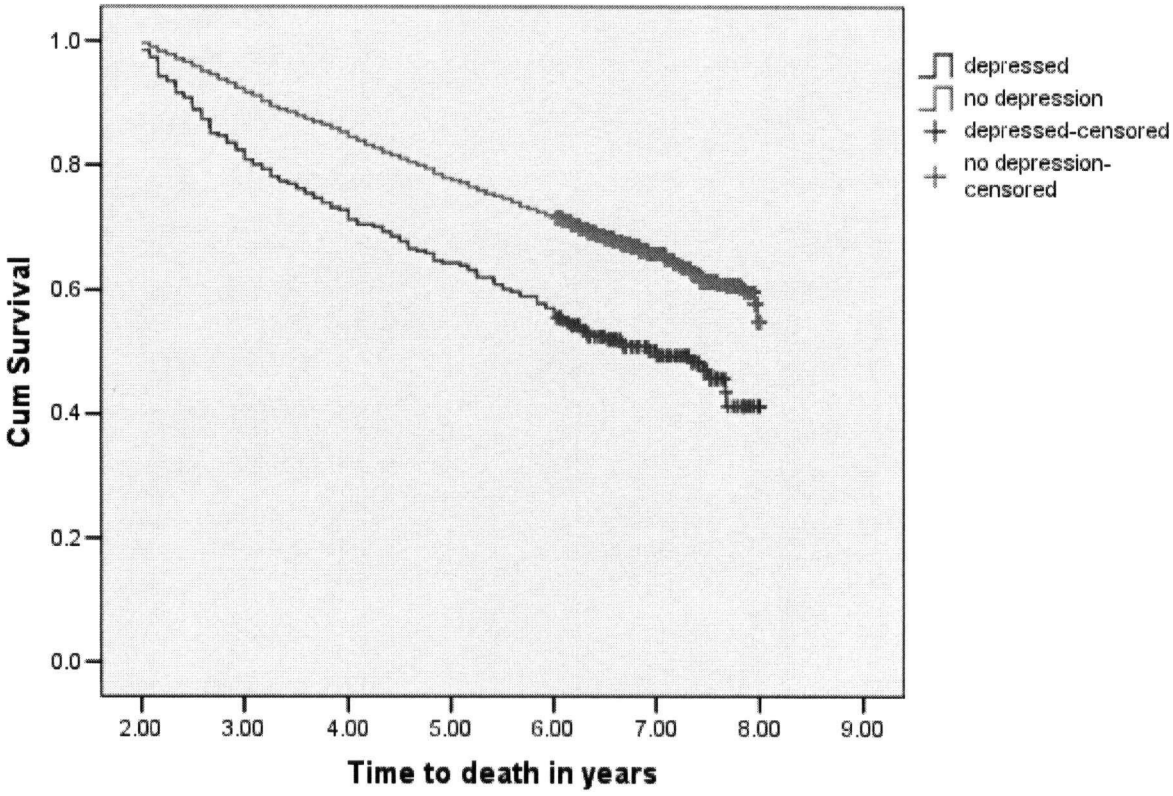


FIGURE 5.11 Kaplan Meier curve for Cohort 4 for depressed vs not depressed

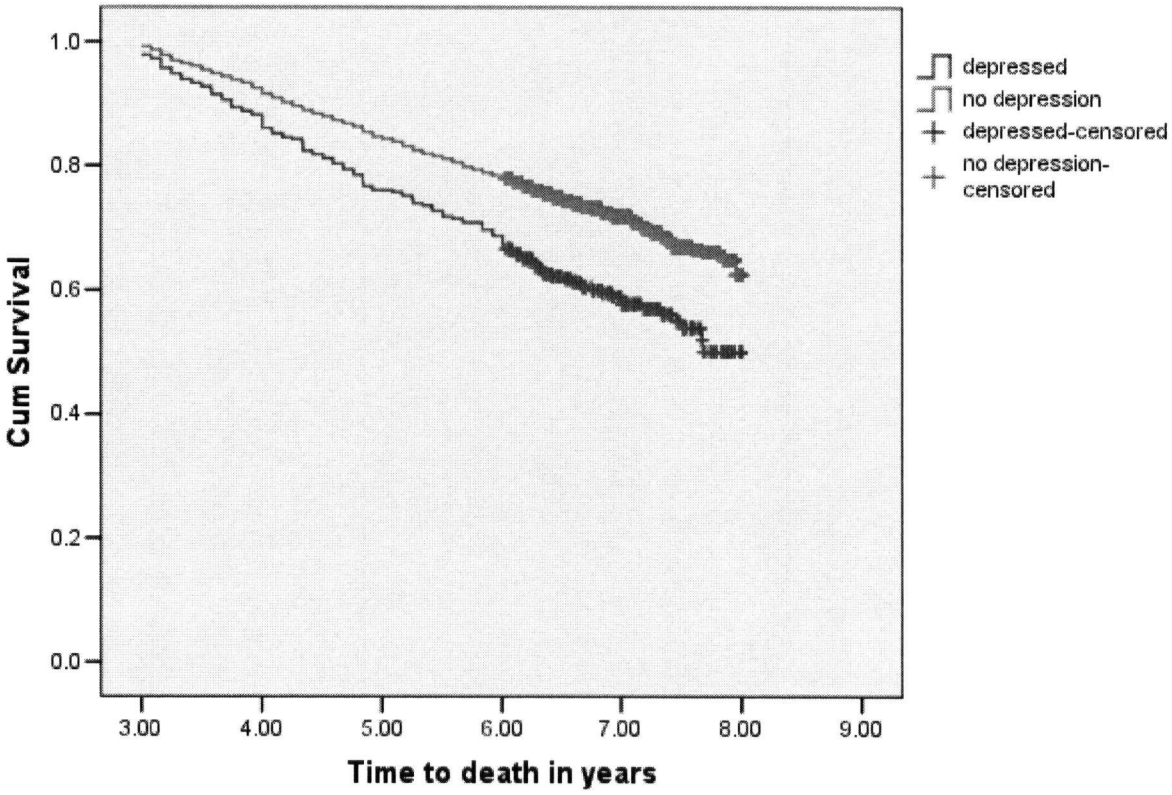


FIGURE 5.12 Kaplan Meier curve for Cohort 5 for depressed vs not depressed

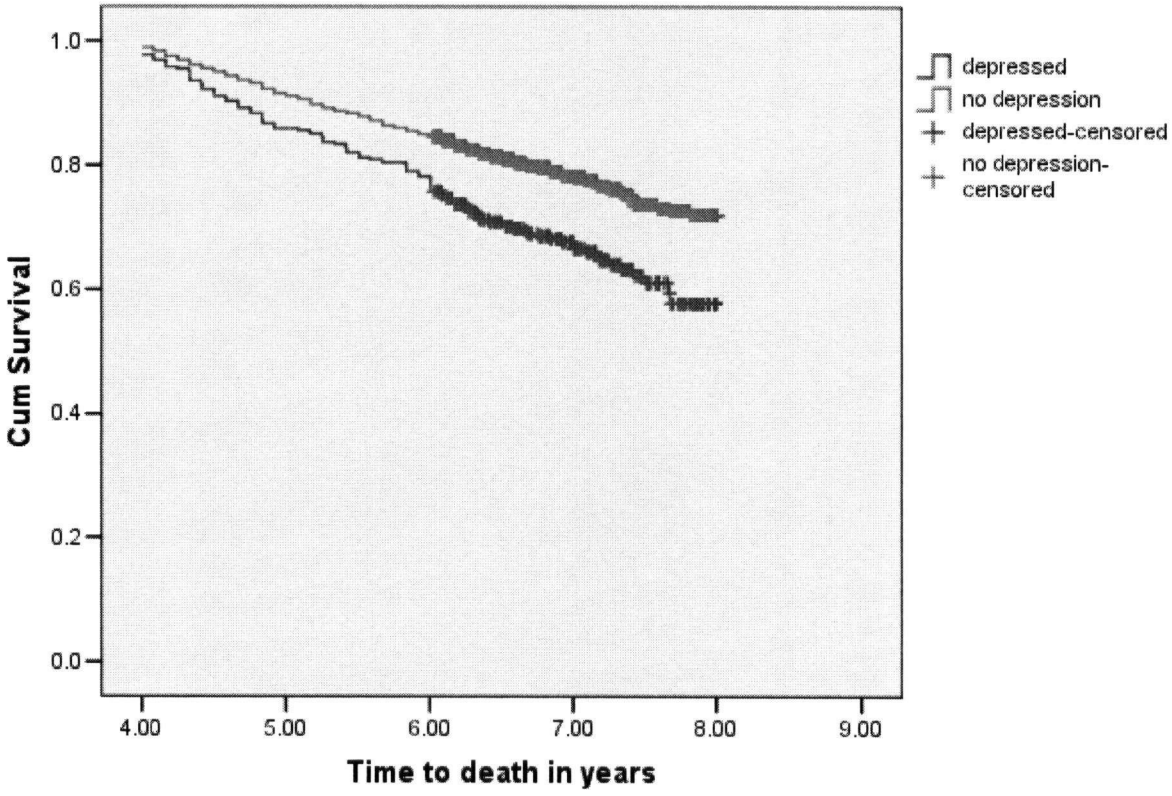


FIGURE 5.13 Kaplan Meier curve for Cohort 6 for depressed vs not depressed

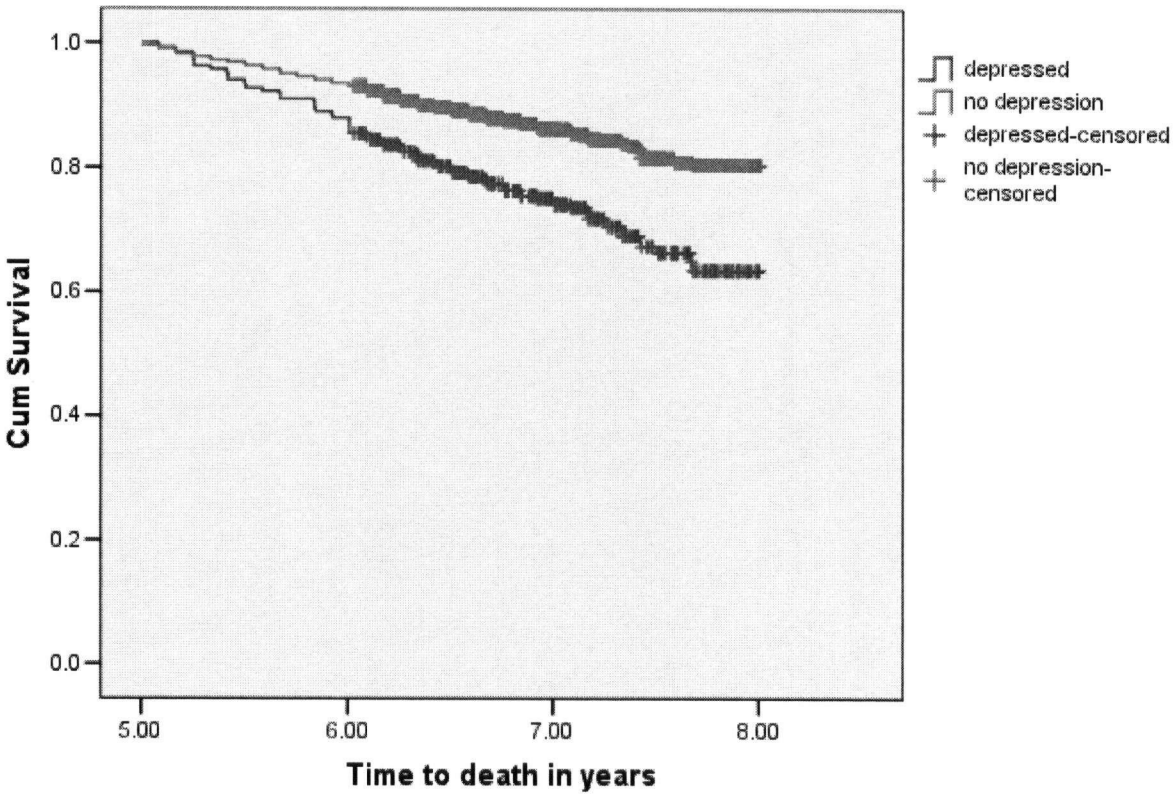
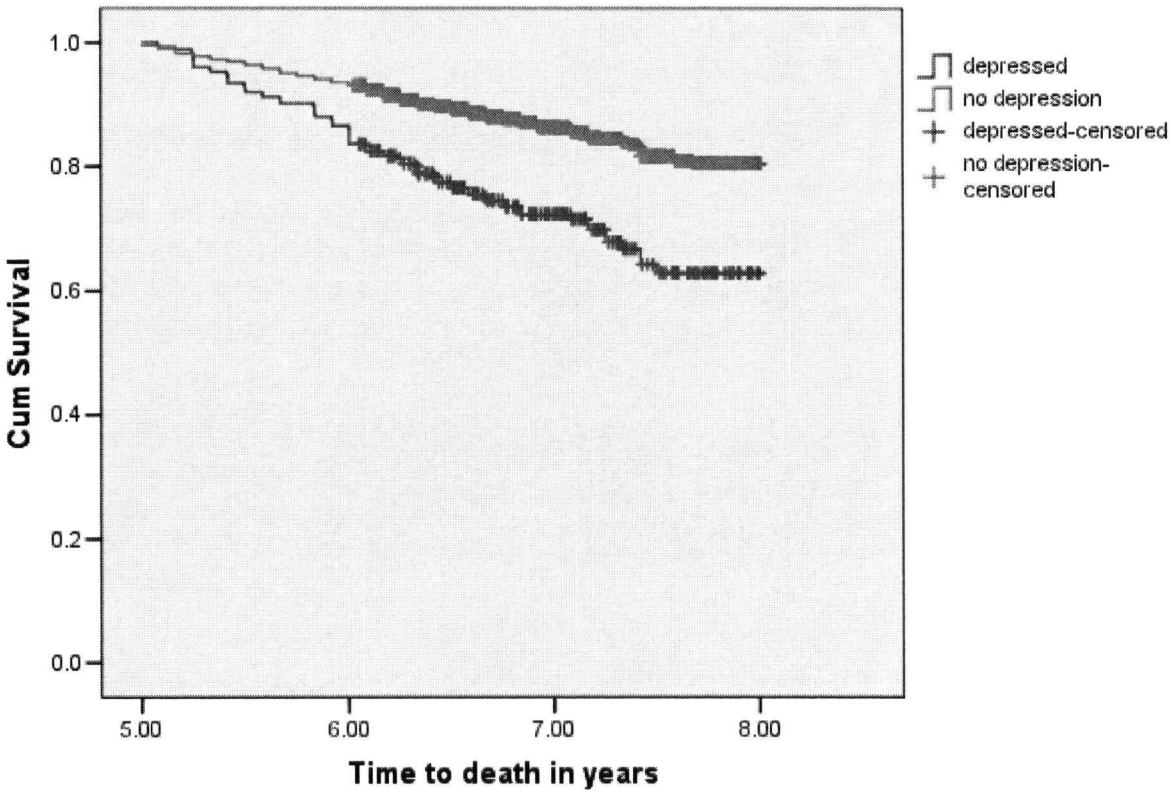


FIGURE 5.14 Kaplan Meier curve for Cohort 7 for depressed vs not depressed



KM curves for the depressed versus the possibly depressed were also constructed and were found to be significantly different. However, for all cohorts there was no difference between the possibly depressed and the not depressed groups. Also, no differences in survival were found between the subgroups of the depressed group, which shows that the depressed group were not different with regard to survival, regardless of the method of determination of depression.

In summary, the depressed individuals had poorer survival compared to the individuals who were possibly depressed or not depressed. However, there was no difference between the individuals who were possibly depressed and not depressed.

5.3.1.2 Cox regression

Cox regression was used to test whether the differences found in the KM analyses were due to confounding factors.

In all seven cohorts, it was found that after controlling for confounders – either by using the OAMIPR (19) or the D'Hoore's adaptation to the Charlson Index (20) – depression remained a strong predictor of survival. Compared to the individuals who were not depressed, depressed individuals were at significantly more risk for shortened survival, however individuals who were possibly depressed were not.

Previous AMI was a strong predictor of mortality. Age was a significant predictor in all cohorts. For example, in Cohort 1, age had a hazard ratio of 1.08 (95% CI 1.07, 1.09) which at first glance may not seem clinically significant, however it shows that there is an increase of about 8% in mortality for each additional year of age. Sex was a significant predictor in Cohorts 1, 2 and 3, with females being at lower risk than males. In most of the cohorts, SES was not a significant predictor of mortality.

The D'Hoore adaptation of the Charlson Index (20) was significant. Most of the comorbidities used in the OAMIPR (19) were found to be significant in the Cox regression analysis.

The hazard ratio for depression increased as the common survival time increased. This could likely be due to the fact that the risk-adjustment methods decreased in their ability to predict mortality as individuals survived longer. This leaves more 'room' for

depression to predict mortality. Interactions between sex and depression, age and depression and between sex and the D'Hoore adaptation of the Charlson Index (20) were tested but were not found to be significant.

The results of the Cox Regression analyses are presented in Tables 5.3 through 5.16 (significant variables are highlighted).

TABLE 5.3 Cox regression for cohort 1 using OAMIPR

	B	SE	Sig.	Exp(B)	95.0% CI for Exp(B)	
					Lower	Upper
Female	-.210	.051	<.001	.811	.734	.895
Unknown sex	-.919	.319	.004	.399	.214	.746
Age	.077	.004	<.001	1.080	1.072	1.089
SES quintile 2	-.042	.072	.556	.959	.833	1.103
SES quintile 3	-.107	.075	.154	.899	.775	1.041
SES quintile 4	-.045	.075	.544	.956	.825	1.106
SES quintile 5	-.001	.081	.991	.999	.853	1.170
SES quintile unknown	.003	.095	.978	1.003	.832	1.208
Previous AMI	.385	.099	<.001	1.469	1.210	1.784
Heart Operation	-.503	.132	<.001	.605	.467	.783
Other Heart operation	-.027	.119	.818	.973	.771	1.228
Diabetes	.404	.056	<.001	1.497	1.341	1.671
Heart failure	.645	.051	<.001	1.906	1.726	2.105
Cancer	.430	.082	<.001	1.537	1.308	1.806
Pulmonary edema	.381	.101	<.001	1.463	1.200	1.784
Acute renal failure	.079	.082	.331	1.083	.923	1.270
Cardiac dysrhythmia	.212	.049	<.001	1.236	1.122	1.362
Chronic renal failure	.589	.099	<.001	1.801	1.482	2.189
Shock	.347	.171	.042	1.415	1.012	1.979
Cerebovascular disease	.543	.072	<.001	1.721	1.495	1.981
Possibly depressed	.155	.083	.060	1.168	.993	1.374
Depressed	.295	.130	.023	1.343	1.041	1.733

TABLE 5.4 Cox regression for cohort 1 using D'Hoore's adaptation of Charlson Index

	B	SE	Sig.	Exp(B)	95.0% CI for Exp(B)	
					Lower	Upper
Female	-.182	.050	<.001	.833	.755	.919
Unknown sex	-.988	.318	.002	.372	.199	.694
Age	.085	.004	<.001	1.089	1.081	1.097
SES quintile 2	-.079	.071	.269	.924	.803	1.063
SES quintile 3	-.151	.075	.044	.860	.742	.996
SES quintile 4	-.108	.075	.147	.897	.775	1.039
SES quintile 5	-.075	.080	.346	.927	.793	1.085
SES quintile unknown	.004	.095	.962	1.004	.834	1.210
Previous AMI	.442	.099	<.001	1.556	1.282	1.888
Heart operation	-.488	.129	<.001	.614	.477	.791
Other heart operation	-.087	.118	.459	.916	.727	1.155
D'Hoore index	.160	.007	<.001	1.174	1.157	1.190
Possibly depressed	.155	.082	.060	1.167	.993	1.371
Depressed	.293	.130	.024	1.341	1.039	1.731

TABLE 5.5 Cox regression for Cohort 2 using OAMIPR

	B	SE	Sig.	Exp(B)	95.0% CI for Exp(B) Lower	Upper
Female	-.214	.055	<.001	.808	.726	.899
Unknown	-.985	.336	.003	.373	.193	.722
Age	.078	.004	<.001	1.081	1.072	1.090
SES quintile 2	-.048	.077	.527	.953	.820	1.107
SES quintile 3	-.142	.082	.085	.868	.739	1.020
SES quintile 4	-.054	.080	.505	.948	.810	1.109
SES quintile 5	.042	.086	.627	1.042	.882	1.233
SES qu[illegible]	.000	.103	.998	1.000	.817	1.223
Previous AMI	.361	.109	.001	1.435	1.159	1.777
Heart operation	-.421	.137	.002	.656	.502	.858
Other heart operation	-.034	.124	.786	.967	.758	1.233
Diabetes	.338	.060	<.001	1.402	1.247	1.577
Heart failure	.664	.055	<.001	1.943	1.743	2.166
Cancer	.355	.076	<.001	1.426	1.228	1.657
Pulmonary edema	.363	.097	<.001	1.438	1.188	1.740
Acute renal failure	.206	.072	.004	1.229	1.066	1.416
Cardiac dysrhythmia	.198	.053	<.001	1.219	1.098	1.352
Chronic renal failure	.345	.106	.001	1.412	1.147	1.739
Shock	.151	.182	.408	1.163	.814	1.661
Cerebovascular disease	.533	.068	<.001	1.704	1.491	1.948
Possibly depressed	.102	.080	.204	1.107	.946	1.296
Depressed	.431	.105	<.001	1.538	1.253	1.888

TABLE 5.6 Cox regression for Cohort 2 using D'Hoore's adaptation of Charlson Index

	B	SE	Sig.	Exp(B)	95.0% CI for Exp(B) Lower	Upper
Female	-.188	.054	<.001	.829	.746	.921
Unkonwn sex	-1.038	.336	.002	.354	.183	.684
Age	.088	.004	<.001	1.092	1.083	1.100
SES quintile 2	-.083	.076	.275	.920	.792	1.069
SES quintile 3	-.194	.082	.018	.824	.702	.967
SES quintile 4	-.114	.080	.154	.892	.763	1.044
SES quintile 5	-.072	.085	.394	.930	.788	1.098
SES quintile unknown	.008	.103	.939	1.008	.824	1.233
Previous AMI	.438	.108	<.001	1.550	1.253	1.916
Heart operation	-.507	.136	<.001	.602	.461	.786
Other heart operation	.002	.124	.990	1.002	.786	1.277
D'Hoore index	.146	.007	<.001	1.157	1.141	1.173
Possibly depressed	.127	.080	.110	1.136	.972	1.328
Depressed	.466	.104	<.001	1.594	1.300	1.954

TABLE 5.7 Cox regression for Cohort 3 using OAMIPR

	B	SE	Sig.	Exp(B)	95.0% CI for Exp(B)	
					Lower	Upper
Female	-.218	.061	<.001	.804	.714	.907
Unknown sex	-1.415	.451	.002	.243	.100	.588
Age	.077	.005	<.001	1.080	1.070	1.090
SES quintile 2	-.133	.086	.119	.875	.740	1.035
SES quintile 3	-.125	.089	.160	.883	.742	1.051
SES quintile 4	-.159	.091	.081	.853	.713	1.020
SES quintile 5	-.019	.095	.842	.981	.815	1.182
SES quintile unknown	-.053	.116	.649	.948	.755	1.191
Previous AMI	.275	.127	.031	1.317	1.026	1.690
Heart operation	-.438	.149	.003	.645	.482	.864
Other heart operation	.081	.134	.545	1.085	.833	1.412
Diabetes	.328	.066	<.001	1.389	1.221	1.579
Heart failure	.662	.063	<.001	1.939	1.714	2.194
Cancer	.299	.075	<.001	1.349	1.164	1.562
Pulmonary edema	.390	.101	<.001	1.477	1.211	1.802
Acute renal failure	.203	.070	.004	1.225	1.068	1.405
Cardiac dysrhythmia	.211	.059	.000	1.235	1.099	1.387
Chronic renal failure	.113	.114	.319	1.120	.896	1.399
Shock	.327	.197	.096	1.387	.943	2.040
Cerebovascular disease	.448	.070	<.001	1.566	1.365	1.796
Possibly depressed	.089	.078	.253	1.093	.938	1.273
Depressed	.410	.094	<.001	1.507	1.252	1.814

TABLE 5.8 Cox regression for Cohort 3 using D'Hoore's adaptation of Charlson Index

	B	SE	Sig.	Exp(B)	95.0% CI for Exp(B)	
					Lower	Upper
Female	-.164	.060	.007	.849	.754	.955
Unknown sex	-1.424	.449	.002	.241	.100	.581
Age	.088	.005	<.001	1.092	1.082	1.102
SES quintile 2	-.157	.086	.067	.855	.723	1.011
SES quintile 3	-.195	.089	.028	.823	.692	.979
SES quintile 4	-.246	.091	.007	.782	.654	.935
SES quintile 5	-.116	.094	.219	.891	.741	1.071
SES quintile unknown	-.067	.116	.564	.935	.745	1.174
Previous AMI	.418	.126	.001	1.519	1.186	1.946
Heart operation	-.532	.148	<.001	.587	.439	.785
Other heart operation	.124	.134	.355	1.132	.871	1.472
D'Hoore index	.127	.007	<.001	1.136	1.120	1.152
Possibly depressed	.139	.077	.071	1.150	.988	1.337
Depressed	.462	.094	<.001	1.587	1.321	1.907

TABLE 5.9 Cox regression for Cohort 4 using OAMIPR

	B	SE	Sig.	Exp(B)	95.0% CI for Exp(B)	
					Lower	Upper
Female	-.165	.070	.018	.848	.739	.972
Unknown sex	-1.106	.451	.014	.331	.137	.802
Age	.080	.006	<.001	1.083	1.072	1.095
SES quintile 2	-.038	.098	.700	.963	.794	1.167
SES quintile 3	-.099	.104	.340	.905	.738	1.110
SES quintile 4	-.081	.106	.448	.922	.749	1.136
SES quintile 5	.096	.108	.371	1.101	.891	1.361
SES quintile unknown	.031	.133	.814	1.032	.795	1.339
Previous AMI	.271	.147	.066	1.311	.982	1.749
Heart operation	-.529	.171	.002	.589	.421	.824
Other heart operation	.178	.153	.245	1.195	.885	1.613
Diabetes	.262	.075	<.001	1.300	1.123	1.505
Heart failure	.655	.073	<.001	1.925	1.668	2.223
Cancer	.280	.080	<.001	1.323	1.132	1.547
Pulmonary edema	.318	.110	.004	1.374	1.107	1.707
Acute renal failure	.155	.074	.037	1.167	1.009	1.350
Cardiac dysrhythmia	.217	.069	.002	1.243	1.086	1.422
Chronic renal failure	.093	.123	.450	1.097	.862	1.396
Shock	.316	.234	.178	1.371	.866	2.172
Cerebovascular disease	.473	.076	<.001	1.605	1.384	1.861
Possibly depresed	-.035	.085	.682	.966	.817	1.141
Depressed	.339	.096	<.001	1.403	1.163	1.693

TABLE 5.10 Cox regression for Cohort 4 using D'Hoore's adaptation of Charlson Index

	B	SE	Sig.	Exp(B)	95.0% CI for Exp(B) Lower	Upper
Female	-.121	.069	.079	.886	.775	1.014
Unknown sex	-1.124	.450	.013	.325	.134	.786
Age	.092	.005	<.001	1.096	1.085	1.108
SES quintile 2	-.031	.098	.752	.970	.800	1.175
SES quintile 3	-.132	.104	.204	.876	.715	1.075
SES quintile 4	-.157	.106	.139	.855	.694	1.052
SES quintile 5	.018	.107	.865	1.019	.825	1.257
SES quintile unknown	.031	.133	.813	1.032	.795	1.339
Previous AMI	.405	.146	.006	1.499	1.125	1.996
Heart operation	-.631	.170	<.001	.532	.382	.742
Other heart operation	.240	.152	.116	1.271	.943	1.713
D'Hoore index	.117	.008	.000	1.124	1.107	1.141
Possibly depressed	.034	.085	.688	1.035	.876	1.221
Depressed	.353	.095	<.001	1.423	1.181	1.715

TABLE 5.11 Cox regression for Cohort 5 using OAMIPR

	B	SE	Sig.	Exp(B)	95.0% CI for Exp(B)	
					Lower	Upper
Female	-.123	.082	.135	.884	.752	1.039
Unknown sex	-1.036	.505	.040	.355	.132	.956
Age	.081	.007	<.001	1.084	1.071	1.099
SES quintile 2	-.101	.115	.380	.904	.721	1.133
SES quintile 3	-.161	.122	.186	.852	.671	1.081
SES quintile 4	-.166	.126	.190	.847	.662	1.085
SES quintile 5	.055	.126	.661	1.057	.826	1.352
SES quintile unknown	-.036	.157	.817	.964	.709	1.312
Previous AMI	.080	.192	.678	1.083	.744	1.577
Heart operation	-.522	.201	.009	.593	.400	.879
Other heart operation	.170	.181	.348	1.186	.831	1.692
Diabetes	.178	.087	.042	1.195	1.007	1.418
Heart failure	.618	.087	<.001	1.856	1.564	2.202
Cancer	.292	.089	.001	1.339	1.124	1.594
Pulmonary edema	.325	.125	.009	1.384	1.083	1.769
Acute renal failure	.110	.084	.191	1.117	.946	1.318
Cardiac dysrhythmia	.219	.082	.008	1.245	1.060	1.462
Chronic renal failure	.298	.131	.023	1.347	1.042	1.740
Shock	.421	.265	.112	1.523	.907	2.559
Cerebovascular disease	.537	.086	. <.00	1.711	1.446	2.023
Possibly depressed	-.052	.097	.590	.949	.785	1.148
Depressed	.328	.105	.002	1.388	1.130	1.707

TABLE 5.12 Cox regression for Cohort 5 using D'Hoore's adaptation of Charlson Index

					95.0% CI for Exp(B)	
	B	SE	Sig.	Exp(B)	Lower	Upper
Female	-.069	.081	.390	.933	.797	1.093
Unknown sex	-1.016	.504	.044	.362	.135	.972
Age	.091	.006	<.001	1.095	1.081	1.109
SES quintile 2	-.061	.115	.596	.941	.751	1.178
SES quintile 3	-.198	.121	.103	.821	.647	1.041
SES quintile 4	-.231	.126	.067	.794	.620	1.017
SES quintile 5	-.007	.125	.954	.993	.777	1.269
SES quintile unknown	-.034	.157	.827	.966	.711	1.314
Previous AMI	.188	.191	.325	1.207	.830	1.754
Heart operation	-.639	.199	.001	.528	.358	.779
Other heart operation	.235	.180	.192	1.265	.889	1.800
D'Hoore index	.112	.008	<.001	1.118	1.100	1.137
Possibly depressed	.024	.096	.801	1.024	.849	1.236
Depressed	.331	.105	.002	1.393	1.133	1.712

TABLE 5.13 Cox regression for Cohort 6 using OAMIPR

	B	SE	Sig.	Exp(B)	95.0% CI for Exp(B)	
					Lower	Upper
Female	-.144	.104	.164	.866	.706	1.061
Unknown sex	-.931	.585	.111	.394	.125	1.240
Age	.080	.008	<.001	1.083	1.065	1.101
SES quintile 2	-.147	.145	.309	.863	.649	1.147
SES quintile 3	-.181	.150	.228	.834	.621	1.120
SES quintile 4	-.197	.160	.216	.821	.600	1.123
SES quintile 5	.084	.156	.589	1.088	.801	1.478
SES quintile unknown	-.256	.212	.227	.774	.510	1.173
Previous AMI	.241	.226	.288	1.272	.816	1.982
Heart operation	-.386	.244	.113	.680	.422	1.096
Other heart operation	.163	.227	.473	1.177	.755	1.834
Diabetes	.005	.111	.962	1.005	.809	1.250
Heart failure	.684	.113	<.001	1.981	1.587	2.473
Cancer	.240	.108	.026	1.271	1.029	1.571
Pulmonary edema	.413	.146	.005	1.511	1.135	2.012
Acute renal failure	.122	.102	.232	1.130	.925	1.381
Cardiac dysrhythmia	.227	.105	.030	1.255	1.022	1.541
Chronic renal failure	.408	.152	.007	1.504	1.117	2.025
Shock	.271	.361	.453	1.311	.646	2.661
Cerebovascular disease	.533	.105	<.001	1.704	1.386	2.095
Possibly depressed	.050	.119	.675	1.051	.832	1.328
Depressed	.492	.123	<.001	1.635	1.284	2.081

TABLE 5.14 Cox regression for Cohort 6 using D'Hoore's adaptation of Charlson Index

	B	SE	Sig.	Exp(B)	95.0% CI for Exp(B)	
					Lower	Upper
Female	-.070	.102	.491	.932	.764	1.138
Unknown sex	-.848	.583	.146	.428	.137	1.343
Age	.089	.008	<.001	1.093	1.075	1.110
SES quintile 2	-.054	.145	.710	.948	.713	1.259
SES quintile 3	-.153	.150	.307	.858	.640	1.151
SES quintile 4	-.225	.159	.157	.798	.584	1.091
SES quintile 5	.052	.156	.738	1.053	.777	1.429
SES quintile unknown	-.216	.212	.308	.806	.532	1.221
Previous AMI	.287	.226	.203	1.333	.857	2.074
Heart operation	-.513	.241	.033	.598	.373	.959
Other heart operation	.238	.224	.289	1.268	.818	1.967
D'Hoore index	.112	.010	<.001	1.119	1.097	1.141
Possibly depressed	.105	.118	.374	1.111	.881	1.400
Depressed	.485	.123	<.001	1.624	1.276	2.067

TABLE 5.15 Cox regression for Cohort 7 using OAMIPR

	B	SE	Sig.	Exp(B)	95.0% CI for Exp(B) Lower	Upper
Female	-0.161	.111	.144	.8516	.685	1.0571
Unknown sex	-.949	.585	.105	.387	.123	1.219
Age	.078	.009	<.001	1.081	1.065	1.100
SES quintile 2	-.176	.154	.252	.838	.620	1.133
SES quintile 3	-.124	.157	.432	.884	.649	1.203
SES quintile 4	-.235	.173	.173	.7901	.563	1.109
SES quintile 5	.172	.166	.299	1.188	.858	1.644
SES quintile unknown	-.175	.215	.414	.839	.551	1.278
Previous AMI	.024	.266	.929	1.024	.608	1.725
Heart operation	-.443	.263	.092	.642	.383	1.076
Other heart operation	.155	.242	.520	1.168	.727	1.876
Diabetes	.009-	.118	.942	.991	.787	1.249
Heart failure	.684	.120	<.001	1.978	1.563	2.502
Cancer	.179	.115	.121	1.196	.954	1.500
Pulmonary edema	.336	.162	.038	1.400	1.019	1.922
Acute renal failure	.084	.109	.441	1.088	.878	1.347
Cardiac dysrhythmia	.248	.110	.024	1.282	1.033	1.590
Chronic renal failure	.440	.157	.005	1.553	1.141	2.113
Shock	.429	.388	.269	1.536	.718	3.287
Cerebovascular disease	.590	.111	<.001	1.805	1.452	2.243
Possibly depressed	.099	.126	.432	1.104	.862	1.415
Depressed	.587	.136	<.001	1.798	1.376	2.348

TABLE 5.16 Cox regression for Cohort 7 using D'Hoore's adaptation of Charlson Index

	B	SE	Sig.	Exp(B)	95.0% CI for Exp(B)	
					Lower	Upper
Female	-.066	.108	.371	.936	.7584	1.157
Unknown sex	-.853	.584	.144	.426	.136	1.337
Age	.086	.009	<.001	1.089	1.071	1.108
SES quintile 2	-.098	.154	.522	.906	.671	1.225
SES quintile 3	-.131	.157	.402	.877	.645	1.192
SES quintile 4	-.291	.172	090.	.748	.534	1.047
SES quintile 5	.085	.164	.606	1.088	.789	1.502
SES quintile unknown	-.151	.214	.482	.860	.565	1.309
Previous AMI	.072	.265	.786	1.075	.639	1.806
Heart operation	-.575	.261	.028	.563	.337	.939
Other heart operation	.225	.239	.348	1.252	.783	2.001
D'Hoore index	.107	.010	<.001	1.113	1.090	1.136
Possibly depressed	.150	.125	.229	1.162	.910	1.485
Depressed	.542	.137	<.001	1.719	1.314	2.249

5.3.2 Outcome: readmissions

Tables 5.17-5.19 show the distribution of the number of readmissions (general, circulatory and emergency). In the univariate analysis it was found that the number of readmissions and the number of circulatory readmissions were associated with depression, however interestingly the number of emergency admissions was not (see Table 5.20). Multivariate analysis was used to investigate whether these differences were due to confounding factors. In the logistic regression analysis, depression was not found to be a significant predictor of readmissions after controlling for confounders.

TABLE 5.17 Number of readmissions to hospital for circulatory system as primary diagnosis during the second, third and fourth years post AMI

		Frequency	*Percent*	*Cumulative Percent*
Number of admissions	0	1861	65.6	65.6
	1	509	18.0	83.6
	2	229	8.1	91.7
	3	113	4.0	95.7
	4	57	2.0	97.7
	5	31	1.1	98.8
	6	18	.6	99.4
	7	6	.2	99.6
	8	5	.2	99.8
	9	3	.1	99.9
	10	2	.1	100.0
	11	1	.0	100.0
	Total	2835	100.0	

TABLE 5.18 Number of readmissions to hospital excluding readmissions for depression as primary diagnosis during the second, third and fourth years post AMI

		Frequency	*Percent*	*Cumulative Percent*
Number of admissions	0	970	34.2	34.2
	1	632	22.3	56.5
	2	413	14.6	71.1
	3	281	9.9	81.0
	4	184	6.5	87.5
	5	130	4.6	92.1
	6	84	3.0	95.0
	7	50	1.8	96.8
	8	38	1.3	98.1
	9	22	.8	98.9
	10	8	.3	99.2
	11	9	.3	99.5
	12	6	.2	99.7
	13	4	.1	99.9
	14	1	.0	99.9
	17	2	.1	100.0
	33	1	.0	100.0
	Total	2835	100.0	

TABLE 5.19 Number of emergency readmissions in the second, third and fourth years post AMI

		Frequency	*Percent*	*Cumulative Percent*
Number of admissions	0	2145	75.7	75.7
	1	448	15.8	91.5
	2	142	5.0	96.5
	3	55	1.9	98.4
	4	22	.8	99.2
	5	10	.4	99.5
	6	6	.2	99.8
	7	3	.1	99.9
	8	1	.0	99.9
	9	1	.0	99.9
	10	1	.0	100.0
	11	1	.0	100.0
	Total	2835	100.0	

TABLE 5.20 Kruskal Wallis test results for the association between depression and readmissions

	Emergency readmissions	Readmissions for circulatory system as primary diagnosis	General readmissions (excluding those for depression as primary diagnosis)
Chi Square	4.223	8.171	11.723
df	2	2	2
p value	0.121	0.017	0.003

5.4 Discussion

There are several new findings in this study. We found that early onset incident depression (occurring within six months post-AMI) was a strong predictor of short- and long-term survival post AMI. The impact of early onset incident depression following AMI on long-term survival has rarely been studied because the follow up period in other studies has been short and most researchers did not distinguish between prevalent and incident depression following AMI. We also found that late-onset depression (depression occurring after the first six months post-AMI and up to five years post-AMI) had an impact on long-term survival. The impact of late-onset depression, up to five years post-AMI, has not been studied previously, making this a new and important finding.

This study, however, did not find that depression had an impact on hospital use. While there was an association between depression and health services use in univariate analysis as found in previous studies, after controlling for confounders, this association diminished. This shows that although depression is associated with higher health services use, this is likely due to factors such as the increased comorbidity associated with depression. By itself, depression did not increase hospitalization over and above that associated with comorbidity. It is possible that if a continuous outcome was used (i.e. the

total number of visits) instead of a binary variable (i.e. had an admission or did not), depression would have been found as a significant predictor.

Sex was not significantly associated with mortality in univariate analysis, however in the Cox regression analysis it was found to be significant in some cohorts, women being at lower risk. This corresponds with the literature on sex differences in survival after AMI. Goldberg et al. (23) found that women have worse in-hospital mortality than men even after adjusting for age. However after multivariate adjustment controlling for prior angina, diabetes and hypertension which were more common in women, there were no sex differences in in-hospital mortality. When investigating long-term survival, the crude risk for women was worse, however after age adjustment there were no sex differences. When controlling for other factors that were significantly different between men and women, men had worse long term survival. Vaccarino et al. (24) investigated the interaction between age and sex on survival two year after myocardial infarction. They found that the overall two years mortality rate was higher in women compared to men. However, when the participants were examined by age group, only women younger than 60 years of age had a higher mortality rate than men of similar age. The sex difference decreased with increasing age, and among the oldest patients, women actually had a lower mortality rate than men. They found that this was not affected by adjustment for demographic characteristics and medical history, clinical characteristics, and hospital and discharge treatments. Vaccarino et al. (25) summarized the literature on sex differences in mortality after myocardial infarction from January 1966 through June1994 and included studies that compared mortality after AMI between men and women controlling at least for age, and studies which had more than 30 outcome

events. They found that the crude rates were higher in women than in men for in-hospital and first month post-AMI mortality, however controlling for age alone or in combination with other factors the differences were reduced in almost all studies. They also found that unadjusted mortality rates among the survivors of the early phase were similar for both sexes in most studies, and control for age and other factors resulted in increased survival rates in women compared with men in several studies, particularly those with a follow up of more than 1 year. They concluded that the increased early mortality after AMI in women is explained by their older age and more unfavourable risk factors. In the long run, when the differences in age and other risk factors are controlled, women tend to have better survival than men.

This illustrates the importance of conducting long-term multivariate analyses when investigating sex differences in survival post-AMI. In the present study, women were found to be at lower risk, after controlling for factors such as depression, which are more common in women. If only a univariate analyses were conducted, women would have had the same risk as men.

An advantage of this study is that we controlled for a larger spectrum of comorbid diseases, including acute variables such as shock, and prior AMI, rather than simply AMI severity variables controlled in previous studies. This may be a more appropriate method to control for overall severity of illness when investigating long-term mortality. (26)

Another advantage of this study was that it used a population-based framework. No sampling was utilized and thus it is easier to generalize the results to the older adult population. However, it would be interesting to determine whether similar results would be found in younger individuals.

In summary, this study presents new information on the impact of early- and late-onset incident depression on short- and long-term survival of AMI patients. The implications and limitations of these results are discussed in the next chapter.

5.5 Bibliography

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6 Chapter VI: Discussion

6.1 Review of findings

There were several important findings in this dissertation. The results of Chapter 3 show that a risk adjustment method developed using data from an AMI patient population (1) for prediction of mortality post-AMI is the preferred method of risk adjustment compared to more general methods such as the Charlson Index. (2) This finding supports previous research (1) however this dissertation expanded on this known evidence by showing that the use of comorbidities that occur during the months and years after the index hospitalization for AMI improved prediction, compared to using only comorbidities that are recorded at the time of hospitalization for the index AMI. In addition, the outcomes used in this dissertation for comparison of the different methods for risk-adjustment included not only short term mortality (up to 1 year) as used in previous studies (1), but also mortality up to 5 years post AMI.

The results in Chapter 4 show that depression is associated with increased comorbidity. This is a relationship that is not usually investigated and a factor that is not usually controlled for when investigating the impact of depression following AMI on survival. As discussed in Chapter 4, this association should be interpreted with caution, because it may be that the association is biased in these data by the fact that the existence of depression may increase the likelihood of the detection of comorbidity, or that the existence of comorbidities may increase the likelihood of the detection of depression. Controlling for comorbidity in multivariate analyses is thus important in order to

delineate the independent effect of depression on survival post-AMI. This was done in Chapter 5.

The findings of Chapter 5 show that depression occurring after AMI has a strong impact on survival, regardless of whether depression occurred shortly after the index AMI or months and years after AMI. Depression was an independent predictor of mortality after controlling for confounders, including comorbidity. Moreover, the group that was categorized as 'possibly depressed' was not found to be different than the 'not-depressed' group. It is likely that these individuals did not have major depression.

6.2 Discussion of methods

This study investigated the impact of depression following AMI on survival using administrative data. Use of administrative data enabled easy access to long term follow up data and it captured the entire population of British Columbia, which makes the results of this study highly generalizable. However, one main challenge when using such data is the ability to control for clinical variable confounding. Because administrative data are not collected for the purpose of research, they frequently do not include the clinical variables that are potential confounders in certain research questions. In this dissertation, this challenge was dealt with in Chapter 3, which compared different methods of adjusting for comorbidity. The risk-adjustment methods found to be superior were used in the multivariate analysis to find the independent effect of depression on survival.

One limitation of the study is that the data available only captured deaths that occurred in BC, or deaths that occurred in a hospital anywhere else in Canada. However, some of the individuals in this study might have died outside of BC, and not in a Canadian hospital and thus they were coded as 'alive' at the end of the follow up.

However, based on the observation that only 32 individuals died in a hospital outside of BC, it is unlikely that a larger number of individuals died outside of Canada or outside of BC and not in a hospital in Canada. Another limitation of the study is that some individuals may have been categorized as not depressed due to undetection of the depression by the physicians. Such misclassification would have led to the results in Chapter 5 being closer to the null hypothesis, and thus the significant results found in this study are likely to be valid and conservative (i.e., the real relationship is probably stronger). For further details on the problem of detection of depression and limitations of the definition of depression, as used in this study, see the discussion in Chapter 4.

There are many theories regarding the way in which depression affects mortality, as discussed in Chapter 1. In Chapter 4 it was shown that depression is associated with increased comorbidity, however it is impossible to determine the temporal relationship between the two variables because they were measured at the same time. Yet, it is known that all individuals who were categorized as depressed had incident depression which occurred after the index AMI and was not present in the year prior to the index AMI.

There is a possibility that the comorbidities were not sufficiently controlled using the methods in this study. A conclusion that an exposure or characteristic has an independent effect on a health outcome has to be based on complete control for confounding. Inaccuracy in the measurement of potentially confounding factors could lead to the underestimation of their impact. Depression can appear to be related to mortality after adjustment for confounding, however, this relationship may exist because of under-adjustment for confounding factors (e.g. severity of AMI as measured by Killip class). In order to deal with this problem, comorbidity was controlled by two different methods.

Depression was found to be consistently significant. Also, the methods used in this study did not control for Killip class type variables as in other studies, but controlled for a larger spectrum of comorbid diseases that may influence mortality, and which may be a more appropriate method to control for overall severity of illness.

Propensity scores have been used increasingly in health research as an alternative for controlling for confounding using regression analysis. Propensity scores represent an attempt to reconstruct, after the fact, a situation similar to random assignment with respect to observed prognostic variables. Propensity scores were not used in this study for two reasons. While the use of propensity scores has advantages over regression analysis when the outcome is rare, the treatment is common, and there are many prognostic variables (3), in this study the outcome (all-cause mortality) was not rare, 'treatment' (i.e. depression) was not extremely common and there were not many prognostic variables to control for. In addition, Capeda et al. (4) showed that when comparing propensity scores and regression analyses, regression is the technique of choice when there are at least 8 events per confounder, as was the case in this research.

One concern with the use of administrative data is accuracy. Coding of AMI in administrative databases has been found to be accurate when compared to a clinical registry. (5) Also, in an audit of hospitals in Ontario with a large number of patients hospitalized for AMI, it was found that of the 70% of hospitals that completed the audit, most had very high self-audit accuracy rates of 94% or higher for their AMI coding. (6) In addition, more evidence of the accuracy of the data used in this study comes from a study that compared hospitalization data from British Columbia to data from patients' charts. (7) The population included individuals who underwent percutaneous coronary

interventions in British Columbia. The comorbidities that were tested included diabetes mellitus, hypertension, hyperlipidemia, previous myocardial infarction, congestive heart failure, cerebovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, and chronic renal failure. The kappa statistic was highest for diabetes, and with good agreement for AMI and chronic renal failure. The lowest level of agreement was found for hyperlipidemia. The levels of agreement were moderate (kappa between 0.52-0.62) for the remaining conditions. This study also conducted multivariate analyses in order to compare adjusted risk ratios between the two methods. There was close agreement between the models yielding almost identical adjusted risk ratios for all-cause mortality as an outcome. These findings give confidence that the data regarding AMI and comorbidities measured in this study have satisfactory to excellent accuracy. In addition, when using the data from MSP, only 3 digits ICD-9 codes were used, as they have been shown to be more accurate than 4 or 5 digit codes. (8)

One major methodological challenge in this dissertation was defining depression. The definition of depression was developed based on logic, in consultation with a psychiatrist prominent in the field of depression and the definition of depression in administrative datasets (Dr. Elliot Goldner, a committee member). As discussed in Chapter 4, the definition used in this study is likely to have been a very specific rather than sensitive definition. This definition likely included most of the individuals who had recognized persistent depression, thus they were probably the more severe cases of depression. However, it is important to consider that this definition of depression may have captured some individuals who have anxiety rather than depression because antidepressants may

be used to treat anxiety and the MSP 50B code includes anxiety. It is important that this definition be validated using an external database or another criterion.

The data used in this study did not include information on methods of treatment of depression other than pharmacological methods (such as cognitive-behavioural therapy). The group categorized as depressed in this study, included those whose depression was recognized, but not necessarily treated. Between 25% (in Cohort 1) and 33% (in Cohort 6) of the individuals categorized as depressed did not receive more than 1 prescription of antidepressants. Thus, the group of individuals categorized as depressed is a mixed group of those who were treated with antidepressants, and those that were not (but may have been treated by methods other than pharmacotherapy such as cognitive-behavioural therapy, methods not captured by these data). However, in the Kaplan Meier analysis in Chapter 5 no differences were found in survival when comparing the different subgroups within the depressed group. Thus, although they may be a somewhat heterogeneous group with regard to their treatment, they were not different with regard to survival. Also, if treatment of depression reduces the risk of mortality (discussed in greater detail below) increased by depression, because the group of depressed individuals is a mixed group of treated and untreated patients, the effect of depression on survival found in this study may be an underestimate of the effect of depression per se.

This study did not include cardiac mortality as an outcome. Such data may have been useful in order to compare whether depression is associated not only with all-cause mortality but also cardiac mortality. Evidence regarding the link between depression and cardiac versus non-cardiac mortality could shed light on the mechanisms through which depression is associated with worse survival. For example if depression would have been

shown to be linked with cardiac but not non-cardiac mortality, one could hypothesize that the association between depression and worse survival is likely explained through specific mechanisms which are related to the cardiovascular dysfunction.

Finally, investigating the impact of depression following AMI on survival using administrative data does not enable to control for variables such as smoking or AMI severity. However, as the benefits of using administrative data over clinical data (larger sample size, longer follow up, population based) outweigh the disadvantages, especially as this study controlled for important comorbidities which could be viewed as proxy variables for severity of AMI (such as shock and heart failure). Moreover, this study focused on long term mortality rather than short term mortality which is more likely associated with comorbidity.

6.3 Significance and implications

Several issues should be noted regarding the significance of this research. First, because this study utilized an administrative dataset that is population-based, the data were collected for all patients who had an AMI who were 66 years and over at the time of the AMI. Thus, the external validity of this study is very high and it is easier to generalize results from this study to other populations compared to findings from studies using only a sample. In addition, using administrative data enabled long-term follow up of the individual, up to 8 years post AMI and also permitted the measurement of depression up to 5 years post AMI, as opposed to only at the time of admission for the index AMI. Unlike previous studies, depression measured in this study was specified to be incident depression which occurred post AMI and not prevalent depression present prior to the AMI.

The main clinical implications of the findings are that physicians treating cardiac patients should be aware of the importance of depression on the survival of the individuals who suffered from an AMI. As found in this study, it is important for clinicians to remember that depression may occur months and years after AMI and has an effect on mortality.

Methodologically, the use of administrative data in this dissertation contributes to the field of epidemiology and health services research. The utilization of administrative data to investigate depression following AMI and the association with survival is an innovating approach not done previously. This will set the stage for other health services, cardiovascular and mental health researchers to investigate such questions using administrative data. The results from the comparison of the various risk-adjustment methods will be useful to researchers interested in the field of post-AMI outcomes. Also, the findings from this study showed that it is important for researchers to control for comorbidity using risk-adjustment methods when investigating the impact of depression following AMI on survival.

6.4 Future research and policy implications

This study showed an association between depression post-AMI and increased all-cause mortality. There are several hypotheses about the mechanisms through which depression affects survival as discussed in Chapter 1. Understanding the pathways in which depression impacts survival will assist clinicians to reduce the risk associated with depression. Linking clinical data with administrative data may provide an efficient and informative method of investigating these pathways.

An important field of methodological research would be further investigation of the definition of depression using administrative data. It is important to investigate how well the definition used in this study, or any definition based on administrative data, captures the construct of depression. This is extremely challenging because defining depression using such data depends on physician recognition or treatment of depression and documentation of these in the data. The challenges of the recognition of depression, specifically in individuals who have cardiovascular disease, are discussed in detail in Chapter 4. Furthermore, as discussed previously, it is may be challenging to distinguish between depression and anxiety using administrative data.

The results of Chapter 5 show that depressed individuals have poorer survival. Because the definition of depression was based on physician recognition or treatment for depression, it is likely that those categorized as 'depressed' in this study were those with the most severe levels of depression. However, it is important to note that these were also the individuals who were most likely treated for depression, unlike individuals with less severe depression who were also less likely to be recognized by a physician. This is supported by the literature (9-11) which shows that patients with unrecognized depression were found to be less severely ill and more functional. This raises two important questions: First, does recognition of depression in the general population (i.e. not specifically individuals who have had an AMI) affect outcomes for these individual? Second, what is appropriate treatment of depression following AMI and does it reduce adverse outcomes associated with depression following AMI?

With regard to the recognition of depression in primary care and the improvement of outcomes, there is conflicting evidence. Ormel et al. (12) found that recognition of

depression was associated with improved outcomes, but Schulberg et al. (13) found no such association. One study (11) found that patients whose depression was recognized did not have better outcomes than those who were unrecongnized. Both the recognized and nonrecognized patients had improved substantially and in a similar degree. This held for both psychopathology and occupational disability. Similar proportions of patients also recovered in each group. Increasing recognition is likely to improve outcomes only if general practitioners have the skills and resources to deliver adequate interventions. Recognition by itself may not necessarily lead to appropriate treatment, and thus may not necessarily improve outcomes.

With regard to the treatment of depression following AMI and its effect on survival, it would be logical to assume that if depression is linked to an increased risk of mortality, then treatment of depression in heart patients may reduce this risk. (14) However, whether any treatment for depression will succeed in increasing cardiac event-free survival depends on whether it is safe and effective and if it either results in beneficial changes in the mechanisms through which depression affects prognosis after AMI or incidentally alters other risk factors. (15)

In contrast to the logical assumption that treatment of depression following AMI would improve survival of depressed individuals, there is conflicting evidence in the literature. A meta-analysis conducted by Linden et al. (16) was designed to quantify whether additional psychosocial treatments can increase effectiveness over "standard" cardiac rehabilitation. They found that individuals in the control conditions changed very little (compared with pretest data) on psychological distress, heart rate, cholesterol levels, and systolic blood pressure, and some got worse. On the other hand, individuals in the

psychosocial intervention group showed a significant difference in these endpoints. They also found that overall psychosocial treatment had a major beneficial effect on reducing nonfatal cardiac events, with an odds ratio showing a 46% reduction in recurrence when the outcome was within 2 years of follow-up and a 39% reduction for follow-up above 2 years. They also found a beneficial effect for the psychosocial intervention group on mortality with a significant OR of 1.70 when the outcome was assessed within 2 years of follow up. However, no significant benefit was found when follow up was longer than 2 years, although a trend toward better outcome was still evident. It is important to note that only three studies provide information on follow up longer than 2 years, which may have limited the generalizability of the results and weakened the power of the analysis. The authors concluded that psychosocial interventions should be routinely included in cardiac rehabilitation programs in addition to drug therapy and exercise regimens. The findings were significant regardless of the nature of the psychosocial interventions, which varied in length, target behaviour, and the type of person delivering them.

Unfortunately, since this meta-analysis was published two large trials have failed to show a significant effect of psychosocial treatment on survival. (17, 18) Jones and West (17) evaluated a rehabilitation program for post-AMI individuals (n=2328). They conducted a randomised controlled trial with a 1 year of follow up. The program included psychological therapy, counselling, relaxation training, and stress management training over seven weekly group outpatient sessions for patients and their spouses. They found that at six months there were no significant differences between the intervention and control groups in reported anxiety (prevalence 33%) or depression (19%). The intervention group reported a lower frequency of angina (median three versus four

episodes a week), medication, and physical activity. However, at 1 year follow up there were no differences in clinical complications, clinical sequelae, or mortality. The authors concluded that such a program has little benefit to patients. Shortly after this study was published, Frasure-Smith et al. (18) also failed to show a significant effect of psychosocial intervention on psychological outcomes and prognosis (n=1376). They investigated the impact of a 1-year program of monthly monitoring of psychological distress symptoms, combined with home-nursing visits in response to high levels of distress on individuals who had an AMI. They found the unexpected result that cardiac and all cause mortality over 1 year were significantly greater among women who were in the treatment group than in the control group. There was no impact on men. The program had no significant impact on the symptoms of depression and anxiety, however this assessment was based only on surviving patients who completed a 1 year follow up questionnaire. The authors suggested that perhaps the program actually increased distress in women. This is a disturbing finding, which emphasizes the importance of evaluating interventions for depression in post-AMI patients, because an intervention that may seem intuitively to be an effective treatment may have adverse effects. This study also showed that when attempting to reduce the effects of distress and depression on post-AMI survival, it is important to stratify any treatment by sex, because various different treatments may work differently in males and females.

It is interesting to note that both the interventions described in these trials (17, 18) were not specifically offered to depressed individuals. In the trial by Frasure-Smith et al. (18) the Beck Depression Inventory (BDI) (19) was used to measure depression. The mean BDI scores were 8.3 and 8.7 for the intervention and control groups respectively.

When stratified by sex, the mean scores for men were 7.4 and 7.2 for the intervention and control groups, respectively and 10.1 and 11.5 for the women in the intervention and control groups respectively. Scores under 10 are considered normal 'ups and downs' whereas scores of 10-18 are considered to be indicative of mild to moderate depression. (19) Only 32.6% and 33.5% of the intervention and control group respectively had BDI scores above 10. Jones and West (17) used a questionnaire developed by Bedford et al. (20). Only 19% of the intervention group and 19% of the control group had depression scores that were clinically significant. It may be that if these interventions were geared towards only individuals with severe depression, as opposed to the general population of individuals who had an AMI, they would have been found to be beneficial, and not harmful. It may also be that the failure to influence survival in both of these studies may be a result of the lack of impact on psychological factors. This suggestion was supported by a meta-analysis published in 1999, which included both of the trials described above (21) and found no effect of cardiac rehabilitation programs on depression and anxiety.

Dusserldorp (21) reviewed studies evaluating the impact of stress management and health education programs for CHD patients on mortality, recurrent AMI, coronary artery bypass graft (CABG) intervention, incidence of angina pectoris, hypercholesterolemia, weight loss, smoking, blood pressure, physical exercise, eating habits, and anxiety and depression. They found a 34% reduction in cardiac mortality and 29% reduction in recurrent AMI with follow up of 2-10 years. Also significant positive effects were found on blood pressure, cholesterol, eating habits, smoking, physical exercise, and body weight. No effects on CABG, depression or anxiety were found. Follow up for these endpoints were between 6 weeks and 2 years. An important finding of this study was a

reduction of 36% in the recurrence of AMI in the intervention studies with success on proximal targets (blood pressure, smoking, cholesterol, eating habits, body weight, physical exercise) versus 2% in studies without success or with only partial success on proximal targets. The reduction in cardiac mortality in studies with success or partial success was 31% versus an increase of 14% for studies with no success.

A secondary analysis of the data from the trial by Frasure-Smith et al. (22) was conducted to examine the relationships between short-term individual changes in psychological distress, mid-term improvement in psychological distress and 1 year outcomes (including depression anxiety, mortality, hospital admission) within the treatment group. The researchers found that individuals who had a decreased to normal scores on the General Health Questionnaire (GHQ) or reduction of the GHQ score by 50% or more in the first two nursing visits, were also more likely to show mid-term reduction and were less likely to die of cardiac causes, as well as less likely to be readmitted for any reason and less likely to have high depression and anxiety at 1 year than patients who did not have a reduction in the GHQ score. However differences in all-cause mortality were not significant. Because success in reducing GHQ score was associated with having close friends, have PTCA or bypass surgery, lower BDI scores and other confounding factors, a multivariate analysis controlling for these factors was conducted. This did not alter the results. In summary, the study found that short-term improvement in psychological distress resulted in better long-term prognosis compared no improvement of psychological distress. Thus, the failure to show improvement in cardiac prognosis in the trial by Frasure-Smith et al. (18) could be a result of failure to reduce distress in most of the individuals in the treatment group. This is supported by the

findings of Dusseldrop et al. (21) described above, which suggest that programs successful in altering mortality outcomes are those that reduce behavioural or psychological risk factors. However, as the design of this secondary analysis by Cossette et al. (22) is not a randomized trial, it is difficult to say with certainty that the intervention affected survival in those individuals who had an improvement in depression. The results simply suggest that the intervention affected survival in a segment of the treatment group, which may have improved their GHQ scores regardless of the intervention. Thus the only conclusion that can be drawn from this analysis is that improvement in GHQ scores is associated with outcomes such as mortality and readmissions. One cannot conclude that the intervention program per se is what led to the change in the GHQ scores and thus the outcomes.

As opposed to the two trials described above (17, 18) which included all individuals post-AMI (i.e. they were not limited to those with depression), Berkman et al. (23) conducted a randomized controlled trial with AMI patients who had depression or low perceived social support (n=2481). The patients were randomized into either an intervention group that included cognitive behavioural therapy or a usual care group. Intervention group patients with high scores of depression or those who showed less than 50% reduction in their scores after 5 weeks were referred to study psychiatrists for consideration of pharmacotherapy. The maximum duration of the behavioural intervention was 6 months. Group therapy could extend an additional 12 weeks and adjunctive pharmacotherapy for up to 12 months, at which time the patient was reevaluated by a psychiatrist. The primary endpoints were recurrent AMI or death. Secondary outcomes included change in depression and perceived low social support

scores. The authors found that the treatment group had improved psychosocial outcomes, however after an average follow up of 29 months, there was no difference in event free survival between the intervention and usual care groups. One interpretation of the findings (24) is that eligible participants, including those in the usual care group, were probably more aware of their depression and this may have affected the treatment of participants in the usual care group. Also, individuals with both minor and major depression were included in the study, and because minor depression may not have the same impact as major depression on survival, this may have contributed to the null findings. (24)

With regard to pharmacological therapy and the impact of it on survival, limited work has been devoted to evaluating effective antidepressant treatments for this subpopulation. Some effects on cardiovascular outcomes have been reported in studies that addressed the antidepressive effect of treatment of depression in patients with ischemic heart disease. (25, 26) However, limitations of these studies include very brief follow up periods (no more than 8 weeks) and, no comparison with untreated patients for obvious ethical reasons. (25)

In a randomized controlled trial of the effect of treating depressed patients with antidepressants on cardiovascular outcomes, sertraline was not found to reduce the risk of severe cardiovascular events (N=369). (27) Swenson et al. (28) found that the use of sertraline for individuals with major depression who had either an AMI or unstable angina resulted in clinically meaningful improvements in multiple quality of life domains (N=369). Both of these studies had relatively short follow up (only 24 weeks) and were funded by a pharmaceutical company.

A larger randomized, controlled trial that examines the effects of treatment of depression with antidepressants on cardiovascular outcomes is ongoing. In this study Van der Brik et al. (29) are investigating whether antidepressive treatment can improve cardiac prognosis for individuals with depression after AMI. They are randomizing patients into antidepressive treatment or usual care groups. First choice treatment consists of placebo-controlled treatment with mirtazapine. In case of refusal or nonresponse, alternative open treatment with citalopram is offered. The endpoints are cardiac death or hospital admission for AMI, unstable angina, heart failure or ventricular tachyarrhythmia, during an average follow up of 27 months to date.

In summary, the evidence regarding the impact of treatment of depression that occurs following AMI on survival is scarce and conflicting. As suggested by Jackson et al. (30) the effects of treating depression might require longer follow-up to show any benefits. Mood per se may respond faster to treatment than the indirect, negative consequences of depression on other outcomes such as survival. Second, some treatments for depression may have more benefit than others, and the optimal treatment regimen is yet to be known. Because some clinical trials have not shown that depression treatment improves survival, a third, yet unknown, factor may cause both the depression and the comorbid disease outcomes. Treating depression may ameliorate some of the negative consequences of depression but may have no effect on this unknown third factor.

Because the link between depression and survival is well established, it is time to focus future research on the treatment of depression following AMI and discovering methods to reduce this risk. Such studies should target individuals who have depression following AMI, and not the general AMI population. Also, the follow up should be

longer than the follow up used in the studies to date. Selective assignment or referral for psychological therapy would be more cost-efficient than giving all patients the same amount and type of intervention. (16)

Health care providers should be aware that depression post-AMI is an important concern due to its adverse impact on survival. This issue has not yet become a common quality indicator discussed with regard to cardiac care follow up. This was shown in a recent study investigating the perceived usefulness of and barriers to use of quality indicators in the care of acute myocardial infarction and congestive heart failure in two provinces in Canada. (31) In this study, physicians involved with cardiac care discussed and identified various quality indicators such as one year mortality, readmission rate, access to cardiac rehabilitation and one year adherence with warfarin after discharge. However there is no discussion of psychological factors, specifically depression which as shown in this dissertation, is an important variable to consider when discussing both short and long term follow-up cardiac care. This may be due to the lack of a clear approach to the management of depression in the post-AMI context, and the lack of evidence that management of depression reduces mortality. However, consideration should be given to, and future research should focus on the impact of depression on post-ami survival demonstrated in this dissertation. For example closer follow-up of individuals who have depression post-AMI is likley beneficial for reducing the risk of mortality

As seen in the analysis of prescription patterns in Chapter 4 there is an increase in the prescription of the category of drugs which includes Bupropion, Mirtazapine, Nefazodone, Nomifensine, Tryptophan, Trazodone and Venlafaxine. Because there is little evidence of the cardiovascular effects of most of these antidepressants, (14) this is

an area which also requires more research. Healthcare providers should be aware that the evidence regarding the safety of these drugs in this population is scarce and that the prescription of such medications should be done with caution until they are proven to be safe.

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Appendix A – Ethics Certificate

Appendix B

Hosmer Lemeshow Chi square values df=8
(Chi square values which are significant are highlighted)

Cohort	*Model*	*Outcome: Died by 1 year (p value)*	*Outcome: Died by 2 years (p value)*	*Outcome: Died by 3 years (p value)*	*Outcome: Died by 4 years (p value)*	*Outcome: Died by 5 years(p value)*
1	1	4.792	4.223	5.412	11.275	13.814
		(0.780)	(0.837)	(0.713)	(0.187)	(0.087)
	2	2.154	3.603	4.277	11.300	13.315
		(0.976)	(0.891)	(0.831)	(0.185)	(0.101)
	3	10.280	7.607	9.535	6.252	6.191
		(0.246)	(0.473)	(0.299)	(0.619)	(0.626)
	4	*16.969*	12.646	11.420	10.133	11.757
		(0.030)	(0.125)	(0.179)	(0.256)	(0.162)
	5	8.088	5.929	10.554	*16.788*	*20.186*
		(0.425)	(0.655)	(0.228)	*(0.033)*	*(0.010)*
	6	10.917	5.279	13.881	2.317	3.957
		(0.206)	(0.727)	(0.085)	(0.970)	(0.861)
	7	4.931	8.420	14.761	14.210	8.514
		(0.765)	(0.394)	(0.064)	(0.076)	(0.385)
	8	2.272	10.890	5.504	9.780	14.256
		(0.972)	(0.208)	(0.703)	(0.281)	(0.075)
	9	7.846	6.556	3.184	8.242	16.866
		(0.449)	(0.585)	(0.922)	(0.410)	(0.032)
2	1		11.420	7.140	10.792	13.359
			(0.179)	(0.522)	(0.214)	(0.100)
	2		7.983	5.663	12.227	14.422
			(0.435)	(0.685)	(0.141)	(0.071)
	3		10.918	3.559	3.641	9.095
			(0.206)	(0.895)	(0.888)	(0.334)
	4		5.675	6.736	5.741	*17.936*
			(0.684)	(0.565)	(0.676)	*(0.022)*
	5		1.439	8.653	7.610	19.237
			(0.994)	(0.372)	(0.472)	(0.014)
	6		9.513	13.580	9.999	9.408
			(0.301)	(0.093)	(0.265)	(0.309)
	7		4.104	6.995	12.359	6.286
			(0.848)	(0.537)	(0.136)	(0.615)
	8		4.523	5.646	10.666	10.910
			(0.807)	(0.687)	(0.221)	(0.207)
	9		*18.109*	2.593	5.086	13.510
			(0.020)	(0.957)	(0.748)	(0.095)

Cohort	*Model*	*Outcome: Died by 1 year (95% CI)*	*Outcome: Died by 2 years*	*Outcome: Died by 3 years*	*Outcome: Died by 4 years*	*Outcome: Died by 5 years*
3	1			3.802	6.691	13.086
				(0.875)	(0.570)	(0.109)
	2			4.837	5.462	5.803
				(0.775)	(0.707)	(0.669)
	3			10.769	5.358	4.295
				(0.215)	(0.719)	(0.830)
	4			7.597	15.935	14.768
				(0.474)	(0.043)	(0.064)
	5			15.278	11.322	9.258
				(0.540)	(0.184)	(0.321)
	6			8.635	8.964	8.698
				(0.374)	(0.345)	(0.368)
	7			9.904	13.311	9.553
				(0.272)	(0.102)	(0.298)
	8			9.066	7.037	5.518
				(0.337)	(0.533)	(0.701)
	9			7.256	10.787	6.603
				(0.509)	(0.214)	(0.580)
4	1				5.827	10.395
					(0.667)	(0.238)
	2				5.254	3.838
					(0.730)	(0.871)
	3				8.837	15.254
					(0.356)	(0.055)
	4				4.616	10.156
					(0.798)	(0.254)
	5				9.035	10.316
					(0.339)	(0.244)
	6				6.801	7.612
					(0.558)	(0.472)
	7				7.199	17.166
					(0.515)	(0.028)
	8				12.437	8.533
					(0.133)	(0.383)
	9				5.279	1.835
					(0.727)	(0.986)
5	1					12.967
						(0.113)
	2					9.117
						(0.333)
	3					6.122
						(0.634)
	4					7.937
						(0.440)
	5					10.892
						(0.208)
	6					6.579
						(0.583)
	7					8.796
						(0.360)
	8					6.247
						(0.620)
	9					5.106
						(0.746)