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Abstract

Title: Depression as a predictor of mortality and morbidity in patients after myocardial infarction

Soudabeh Khojasteh Banankhah, PhD, 2012

Dissertation Directed by Dr. Erika Friedmann

Background: Recent studies show depression as a predictor of morbidity and mortality in patients after myocardial infarction (MI) and treating depression does not improve their survival. Not all depressed patients respond adequately to treatment. Treatment-resistant-depression (TRD) may be the reason why previous studies did not demonstrated survival benefits in treated depressed post-MIs.

Purpose: To examine depression severity (DS) and progressively worsening depression symptoms (PWDS) contributions to morbidity and mortality of depressed post-MIs. It compared mortality rates between TRD and treatment responsive depression in depressed post-MIs independent of biosocial predictors.

Methods: A secondary data analysis using data from the 1834 depressed post-MIs in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial, which included 770 patients who were treated for depression. The TRD, as<50% reduction in HAM-D score from baseline to 6 months and a total HAM-D score>10 at 6 months, occurred in 13.4% (n=103) of the depressed post-MIs who were treated. Cox regression analyses were used to examine the independent contributions of DS, PWDS, and TRD to morbidity and mortality after controlling for the biosocial predictors.

Results: Depression severity was associated with increased risk of mortality for men, not women (HRs: male low severity=1; male high severity=1.42; female low severity=1.80; female high severity=1.61). The PWDS predicted mortality, depending on minority status after controlling for biosocial factors. Among depressed post-MIs, PWDS was associated with increased risk of mortality, greater in minorities than in whites (HRs: white no progression=1; white worsening=2.83; minority no progression=0.71; minority worsening=8.20). The DS (HR=1.013) and PWDS (HR=1.026) were significant independent predictors of morbidity. TRD significantly predicted mortality (HR=2.783) among the treated depressed post-MIs.

Conclusion: This study demonstrated that DS and PWDS are independent contributors to the risk of mortality and morbidity in depressed post-MIs. TRD is also associated with increased mortality in treated depressed patients. It is important to continue to monitor depression among treated post-MIs. Since, TRD post-MIs are at higher risk for mortality, closer follow-up and more aggressive risk factor modification needed to improve cardiac outcomes. This may lead to an integrated treatment strategy that may decrease risk of morbidity and mortality in post-MIs.

Depression as a predictor of mortality and morbidity in patients after myocardial infarction

by
Soudabeh Khojasteh Banankhah

Dissertation submitted to the faculty of the Graduate School
of the University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
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DEDICATION

To my beloved husband, Majid

To my loving children, Peymaan and Pegah

and

To my loving and supportive parents, Maryam and Mahmoud Khojasteh

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CHAPTER 1: INTRODUCTION

The background, purpose, and significance of the study are elaborated. The conceptual framework of the study is illustrated in this chapter. The aim of the research and hypotheses are declared and assumptions are acknowledged.

1.1 Background

Depressive Disorder (DD) is one of the most prevalent, commonly diagnosed, widely distributed in the population, and life-altering mental illness in the United States (Kessler et al., 2003). DD is defined as decrease in cognitive, affective, biological, and interpersonal activities for more than several weeks (APA, 1994).

The most widely used criteria for DD is found in the American Psychiatric Association's revised fourth edition of the Diagnostic & Statistical Manual of Mental Disorders (DSM-IV) (APA, 1994) which use the criteria for major and minor depressive disorder (see Table 1.1 & 1.2). Observable criteria for DD using DSM-IV criteria include depressed mood, fatigue, difficulty thinking (problem with concentrating and making decisions), unpleasant feeling (such as negative thoughts, loss of interest, guilt, helplessness and hopelessness), sleep disturbances (insomnia/hypersomnia), behavior changes (such as neglecting personal hygiene), avoiding socialization, and recurrent thoughts of death or suicide.

Table 1.1: DSM-IV criteria for depressive disorders

	Symptom	**Duration**	**Reported by**
a.	1.Depressed mood	Most of the day	Subject or others
	2.Diminished interest in all or almost all activities	Most of the day & nearly everyday	Subject or others
	3.Significant wt loss or gain without dieting	More than 5% of body wt in one month	Subject or others
	4.Insomnia or hypersomnia	Nearly every day	
	5.Psychomotor agitation or retardation	Nearly every day	others
	6. Fatigue and loss of energy	Nearly every day	
	7. Feeling worthlessness or excessive or inappropriate guilt	Nearly every day	
	8. Diminished ability to think or concentrate or indecisiveness	Nearly every day	Subject or others
	9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide		
b.	1. No evidence of concurrent manic depression is present		
c.	1. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.		
d.	1. The symptoms are not due to the direct physiological effects of a substance or a general medical condition (e.g., hypothyroidism).		
e.	1. The symptoms are not accounted for by acute bereavement such as loss of a loved one.		

Table 1.2: DSM-IV criteria depressive disorders

Major Depression	The diagnosis of major depression requires that all criteria (“a” through “e”) be met. Five or more of the category “a” symptoms have been present for two weeks without previous history of major depression or present for one week in patients with a history of major depression. At least one of the symptoms is either depressed mood or loss of interest/pleasure.
Minor Depression	The diagnosis of a minor depression requires that all criteria (“a” through “e”) be met. At least two but less than five of the category “a” symptoms have been present for two weeks or one week for patients with a history of major depression. At least one of the symptoms is either depression mood or loss of interest/pleasure.
Dysthymia	Dysthymia, as defined by DSM-IV, is a form of chronic, mild depression. Its symptoms are similar to minor depression disorder with persisted symptoms for at least two years. Due to its chronicity, dysthymia may be more difficult to treat than acute minor depression.

Studies show that psychological factors, such as depression, are predictors of morbidity and mortality in patients after myocardial infarction (MI) (Carney et al., 2004; Huffman et al., 2008; Lane, Carroll & Lip, 2003). Prevalence of depression is about 20% in patients with MI, compared to 5% in the general population (Rudish & Nermeroff, 2003; Thombs et al., 2006). Evidence suggests that depression predicts the development of coronary heart disease (CHD) (Herbst et al., 2007; Lichtman et al., 2008) and CHD patients with depression have a higher morbidity and mortality than CHD patients without depression (Rugulies, 2002). The nature of the relationship between depression and mortality in post MI patients may not have been completely understood: however, a number of possible mechanisms believed to underlie this association. Depression may lead to several physiological changes and perilous health behavior. Physiological changes due to depression includes; increase of sympathetic tone, elevation of cortisone and catecholamine levels, abnormal platelet activation and endothelial function, and increase in inflammatory markers (Lederbogen et al., 2001; Lett et al., 2004). Perilous health behaviors associated with depression includes; smoking, excessive alcohol intake, unhealthy eating habits, and physical inactivity (Lehto et al., 2000). Patients with depression have a higher risk of non-adherence with prescribed therapies and recommended health behaviors (Carney et al., 1995; DiMatteo, Lepper & Croghan, 2000), leading to decreased survival in post MI patients (Horwitz et al., 1990).

According to current evidence, there is an association between the severity of depression and mortality. Major depression is an independent risk factor for mortality in cardiovascular disease (CVD) patients. Studies suggest that major depression is

associated with increased risk of mortality (Geerlings et al., 2002; Kouzis, Eaton & Leaf, 1995; Pulska, Pahkala, Laippala & Kivela, 1999; Schoevers et al., 2000; Zheng et al., 1997; Zubenko et al., 1997). The prevalence of major depression in CVD patients is reported to be about 20% (Strik, Denollet, Lousberg & Honig, 2003). Based on Geerlings et al. (2002)'s Aging Study, the severity of depression increases the chances of mortality. This study shows that both high baseline depression symptoms and increasing depression symptoms from the baseline are predictors of mortality in older adult patients. Based on this evidence, it is logical to believe depression treatment that prevents depression or decreases severity will reduce the risk of mortality in older adults.

Depression predicts a poorer prognosis and lower functional status in post MI patients (Bush et al., 2001; Frasure-Smith, Lesperance & Talajic, 1993), though appropriate treatments for patients with depression may improve their long-term prognosis. However, treating depression has yet to show any improved survival in depressed post myocardial infarction patients (Berkman et al., 2003; Glassman et al., 2002; van Melle et al., 2002).

The Enhancing Recovery In Coronary Heart Disease (ENRICHD) was the first and largest randomized multi-center study that was designed to examine the effect of intervention on depressed post MI patients. In this study, participants were randomly assigned to either intervention or usual care groups. Patients in the usual care received only the care provided by their physicians. Participants in the intervention group received both the usual care provided by their physicians in addition to the ENRICHD intervention. Cognitive Behavioral Therapy (CBT) was utilized as the standard of the ENRICHD intervention. CBT is a psychotherapeutic approach with the aim of solving

the problems of dysfunctional emotions, behaviors, and cognitions through systematic procedures, administered by clinical psychologists and psychiatrists (Beck, Ruch, Shaw & Emery, 1979). After 5 weeks, the intervention group patients with unsatisfactory improvement in their depression symptoms were considered for pharmacotherapy (Berkman, 2003).

The ENRICHD study did not find evidence that depression treatment affects cardiac outcomes. Among the depressed post MI patients in the ENRICHD study, there was no difference in event-free survival between the intervention and usual care group (75.5% vs. 74.7%). Similarly, the Myocardial Infarction and Depression-Intervention Trial (MIND-IT) found no evidence that depression treatment affects cardiac outcomes (van Melle, 2002). MIND-IT was a double-blinded randomized trial that examined the efficacy of depression treatment when compared to usual care. Cardiac event-free survival in the MIND-IT trial was 86.2% for the treatment group and 87.3% for patients in the control group. The intervention in both studies only had a modest effect on depression. After months of treatment, half of the subjects in the intervention group still suffered from depression symptoms. It is difficult to demonstrate that depression treatment improves survival when half of the intervention group remains depressed. If depression is associated with decreased survival and half of the intervention group is still depressed, changes in survival could not be demonstrated. Current treatments for depression have modest effect on improving depression symptoms, and until more efficacious treatments for depression are discovered, it may be challenging to appreciate the effectiveness of successfully treating depression on cardiac outcome.

Secondary data analysis of the ENRICHD dataset was conducted by Taylor et al. (2005) to determine the effect of antidepressants on morbidity and mortality, regardless of their designated group (intervention or usual care group). The results show a significantly lower risk of recurrent MI and death in patients taking selective serotonin reuptake inhibitors (SSRI). SSRI use was associated with a 43% reduced risk of death or nonfatal MI, or a 43% lower risk of all-cause mortality (adjusted HR, 0.57; 95% CI, 0.38–0.85). Taylor et al. found improvement in survival in those patients treated with antidepressants; however, they did not examine the difference between survival in respondent and non-respondent to depression treatment. Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) was a randomized trial that examined the effect of antidepressant medication (sertraline) on depressed patients with heart disease (Glassman et al., 2002). Initial finding of the study revealed a non-significant reduction in re-current MI and death (RR=0.77;95%CI=0.51-1.16). At this time, they did not examine the difference between survival in respondent and non-respondent to depression treatment. The 7-year follow-up analysis of the SADHART trial found that patients who responded to treatment with sertraline had a reduction in mortality versus non-responders (15.6% vs. 28.4%; HR, 2.39) (Glassman, Bigger & Gaffney, 2009).

Carney et al. (2004) conducted a secondary data analysis using the ENRICHD dataset on depressed patients with prior history of major depression using only the intervention group. In this study, respondent and non-respondent to depression treatment were compared. Carney proposed that only the unimproved patients in the intervention arm with a history of major depression were at a high risk for mortality. The lack of improvement in depression did not increase mortality in the usual care arm. Fewer

patients in the intervention arm failed to improve (15% vs. 26%); however, the incidents of mortality were higher among the unimproved in the intervention arm than in the usual care arm (21.2% vs. 10.4%). Even with extensive effort to treat depression, unimproved patients in the intervention arm did not improve their Beck Depression Inventory (BDI) (Beck, et al, 1961) score by the end of the 6-month treatment. Instead, they seem to have a treatment refractory depression that was resistance to current available therapy. The valuable knowledge gained through this study needs to be further explored and examined.

Clinical studies revealed that not all depressed patients respond adequately to treatment, and their depression does not improve significantly with current depression treatments. These depressed patients are labeled as treatment resistant. Fava & Davidson (1996) meta-analysis of 36 clinical trials showed that about 50% of depressed patients have an adequate response to antidepressant therapy, 15% have partial response, and 20-35% did not respond to depression treatment.

Studies have defined treatment resistant depression (TRD) in variety of ways. General consensus shows that depression is considered resistant to treatment when at least two trials of different antidepressant therapy with adequate dose/duration/compliance have failed to produce a significant clinical improvement in depression symptoms (Berlim & Turecki, 2007).

Presently, no study shows improved outcomes in depressed post MI patients by treating depression (Berkman et al., 2003; Glassman et al., 2002; Van Mille et al., 2002). One explanation of this may be that a sub-group of TRD patients in previous studies of post MIs may have influenced the results. The presence of this sub-group may have

caused a failure in the study's ability to show improved survival in the intervention group.

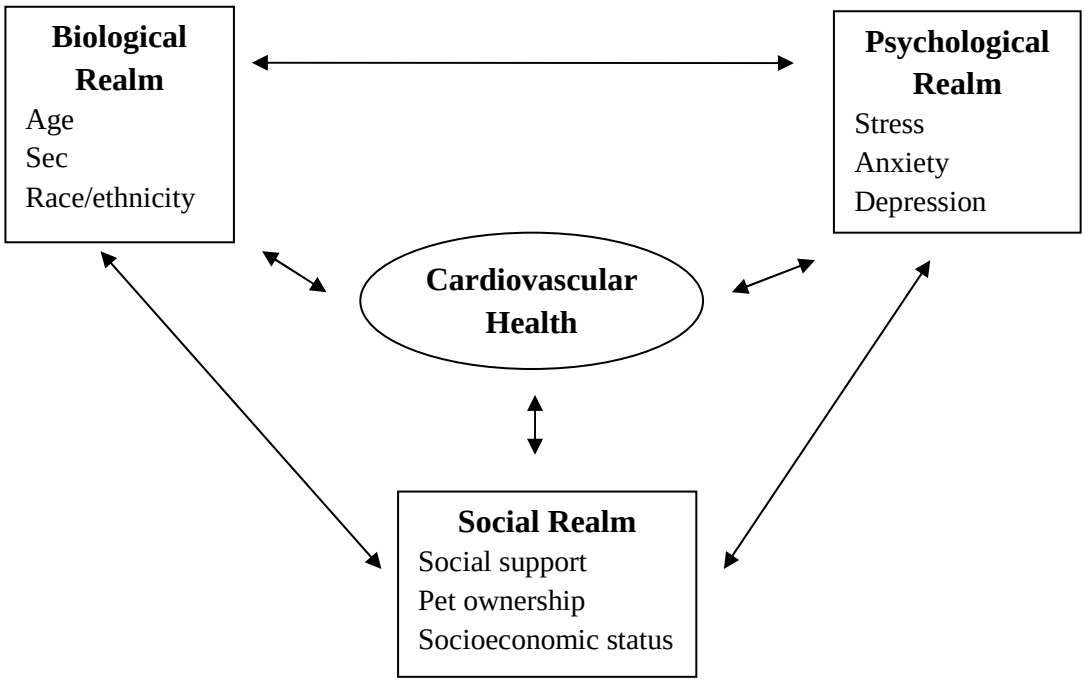
1.2 Conceptual Framework

This study proposed the use of biopsychosocial holistic model as advanced by Dr. Thomas (2008) for cardiovascular health. This model provided a conceptual framework appropriate for studying the effect of depression on mortality after MI. It has a multi-dimensional approach toward health. Health is impacted by a dynamic interaction of biological, psychological, and social influences as triadic reciprocally. In other words, biological, psychological, and social factors interactively influence each other. Any alteration of a factor will have an impact on the other factors.

Figure 1.1 demonstrates the conceptual framework of biopsychosocial holistic model of cardiovascular health. This figure discloses that cardiovascular health is a dynamic process that is constantly impacted by biological (age, sex, and race/ethnicity), psychological (stress, anxiety, and depression) and social (social support, pet ownership and socioeconomic status) factors interactively.

Depression, a psychological factor that impacts health by affecting biological and social factors, may result in an alteration of a person's cardiovascular health. The advantage of this model includes the ability to view a person as a holistic entity and incorporate all factors that impact a person's health. This holistic model appeared to be an appropriate approach for the assessment of depression in post MI patients.

Figure 1.1 Conceptual framework of the Biopsychosocial Model of Cardiovascular Health (2008). (Used with permission)



1.3 Purpose

The purpose of this study included the following: examining the contribution of depression severity at baseline on depressed post MI patients' outcomes, investigating the contributions of progressively worsening depression symptoms from baseline to depressed post MI patients' outcome, and comparing mortality rate between treatment-resistant and treatment respondent depression in depressed post MI patients after controlling for biological and social factors.

1.4 Significance and Clinical Application

Depression predicts the development of cardiovascular disease (CVD) (Herbst et al., 2007; Lichtman et al., 2008), which remains the leading cause of death in the United States, claiming a life every 39 seconds (AHA, 2011). The prevalence of depression is higher in patients with recent MI than in the general population (20% vs. 5%) (Rudish & Nermeroff, 2003; Thombs et al., 2006). The severity of depression symptom is also associated with greater mortality risk, in that patients who start with elevated depression symptoms or have worsening of depression symptoms are at a higher risk of mortality, while those who have mild depression are at less risk (Geerlings et al., 2002; Pulska et al., 1999; Schoevers et al. 2000). This study explored the contribution of depression symptom severity and duration on depressed post MI patient outcome after controlling for biological and social factors. This study provided evidence that severity and worsening of depression symptoms increase the risk of morbidity and mortality in depressed post MI patients. Based on this, it was reasonable to believe that early detection and depression treatment that decreases depression symptom severity and duration would reduce the risk of mortality in depressed post MI patients.

Treatments for patients with depression may improve their long-term prognosis; however, there was no study that showed that the outcome of acute myocardial infarction may be improved by treating depression. One explanation of this may be that a sub-group of post-MI patients with TRD may have impacted the results. The presence of this subgroup may cause failure to show improved survival in the intervention group. The knowledge gap based on recent literature is the paucity of studies that investigate the effect of TRD on depressed post-MI patient outcome. This proposed study was designed

to explore this not well-known phenomenon. This was significant, considering that one third of depressed patients who had received depression treatment did not respond to treatment (Fava et al., 1996). If patients with TRD were at a higher risk of mortality, it might be possible to improve survival of these patients by aggressively treating or modifying their other risk factors. This would impact the current treatment of post-MI patients with depression, even though there is no existing effective treatment for this condition. Patients with TRD should be followed more closely and more aggressively than patients that respond positively to depression treatment. The result of this study may lead to development of clinical guidelines for treatment of depressed post- MI patients.

1.5 Research Aims and Hypothesis

These are the aims and hypotheses of the study:

Aim 1: To examine the relation of depression symptom severity at baseline to morbidity and mortality in depressed post MI patients after controlling for biological and social factors.

Hypothesis 1.1: Depression symptom severity in depressed post MI patients predicts morbidity and mortality after controlling for biological and social factors.

Aim 2: To examine the relation of progressively worsening depression symptoms from baseline on morbidity and mortality in depressed post MI patients after controlling for biological and social factors.

Hypothesis 2.1: Progression of baseline depression symptoms at 6 months predicts morbidity and mortality in the depressed post MI patients after controlling for biological and social factors.

Aim 3: To compare mortality between treatment-resistant and treatment respondent depression in depressed post MI patients after controlling for biological and social factors.

Hypothesis 3.1: Depressed post MI patients with TRD have a higher risk of mortality than treatment respondent patients after controlling for biological and social factors.

1.6 Assumptions of the Study

The assumptions of this study were as follows:

1. Study participants responded truthfully to the questionnaires.
2. The clinical data were collected correctly by the ENRICHD study centers.
3. Assumptions related to the data analysis techniques are discussed in the data analysis section.

1.7 Summary

Knowledge gap based on recent literature are paucity of studies that examine the contribution of depression severity and progression of depression symptoms to morbidity and mortality in depressed post-MI patient and scarcity of studies that investigated the effect of TRD on depressed post-MI patients' mortality. This study intended to investigate the contribution of severity and progression of depression symptoms with cardiac outcome in depressed post MI patients after controlling for biological and social factors. In this study, there was an interest in learning more about TRD in depressed post-MI patients and their risk of mortality when compared to treatment respondent depression. This was extremely significant, considering that about one third of depressed patients receiving depression treatment do not respond to the treatment.

CHAPTER 2: LITERATURE REVIEW

This review is divided into three sections: 1) studies assessing the relationship between depression and cardiovascular disease, 2) studies that examined the effect of depression in post MI patients' outcome, and 3) studies reporting the effect of depression treatment in depressed post MI patients.

2.1 Depression and Cardiovascular Disease

Cardiovascular disease is the leading cause of death in the United States, resulting in 1.5 million myocardial infarctions (MI) and over 500,000 deaths each year (Lloyd-Jones et al., 2010).

Recent studies show that psychosocial factors, such as depression, play an important role in cardiovascular morbidity and mortality (Bush et al., 2001; Frasure-Smith et al., 1993). Major depression is an independent risk factor for mortality in cardiovascular disease (CVD) patients. Studies suggest that major depression is associated with increased risk of mortality (Geerlings et al., 2002; Kouzis et al., 1995; Pulska et al., 1998; Schoevers et al., 2000; Zheng et al., 1997; Zubenko et al., 1997). The coronary heart disease (CHD) patients with depression have a higher rate of morbidity and mortality than CHD patients without depression (Rugulies, 2002). The results of the World Mental Health Survey (Ormel, 2007) indicated a twofold increased risk of depression for patients with heart disease compared to patients without heart disease. Rugulies (2002) meta-analysis reported that depression predicts the development of CHD in initially healthy people. It was also reported by Lett et al. (2004) meta-analysis that depression increases the risk of coronary artery disease by 1.5 to 2 times in otherwise physically healthy individuals.

The nature of the relationship between depression and CHD may not have been completely understood; however, a number of possible mechanisms believed to underlie this association. Depression may lead to several physiological changes and perilous health behaviors. Physiological changes due to depression includes; increase of sympathetic tone, elevation of cortisone and catecholamine levels, abnormal platelet activation and endothelial function, and increase in inflammatory markers (Lederbogen et al., 2001; Lett et al., 2004). Depressed patients are at greater risk of dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis that is closely related to sympathetic nervous system activity (Musselman, Evans & Nemeroff, 1998). Chronic stimulation from the HPA axis increase sympathetic nervous system activity leading to elevated autonomic activity, insulin resistance, hypertension, exaggerated inflammatory response, platelet activation, endothelial dysfunction, and somatic effects (Rozanski et al., 2005).

Platelets play an important role in cardiovascular disease both in formation of atherosclerosis and in development of acute thrombotic events (Markovitz & Matthews, 1991). Platelet dysfunction has been associated with increased negative outcome in depressed patients with CHD (Glassman et al., 2002; Lahlou-Laforet et al., 2006; Pollock, Laghrissi-Thode, & Wagner, 2000; Serebruany et al., 2003). Studies suggested that increased platelet activity has been associated with higher levels of depression among individuals with CHD (Laghrissi-Thode et al., 1997). This association may possibly due to the role of serotonin in both platelet activity and the level of depression.

One of the platelet main functions is the development of thrombus formation in damaged endothelial vascular beds. Platelets are activated by multiple factors including serotonin. Serotonin is a vasoconstrictor and a platelet aggregator that increases platelet

coagulation activity and enhances platelet adhesion to other platelet agonists; this leads to thrombus formation (Lopez-Vilchez, 2009). Severity of depression has shown to correlate with platelet activation and improvement of depression has shown to reduce the platelet activity. With the intake of antidepressant medication, selective serotonin reuptake inhibitors (SSRIs), as plasma serotonin levels decreases and depression symptoms improves, the thrombus formation lessens (Lopez-Vilchez, 2009). Other studies showed that the survival benefits of SSRIs are linked to their antidepressant properties (Shapiro et al., 1999), regulation of sympathetic and parasympathetic balance (Cohn et al., 2000; Glue, 1996), and modulation of vascular tone via dopamine and norepinephrine blockade (Healy & McKeon, 2000; Montgomery, 1999).

The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) Platelet Substudy was the first documented evidence that revealed that platelet function strongly correlates with the plasma levels of sertraline and its metabolites. Treatment with SSRIs was associated with decreased activation of platelet biomarkers when compared to placebo and the survival benefits of SSRIs are related to platelet inhibition (Serebruany et al., 2005).

The findings reported in multiple studies on the relationship of platelet function to depression and CHD are mixed. Wittstein (2010) proposed that the differences in the findings were related to different methodologies used in these studies. Von Kanel (2004) meta-analysis of 34 studies suggested that data on platelet activity in depression were inconclusive and prospective studies with larger sample size that control for confounders of platelet functioning are needed to clarify this relationship.

Inflammation has been proposed to be the underlying process associated with atherosclerosis (Grundy et al., 2001; Ross, 1999). Studies have shown that increased production of inflammatory cytokines such as C-reactive protein (CRP), tumor necrosis factor (TNF), and interleukin-6 (IL-6) have been found to predict new onset or recurrent CHD (Cesari et al., 2003; Ridker et al., 2000). Elevated CRP and IL-6 are found to be strongly associated with depression (Maes et al., 1997; Miller et al., 2002). Cardiovascular Health Study (Kop et al., 2002) has also found that depression was significantly associated with elevated CRP after adjusting for other factors. Results from the Third National Health and Nutrition Examination Survey noted that a lifetime history of depression was associated with higher CRP levels (Ford & Erlinger, 2003). Elevated inflammatory markers have been observed among the Health, Aging, and Body Composition study. In this study of healthy older adults (70 to 79 years), IL-6, TNF, and CRP were higher in depressed participants. Administration of inflammatory markers shown to induce symptoms similar to depression such as fatigue, malaise, lethargy, psychomotor retardation, irritability, and anorexia (Miller, Maletic & Raison, 2009). This may suggest that there is a bidirectional relationship between depression and inflammation; depression predisposes patients to greater inflammation and inflammation increases patients' depression symptoms. More studies are needed to determine conclusively the relationships between inflammation, depression, and CHD.

Depressed patients are at greater risk of dysregulation of the autonomic nervous system (ANS) (Carney, Freedland & Eisen 2000). Dysregulation of ANS has been linked to CHD. Hyperactivity of the sympathetic nervous system (SNS) is related to hypertension, decreased heart rate variability (HRV), and decreased vagal tone (Louis,

Doyle & Anevekar, 1975) that are associated with CHD mortality (Curtis & O'Keefe, 2002; Rosenwinkel, Bloomfield, Arwardy & Goldsmith, 2001; Brook & Julius, 2000). The SNS activation may cause coronary vessel constriction in CAD patients; which may result in myocardial ischemia (Dakak, Quyyumi, Eisenhofer & Goldstein, 1995; Hossack, Brown, Stewart & Dodge, 1984). Conflicting evidence suggests that depression is not associated with a generalized increased or decreased in ANS activity, but it is more of an ANS dysregulation (Lechin et al., 1995; Delgado & Moreno, 2000; Ressler & N emeroff, 2000). The ANS dysregulation seen in several studies has shown that depressed CHD patients have a decreased HRV (Carney et al., 1995; Carney et al., 2001; Stein et al., 2000). In a healthy heart with normal HRV, there is a balanced between sympathetic and parasympathetic regulation in response to stress and rest. However, in a heart that endured ischemic event from CHD, this balance is blunted and results in decreased HRV (Sztajzel, 2004). Stein et al. (2000) found that 47% of depressed patients in their study had evidence of decreased HRV when compared to 13% in a similar non-depressed group. The decrease in HRV was associated with increased relative risk of mortality in the depressed patients. Carney et al. (2001) has also noted similar findings in post MI patients. The depressed post MI patients had 16% decrease in HRV compared to 7% in the non-depressed post MI patients.

Perilous health behavior associated with depression includes; smoking, excessive alcohol intake, unhealthy eating habits, and physical inactivity (Lehto et al., 2000). Patients with depression have a higher risk of non-adherence with prescribed therapies and recommended health behaviors (Carney et al., 1995; DiMatteo et at, 2000), leading to decreased survival in post MI patients (Horwitz et al., 1990). Panagiotakos et al. (2001)

study showed that depression accompanied by alcohol use, physical inactivity and/or smoking was associated with increased risk of developing CHD. Heart and Soul study found that 5% of non-depressed, 7% of mildly depressed, and 14% of depressed participants reported non-adherence with prescribed therapies (Gehi et al., 2005). Non-adherence to recommended health behavior and prescribed treatments is associated with decreased survival for CHD patients (Horwitz et al., 1990; McDermott et al., 1997), suggesting that adherence may be another mechanism linking depression and CHD outcomes.

2.2 Depression in Post MI patients

Recent studies show that psychological factors, such as depression, are predictors of morbidity and mortality in patients after myocardial infarction (MI) (Carney et al., 2004; Huffman et al., 2008; Lane et al., 2003). Prevalence of depression is significantly higher in patients with a recent MI, compared to the general population (Rudish & Nermeroff, 2003; Thombs et al., 2006;). There is a fourfold increased risk of depression in patients with recent MI (20%) compared to general population (5%) (Rudisch & Nermeroff 2003; Thombs et al., 2006).

Carney et al. (2003) examined the association of depression with recurrent MI and mortality in patients who had suffered myocardial infarction. In this study, 358 depressed post MI patients and 408 non-depressed post MI patients were followed for up to 30 months. During the 30-month follow-up, patients with depression were 2.8 times more likely to die and 1.5 times more likely to have non-fatal recurrent MI than non-depressed patients. Carney et al. (2003) reported that depression was an independent risk factor for

death after MI. However, the effect is only significant about a year after the acute event. This demonstrated the importance of longer follow-ups for depressed post MI patients.

According to the current review, the association between the severity of depression and mortality has not been widely examined in depressed post MI patients. The evidence that support the relationship between the level of depression and cardiac outcome is limited. Penninx et al. (2001) documented a relationship between the level of depression symptom severity and 4-year cardiac mortality among 2847 older community residents. The risk for cardiac mortality increased 1.6 times in minor and 3 times in major depression patients when compared to non-depressed participants. The baseline depression symptom severity was examined in Lesperance et al. (2002) study. This study revealed that the level of depression symptom during hospital admission for MI is more predictive of long-term survival than the level at 1-year. Lesperance (2002) study found that higher baseline depression symptom severity is associated with higher 5-year death rate. This is also seen in The Cardiovascular Health Study (2000) evaluating 5201 subjects with a follow-up of 6 years. This study found that higher baseline depressive symptoms were associated with higher mortality compared to lower baseline depression in older adults. This finding is similar to Cardiac Arrhythmia Pilot Study (CAPS) that found that baseline depression scores (BDI) predicted 1-year mortality and cardiac arrest after controlling for other risk factors (Ahern et al., 1990).

Recent studies suggested that depression symptom severity was associated with CAD severity only in patients with new onset of depression during the initial post MI period (Goodman et al., 2008). This association between depression symptom severity and CAD severity was not appreciated in patients with recurrent depression in the

immediate post MI period. This evidence suggests that patients who experience depression after MI for the first time may represent a clinically different subtype when compared with patients with recurrent depression.

The association between depression and mortality may be gender-related (Zheng et al., 1997); however, this phenomenon has been rarely examined in post MI patients. The presence of depression symptom is independently associated with higher mortality in men. According to Wolk & Weisman (1995), even though the prevalence of depression is 2.4 times higher in women than in men, the negative effect of depression on women's survival is less prominent. In this study, 75% of men with major depression died within the six years of follow-up compared to 41.4% of women with major depression. The finding of this study is consistent with Zheng, et al. (1997) longitudinal study of 57,897 adults. It demonstrated that an increase of all causes of mortality in patients with major depression was more predominant among men. According to The Cardiovascular Health Study (2000), male gender has 2.42 times the risk of mortality when compared to female gender. However, no studies show that the presence of depression symptom after MI is associated with differences in mortality between genders. The finding of Frasure-Smith et al., (1999) study suggested that depression after MI is a risk factor for mortality in one-year both for men and women after controlling for other cardiac risk factors. Although post MI women were twice as likely to report depression, as men were, the mortality rate of women were the same as men. This is also seen in Parashar et al. (2009) study, which suggests that depression symptoms in women does not contribute to higher mortality after MI when compare to men. One possible explanation may be that women are culturally more prone to report depressive complaint that may result in higher depression rate than

men. Future studies needed to explore the relationship between depression symptom severity and gender differences in post MI patients.

The presence of CHD is associated with higher mortality in young minority when compared to whites after controlling for other cardiac risk factors (Hurley et al., 2010). However, there are limited studies done that examines the contribution of race/ethnic in depressed post MI patients. Minorities include different racial and ethnic groups with diverse mixed backgrounds. They have their own histories, spiritual practices and cultures that may affect the way they report depression symptom and seek depression treatment. These behaviors may lead to differences in survival in minority patients. Future studies are needed to address race and ethnic disparities in depressed post MI patients and to understand the underlying causes that lead to these disparities.

Increasing evidence suggests that depression is related to mortality in post MI patients (Geerlings et al., 2002; Kouzis et al., 1995;; Pulska et al., 1998; Schoevers et al., 2000; Zheng et al., 1997; Zubenko et al., 1997). However studies that examined the contribution of worsening of depression symptoms to mortality are limited. Based on Geerlings et al. (2002)'s Aging Study, increasing depression symptoms from baseline were predictors of mortality in older adult patients. Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) was a randomized trial that examined the effect of antidepressant medication (sertraline) on depressed patients with heart disease (Glassman et al., 2002). Initial finding of the study revealed a non-significant reduction in re-current MI and death. The seven-year SADHART follow-up study suggested that failure to improve depression symptom during the 6 months following MI predicted more

than doubling of mortality over 6 years of follow-up; the persistent depression increased mortality in post MI patients (Glassman A.H., Bigger, T. & Gaffney, M., 2009).

2.3 Depression Treatment in Depressed Post MI

Depression predicts a poorer prognosis and lower functional status in post MI patients (Bush et al., 2001; Frasure-Smith et al., 1993), though appropriate treatments for patients with depression may improve their long-term prognosis. However, treating depression has yet to show any improved survival in depressed post MI patients (Berkman et al., 2003; Glassman et al., 2002; van Melle et al., 2002).

ENRICHD sponsored by the National Heart, Lung, and Blood Institute (NHLBI), was the first randomized multi-center study to examine the effects of cognitive behavioral therapy (plus adjunctive sertraline treatment in the case of insufficient response to depression) on mortality and nonfatal infarction in post MI patients with depression or/and low perceived social support (LPSS) (Berkman, 2003). ENRICHD study did not find evidence that depression treatment affects cardiac outcomes. Among the depressed post MI patients in the ENRICHD study, there was no difference in event-free survival between the intervention and usual care group (75.5% vs. 74.7%). Berkman et al. (2003) reported that the intervention generated significant differences in depression score between intervention and usual care groups. At 6 months after randomization, the mean BDI of depressed patients in intervention group was 9.1 vs. 12.2 in the depressed usual care group. Even though statistically significant, the magnitude of the effect may not have been sufficient to influence medical morbidity and mortality. This difference in BDI scores was diminished over time and there were no difference after 30 months ($p = 0.61$). The ENRICHD study did not find that treatment of depression in depressed post MI

patients decreased mortality and morbidity. This finding and other subsequent analysis of ENRICHD studies left health professionals without clear direction for the treatment of depression in post MI patients.

Similarly, the Myocardial Infarction and Depression-Intervention Trial (MIND-IT) found no evidence that depression treatment affects cardiac outcomes (van Melle et al., 2002). MIND-IT was a double-blinded randomized trial that examined the efficacy of depression treatment when compared to usual care. Cardiac event-free survival in the MIND-IT trial was 86.2% for patients in the treatment group and 87.3% for patients in the control group.

Today, the best available treatments have only modest effect on depression. In the ENRICHD study, the effect size of CBT supplemented with adjunctive sertraline when indicated was small (0.22). Because of the small effect size, it is difficult to assemble large enough sample size to produce sufficient statistical power to demonstrate the effect of depression treatment on survival. Perhaps, more effective depression treatments are needed to attain sufficient statistical power to test the hypothesis.

A confounding factor in the ENRICHD study was the parallel use of antidepressant medication in the two groups. The collective rates of antidepressant use in the usual care vs. intervention group, respectively, were 13% vs. 21% at 6 months, and 21% vs. 28% by the end of the follow up period.

Intriguingly, antidepressant medication use was associated with significant decrease in re-infarction and mortality. Secondary data analysis of the ENRICHD dataset was conducted by Taylor et al. (2005) to determine the effect of using antidepressants on morbidity and mortality in depressed post MI patients, regardless of their designated

group (intervention or usual care group). The analysis was conducted on 1834 patients enrolled with depression, with or without low perceived social support. The result shows significantly lower risk of recurrent MI and death in patients taking selective serotonin reuptake inhibitors (SSRIs). During an average of 29 months of follow-up, 26% of patients who did not receive antidepressants died or had a recurrent MI versus 21.5% of patients on antidepressant therapy. The SSRIs use was associated with a 43% reduction in risk of death or nonfatal MI, or a 43% lower risk of all-cause mortality. This study shows a clear benefit on cardiovascular mortality in depressed patients when SSRIs are administered (adjusted HR, 0.57; 95% CI, 0.38–0.85). This result was also seen in the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) (Glassman et al., 2002). SADHART was a randomized trial that examined the effect of antidepressant medication (sertraline) on depressed patients with heart disease. A total of 369 depressed patients with recent acute coronary syndrome (ACS) were randomly assigned to SSRIs antidepressant medication sertraline vs. placebo. The sertraline dose used in the intervention arm of the study ranged from 50 to 200 mg per day for 24 weeks. Initial finding of the study revealed a non-significant reduction in recurrent MI and death (RR=0.77;95% CI=0.51-1.16). This study suggested that antidepressant treatment with sertraline is both safe and effective. At this time of the study, they did not examine the difference between survival in responsive and non-responsive to depression treatment. The new 7-year follow-up analysis of the SADHART trial found that patients who responded to treatment with sertraline had a reduction in mortality vs. non-responders (15.6% vs. 28.4%) (HR, 2.39) (Glassman A.H., Bigger, T. & Gaffney, M., 2009).

Cardiovascular disease combined with depression increases the risk of morbidity and mortality, though the mechanism of action is not well known. A possible reason may be that depressed patients have central nervous system abnormalities regarding serotonin metabolism that extends to their platelets (Carney et al., 2002; Musselman 1996; Shore et al., 2001). Platelet dysfunction leads to increase platelet activation and aggregation that could worsen CHD, leading to more fatal and nonfatal MIs (Carney et al., 2002; Musselman 1996; Shore et al., 2001). The SSRIs ability to improve platelet function and reduce depression may be the reason for the decrease in cardiovascular mortality in depressed CHD patients treated with SSRIs. Future studies in depressed CHD patients are needed to document the effects of SSRIs on platelet function and to examine the effect of platelet function on cardiac outcome.

Recovery from heart attack is affected by numerous factors, which vary based on gender and race. The ENRICHD trial had a large diversity of race and gender, which included 973 (39%) white males, 674 (27%) white females, 424 (17%) minority males, and 410 (17%) minority females. This population provided an opportunity for post hoc analysis to examine how the treatment effectiveness is affected by race and gender in post MI patients. Schneiderman et al. (2004) found that ENRICHD intervention had a significant treatment efficacy for white males regarding recurrent MI and cardiac mortality (HR = 0.63, P = 0.004). In all other subgroups (minority men, minority women and white women), there were no significant differences between the treatment setting and the outcome. Based on Schneiderman, et al. (2004) finding, white men, but not other subgroups, benefited from the intervention. Gender and ethnicity may represent potentially significant differences in social, economic and medical factors. By comparing

these factors, we may understand the underlying principle for the exceptional benefit of the intervention for white men.

In the ENRICHD study, white men were significantly younger, better educated, and were less likely to live alone. White men tend to be healthier and less likely to have diabetes, hypertension or multiple co-morbidities and more likely to receive thrombolytic therapy and revascularization. However, white men were more likely to be current smokers, have low ejection faction or atrial fibrillation. Even after adjusting for age, education, living alone, co-morbidity score, ejection fraction, hypertension, major depression, antidepressant use, performance of cardiac catheterization, the magnitude of difference in treatment efficacy between white men and all other subgroups was not reduced (p value is attenuated from $p = 0.02$ without adjustment to $p = 0.04$ after adjustment). White men in the ENRICHD study received more intensive medical treatment than women and minority participants. Health care disparities may impact medical outcome that leads to increased recurrent infarction and mortality.

The differences in treatment efficacy between subgroups may have played an important role in medical outcome. Schneiderman et at. (2004) post hoc study presents an important point that ENRICHD intervention was based on knowledge gained in clinical trials conducted mainly in white men and the treatment benefit did not extend to minorities and women. Future clinical trials need to include more minorities and female. This will ensure examination of treatment benefits for all subgroups.

One of the reasons that ENRICHD original report failed to demonstrate survival benefit from the intervention might be that too many patients with mild, transient depression were enrolled in the study. According to Carney et al. (2004), patients were

recruited for the study within a few days of their MI. This is a life-changing event in a person life that may lead to temporary psychological difficulty and transient depression. After the initial distress, transient depression would probably have resolved without treatment within weeks after the MI. Carney et al. (2004), conducted a secondary data analysis with this point in mind. They focused on the subgroup of ENRICHD participants who had at least one prior episode of major depression. From the 1834 patients enrolled in the ENRICHD study on the basis of depression, a subgroup of 858 were selected for this study that had a history of major depression in the past and lived long enough to complete the post intervention 6 month follow up. Carney's (2004) secondary data analysis was performed on this subgroup. The baseline demographic and medical characteristics of these patients revealed no differences between the intervention and the usual care group. The mean change in BDI score from baseline to 6 months between the intervention and usual care group in this sub-study was 3.4, compared to a mean difference of 2.8 among all of the depressed ENRICHD participants. However, there were no differences in late survival between the intervention and usual care group. This analysis suggests that successful treatment of depression in this subgroup, did not translate to improved late survival.

Next, the patients in the intervention group who did not improved with treatment were compared with patients that improved with treatment. Patients who did not improve with treatment had lower BDI score at baseline and a higher body mass index than patients whose BDI decreased over the first 6 months. The unimproved patients were more likely to have had at least one psychiatric hospitalization before enrollment and they were more likely to be on antidepressant maintenance therapy. The improved

patients in the intervention arm of the study were at lower risk of late mortality than the unimproved patients. When examining the usual care arm of the study, there was no significant relationship between the change in depression and late mortality. Carney et al. (2004) proposed an interesting point that only the unimproved patients in the intervention arm present a high risk for mortality in the depressed post MI patients with the history of prior major depression. The lack of improvement in depression did not increase mortality in the usual care arm. Fewer patients in the intervention arm failed to improve (15% vs. 26%). However, the incidence of mortality was higher among the unimproved in the intervention arm than in the usual care arm (21.2% vs. 10.4%). Even with extensive effort to treat their depression, the unimproved patients in the intervention arm did not improve their BDI score by the end of 6 months of treatment. Instead, they seem to have a treatment refractory depression that is resistance to current available therapy. This valuable knowledge, gained through this study, needs to be further explored and examined.

Clinical studies show that not all depressed patients respond adequately to treatment, and their depression does not improve significantly with current depression treatments. These depressed patients are labeled as treatment resistant. Fava et al. (1996) meta-analysis of 36 clinical trials demonstrated that about 50% of depressed patients have an adequate response to antidepressant therapy, 15% have partial response, and 20-35% did not respond to depression treatment.

Recent studies have defined treatment resistant depression (TRD) in variety of ways. General consensus reveals that depression is considered resistant to treatment when at least two trials of different antidepressant therapy with adequate

dose/duration/compliance have failed to produce a significant clinical improvement in depression symptoms (Berlim & Turecki, 2007).

Currently, there is no study that has found treating depression improve outcomes in depressed post MI patients (Berkman et al., 2003; Glassman et al., 2002; Van Mille et al., 2002). One explanation of this may be that a sub-group of TRD patients in previous studies have influenced the results and indeed, the presence of this sub-group may have caused a failure in the study's ability to show improved survival in the intervention group. Future research is needed to focus on improving survival in depressed post-MI patients with TRD. This present study's aim was to bring a better appreciation regarding TRD patients' mortality when compare to non-TRD patients. This knowledge may bring awareness to primary care providers that TRD is a risk factor for higher mortality. With current depression treatment, we may not be able to alleviate depression symptoms in TRD patients, however, closer follow-ups and aggressive adjustment of other modifiable cardiac risk factors may improve their survival.

2.4 Summary

This chapter was divided into three sections: 1) studies assessing the relationship between depression and cardiovascular disease, 2) studies that examined the effect of depression in post MI patients' outcome, and 3) studies reporting the effect of depression treatment in depressed post MI patients.

The nature of the relationship between depression and coronary heart disease may not be completely understood; however, there are a number of possible mechanisms believed to underlie this association. Depression may lead to several physiological changes and perilous health behaviors. Physiological changes due to depression includes;

increased sympathetic tone, elevation of cortisone and catecholamine levels, abnormal platelet activation and endothelial function, and increase in inflammatory markers.

Perilous health behavior associated with depression includes; smoking, excessive alcohol intake, unhealthy eating habits, and physical inactivity. Patients with depression have a higher risk of non-adherence with prescribed therapies and recommended health leading to a decreased survival in post MI patients.

Depression is an independent predictor of morbidity and mortality in patients after myocardial infarction. Prevalence of depression is significantly higher in patients with a recent MI, compared to the general population. The association between the severity of depression and mortality has not been widely examined in depressed post MI patients. Lesperance (2002) study found that higher baseline depression symptom severity is associated with higher 5-year death rate.

The association between depression and mortality may be gender-related; however, this has been inconclusive and rarely examined in post MI patients. Studies that examined the contribution of worsening of depression symptoms to mortality are limited. The seven-year SADHART follow-up study suggested that failure to improve depression symptom during the 6 months following MI predicted mortality over 6 years of follow-up and persistent depression increased mortality in post MI patients.

Depression predicts a poorer prognosis and lower functional status in post MI patients. Depression treatments for depressed post MI patients should improve their long-term prognosis. However, treating depression has yet to show any improved survival in depressed post myocardial infarction patients. Recent clinical studies show that not all depressed patients respond adequately to treatment, and their depression does not

improve significantly with current depression treatments. The reason may be that a sub-group of treatment resistant depression patients in previous studies has influenced the results and indeed, the presence of this sub-group may have caused a failure in the study's ability to show improved survival in the intervention group. Future researches needed to focus on improving depressed post-MI patients with TRD survival. With current depression treatment, we may not be able to alleviate depression symptoms in TRD patients, however, closer follow-ups and aggressive adjustment of other modifiable cardiac risk factors may improve their survival.

CHAPTER 3: METHODOLOGY

Chapter 3 describes the research methodology used in this study, including; design, data source, sample selection, data files, questionnaires, and data analyses. The Enhancing Recovery In Coronary Heart Disease (ENRICHD) dataset was used to examine the study hypotheses.

3.1 Research Design

This is a secondary data analysis study using longitudinal data from the ENRICHD randomized trial.

3.2 Data Source

ENRICHD was the first randomized multi-center study to examine the effect of psychosocial intervention on survival in depressed and/or low perceived social support (LSSP) patients post myocardial infarction (MI). Sponsored by National Heart, Lung, and Blood Institute (NHLBI), the goal of ENRICHD was to increase patient social support and to alleviate depression. NHLBI Project Office that managed the overall trial and local institutional review boards approved the study protocol before recruitment. Recruitment started in October 1996 and ended in October 1999.

3.2.1 ENRICHD study protocol

The first six months after acute MI encompasses the highest risk for re-infarction and mortality (Berkman et al., 2003). For this reason, patients were enrolled in ENRICHD study within 28 days of acute MI, which permits earlier accessibility of treatment to the intervention arm of the study.

A Medical Eligibility form (MEA) was completed for all patients with acute MI that were admitted to one of the participating hospitals. MEA assessed the nature and severity of MI and was used to screen for patients that met the acute MI eligibility of the study (see Table 3.1). Patients that met acute MI eligibility and completed the informed consent to participate in the study were screen for depression and/or low perceived social support. After determining that the participant met criteria for depression and/or low perceived social support using the Depression Interview and Structured Hamilton (DISH) and the ENRICHD Social Support Instrument (ESSI) respectively, patients were randomly allocated to intervention or usual care arm. Treatment distribution was acquired by phone randomizing system maintained in the ENRICHD Coordination Center (Berkman et al., 2003). Patients were recruited over a 36 month period and follow-up was continued until all patients completed their 18 months follow-up. Patients had follow-up examination at 6 and 18 months and annually thereafter. Patients were contacted by telephone at 6 month point between annual visits. The primary end point of the study was the occurrence of re-infarction and mortality of any cause (Berkman et al., 2003).

3.2.2 ENRICHD intervention

Cognitive Behavioral Therapy (CBT) was utilized as the standard of the ENRICHD intervention. Intervention group patients with scores higher than 24 on the Hamilton Rating Scale for Depression (HAM-D) or who had less than 50% reduction in BDI score after 5 weeks were referred to study psychiatrists for pharmacotherapy consideration. If there were no contraindications, sertraline hydrochloride was used as the drug of choice. The maximum CBT duration was six months (Berkman et al., 2003).

Patients in the usual care arm of the study received only the care provided by their primary care providers, which was standard medical care for post MI patients.

Patients in both groups received health education regarding cardiovascular disease and its management and both groups received standard medical treatment as practiced in that institution.

3.2.3 ENRICHD measures

Baseline measurements for ENRICHD study collected using the Medical History form (MHA) that included demographics, cardiovascular health history, risk factors, and current medications and The Baseline Examination form (BEA) that contained the detailed medical record documentation and the course of treatment for the acute MI. An ECG was performed on the subjects, along with the DISH, Beck Depression Inventory (BDI) (Beck et al., 1961), and ESSI (see Table 3.2).

The depression measurement instrument that was used in the ENRICHD study to assess depression severity at baseline and during treatment and follow-up were DISH and BDI.

The social support measurement instrument that was used in the ENRICHD study to assess perceived social support at baseline and during treatment and follow-up was ESSI.

Table 3.1: Eligibility criteria for ENRICHD study

Inclusion Criteria	
Acute MI:	Hospitalized for MI with protein marker twice the upper limit and at least one of the following: (a) Symptoms compatible with acute MI; and/or (b) Characteristic evolutionary electrocardiographic ST-T changes or new Q waves. **a. Enzyme criteria for MI:** If CKMB is the marker used locally and if values are increased above the upper bound of the reference range. **b. Patients who undergo acute angioplasty**: Patients who present with ST segment elevation and classic signs and symptoms of MI and meet ENRICHD criteria for marker protein elevations after acute angioplasty.
Depression:	Structured Hamilton (DISH) was used to determine depression. All patients met the ENRICHD modified DSM-IV criteria for major or minor depression or dysthymia based on modified DSM-IV criteria (see Table 1.1& 1.2).
Low perceived social support:	Patients that scored 2 or lower on at least two items of the ENRICHD Social Support Instrument (excluding item 4) or had a score of 3 or less on two or more items (excluding items #4 and 7) and a total score of 18 or less within 14 days of the onset of acute MI.
Exclusion Criteria	
1.Post-procedure MI 2. Presence of conditions likely to end fatally within one year 3. Conditions likely to limit the physical capacity to participate 4. Participation in concurrent research protocols 5. Major psychological co-morbidity as following: • Schizophrenia, bipolar disorder, or psychotic disorder • Dementia evidenced by a Short BLESSED score >10 • Current substance abuse evidenced • Other major psychological conditions preventing participation in trial 6. Imminent Suicide Risk 7. Unwillingness to Provide Informed Consent 8. Inability to Complete Screening Visits 9. Inaccessibility for Intervention and/or Follow-up 10. Currently in Active Psychotherapy or Taking Antidepressant Medication for less than 14 days	

Table 3.2: ENRICHD measurement tools

Instrument	Scale	Description
BDI (Beck Depression Inventory)	Ranging from 0 to 64, score over 10 indicates depression, the higher the score the more severer the depression symptoms	Measures the severity of depression
DISH (Depression Interview and Structured Hamilton)	Ranging from 0 to 50, score over 10 indicates depression, the higher the score the more severer the depression symptoms	Diagnose the level of depression
ESSI (ENRICHD Social Support Instrument)	Ranging from 6 to 30, scores less than 18 indicates low perceive social support, the lower the score the less social support	Diagnose low social support and measures the severity and change in social support

Depression Interview and Structured Hamilton (DISH)

DISH is a semi-structured interview developed for the ENRICHD study (Freedland et al., 2002). DISH was used to diagnose current depressive episodes using principles and criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) (see Table 1.1 & 1.2).

The DISH incorporated material from the 17-item version of the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960), the Structured Interview Guide for the Hamilton Depression Scale (SIGH-D) (Williams, 1988), the Diagnostic Interview Schedule (DIS) (Robins, Helzer, Croughan, & Ratcliff, 1981), and the modified versions of the DIS (Carney et al., 1988).

The DISH depression severity score was based on the 17-item HAM-D. The first 9 items on HAMD-D are 5 point Likert format ranging from 0 (absent) to 4 (severe). The last 8 items are 3 point Likert format ranging from 0(absent) to 2 (clearly present). The

possible score ranges from 0 to 50. Scores of greater than 10 indicates the presence of depression symptoms. Higher total scores indicate more depression symptom severity.

According to the DISH validity study, the concurrent validity of DISH was evaluated using the Pearson correlation coefficient between 17-item HAM-D embedded in the DISH and BDI scores that resulted in a correlation of 0.76 ($p<0.001$) (Freedland et al., 2002).

Interrater reliability and test-retest reliability of the DISH was not evaluated in the DISH validity study. However, HAM-D that is embedded in DIS has an adequate internal and interrater reliability. The interrater reliability was measured by using Pearson's r coefficient. For two raters, the correlation between summed scores for the first 10 patients was $r=0.84$ and for the first 70 patients the correlation increased to $r=0.90$ (Hamilton, 1960).

DISH was administered at the screening phase of the ENRICHD study and at 6 months follow-up.

Beck Depression Inventory (BDI)

Beck Depression Inventory (BDI) (Beck, 1961) is used to evaluate baseline depression status and assess progress during treatment and follow-up. BDI is the most widely used instrument in clinical and research settings. BDI is considered one of the best methods to assess presence and severity of depression. It is easy to use and only takes five minutes to complete by the patients or providers. BDI is a 21-item inventory, and each item is rated on a 0 to 3 scale with a total score ranging from 0 to 64. BDI scores greater than 10 indicate depression, scores of 10-15 mild depression, 16-23 moderate depression, and 24-64 severe depression.

BDI reliability was estimated by using test-retest reliability with a 0.95 value which indicates a good reliability. The internal reliability was measured with the use coefficient alpha which resulted in alpha of 0.91 which indicates a high internal consistency (Beck, Steer, & Brown, 1996).

Concurrent validity of BDI was established by comparing BID to HAM-D that positively correlated (r=0.71, n=87). This indicates an acceptable concurrent validity of BDI.

The BDI was administered to all participants at baseline, 6 months, 12 months, 18 months and annually thereafter.

ENRICHD Social Support Inventory (ESSI)

ESSI was developed for ENRICHD study to measure functional social support. The ESSI was used as a screening tool to determine patients' eligibility for ENRICHD based on low social support, and to assess changes in patients' social support following treatment.

ESSI is a 7-item inventory, and item 1 to 6 is rated on a 1 to 5 scale which indicates none to all respectively. Item 7 is not rated on numeral scale. The total score ranging from 6 to 30 with lower scores indicates lower perceived social support. A score of less than 3 on 2 or more items and a total score of less than 18, or a score of 2 on 2 items without regard to total score indicated low perceived social support (Vaglio et al., 2004).

ESSI reliability was estimated by using test-retest reliability that showed no significant differences in mean scores administered 1 month apart (p=0.98) which indicates a good reliability. The internal reliability was measured with the use of

Cronbach's alpha that revealed an alpha of 0.88 which indicates a high internal consistency. The intra-class correlation coefficient was 0.94, reflecting excellent reproducibility (Vaglio et al., 2004).

ESSI concurrent validity was established by examining the correlations between the ESSI total score and other well-validated social support scales that revealed statistically significant correlations with these measures (r= 0.13-0.36). This indicates a modest but significant concurrent validity of ESSI.

The ESSI was administered to all participants at baseline, 6 months, 12 months, 18 months and annually thereafter.

3.3 Sample and Setting

The ENRICHD study enrolled 2481 patients hospitalized for acute MI (within the past 28 days) who were admitted in one of the 73 hospitals affiliated with 8 participating clinical centers (Washington University, St. Louis, Missouri; Duke University, Durham, North Carolina; Harvard University, Boston, Massachusetts/Yale University, New Haven, Connecticut [combined]; Stanford University, Stanford, California; University of Miami, Miami, Florida; University of Alabama, Birmingham, Alabama; University of Washington, Seattle, Washington; and Rush Presbyterian Hospital, Chicago, Illinois) (Berkman et al., 2003). This current study was focus on the 1834 patients with depression (849 females and 985 males); 958 (52%) with major depression, 811 (44%) with minor depression, and 66 (4%) with dysthymia (see Table 1.1 & 1.2).

3.4 Eligibility Criteria

All patients with acute MI admitted to the participating hospitals were considered for enrollment in the ENRICHD trial. Acute MI was documented by cardiac enzymes and

by chest pain with typical ST-T changes or new Q waves. Patients who met the eligibility criteria for acute MI and gave written informed consent were screened for the presence of depression and/or LPSS. This current study inclusion criteria is the same as ENRICHD (see Table 3.1), except for excluding patients with LPSS only diagnosis.

Patients were excluded from the ENRICHD study if they had other life-threatening medical illnesses, cognitive impairment, other major psychiatric disorders, were at imminent risk of suicide, were too ill or unable to participate, had other barriers, had been taking an antidepressant for less than 14 days, were exempted by their cardiologist from participating in the study. In addition to the ENRICHD exclusion criteria (see Table 3.1), patients without depression were also excluded from this present study.

3.5 Study Variables

The theoretical and operational definitions for the variables of interest include the independent variables (biological, psychological, and social variables) and outcome variables (mortality and morbidity).

3.5.1 Independent variables

The independent variables that were addressed in the study model were biological, psychological, and social factors.

Biological factors

Biological factors that were included in the current study were age, gender, race, and presence of diabetes, history of heart failure, hypertension, prior MI, prior stroke, and current smoker. For theoretical definitions, operational definitions and the level of measurement for each variable see Table 3.3.

Table 3.3: Biological factors included in the study

Biological factors	**Theoretical definition**	**Operational definition**	**Reported**	**Level of measurement**
Age	The length of time a person has lived	Patient's age at the time of randomization.	Age in years	Continuous
Gender	Sexual identity of a person	Sexual characteristics of a person	male and female	Nominal
Race	Racial background of a person	Race classification according to clinical trial center	Minority and non-minority	Nominal
Presence of Diabetes	Disease that the body does not produce or properly utilize insulin	Medical record documentation of diabetes	Yes/No	nominal
History of heart failure	Weakness of the heart muscle that leads to buildup of fluid in body tissue	Medical record documentation of heart failure	Yes/No	Nominal
History of Hypertension	Blood pressure of 140/90 or greater	Medical record documentation of hypertension	Yes/No	nominal
Prior MI	History of heart attack prior to recent MI	Medical record documentation of prior MI	Yes/No	nominal
Prior Stroke	History of stroke prior to the enrollment of the study	Medical record documentation of prior stroke	Yes/No	nominal
Current Smoker	Use of tobacco when enrolled in the study	Medical record documentation of smoking status	Yes/No	nominal

Psychological Factors

Psychological factors that were included in the study were depression, depression symptom severity, worsening of depression symptoms, treatment resistant depression. See Table 3.4 for theoretical definitions, operational definitions and the level of measurement for each variable.

Table 3.4: Psychological factor included in the study

Psychological factors	**Theoretical definition**	**Operational definition**	**Reported**	**Level of measurement**
Depression	A compilation of five or more symptoms (listed in Table 1) which have been noted within a 2-week period that deviate from normal behavior for an individual. At least one of the symptoms must include loss of interest or depressed mood (American Psychiatric Association, 1994)	Patients with greater than 10 on the BDI considered depressed. BDI less than ten will indicate a non-depress patient (see Table 2).	Total score of BDI	Continuous
Depression symptom severity	The degree of depression and how many of the depression symptoms are presented (see Box 1) (American Psychiatric Association, 1994).	The BDI scores greater than 10 indicate depression: patients with scores of 10-15 reflect mild depression; 16-23 reflect moderate depression; and 24-63 reflect severe depression.	Total score of BDI	Continuous
Worsening of depression symptoms	When depression symptoms are amplified in occurrence or intensity from baseline.	when the six month re-assessment of depression score reveals a higher degree of depression compared to baseline	Change of BDI at 6 months from baseline	Continuous
Treatment resistant depression	When depression symptoms are not improved after treatment of depression is completed	When total HAM-D score is not decreased more than 50% from baseline with a total HAM-D score above 10 after completing depression treatment	Treat resistant depression/ non treatment resistant depression	Nominal

Social Factors

Social factor that were included in the study were living alone, perceived social support, social isolation. For theoretical & operational definitions and the level of measurement for each variable, see Table 3.5.

Table 3.5: Social factors included in the study

Social factor	**Theoretical definition**	**Operational definition**	**Reported**	**Level of measurement**
Live alone	Not living with another person	The answer to question 7 of ESSI (do you live alone?).	Yes/No	Nominal
Perceived Social Support	The apparent availability of people whom the individual trusts and make the person feel cared and valued	The total score on ESSI scale that ranges from 6 to 30.	Total score of ESSI	Continuous
Social Isolation	A state in which a person feels that they do not have another individual support and care	The score on ESSI with low perceived social support defined as patients that scored 2 or lower on at least two items of the ENRICHD Social Support Instrument (excluding item 4) or had a score of 3 or less on two or more items (excluding items #4 and 7) and a total score of 18 or less	Yes/No	Nominal

3.5.2 Dependent variables

Dependent variables that were included in the study were mortality and morbidity. Morbidity defined as recurrent non-fatal MI and mortality. The contribution of recurrent non-fatal MI to morbidity was 45 percent and the contribution of mortality to morbidity

was 55 percent. See Table 3.6 for theoretical definitions, operational definitions and the level of measurement for each variable.

Table 3.6: Dependent variables included in the study

Dependent variables	**Theoretical definition**	**Operational definition**	**Reported**	**Level of measurement**
Morbidity	A diseased state, disability, or poor health due to any cause	Grouping of recurrent non-fatal MI and mortality	Time enrolled in the study to time of morbidity	Continuous
Mortality	Permanent termination of the biological functions that sustain a living organism	Verified and documented death	Time enrolled in the study to time of mortality	Continuous
Recurrent non-fatal MI	The interruption of blood supply to a part of the myocardial that leads to ischemia or death of the heart cells	An elevation of cardiac enzymes and having chest pain with typical ST-T changes or new Q waves	Time enrolled in the study to time of morbidity	Continuous

3.6 Data Files

3.6.1 Analytic data file formation

An analytical data file was created by collecting variables and measurement instrument scores from the dataset in the ENRICHD trial. The ENRICHD data files and codebooks were obtained from NBLHI. A detailed list of the data file name, variable name, and unit of measure were created. Data file was created by transferring the text data files to Statistical Package for the Social Sciences 20 (SPSS 20) data format. Then, the data files were screened for variables that were not being used in the analysis and

those variables were deleted from the data file. Variables that were used in the analysis were included in the data file.

3.7 Statistical Methods

3.7.1 Data analysis

Statistical procedures were performed using SPSS version 20.0 software. Each variable in the dataset was inspected, cleaned and transformed when necessary. Normality of distributions was examined by computing skewness and kurtosis; no variables had extreme values that needed transformation (Tabachnick & Fidell, 2007). Missing data was less than five percent thus there was not a need to examine patterns of missing data (Tabachnick & Fidell, 2007). All inferential tests conducted at the 0.05 level of significance.

Descriptive statistics used to summarize the demographic characteristics of participants with depression symptom severity, progression of depression symptoms, and treatment resistant depression.

Cox Regression

Cox Regression Analyses was used to examine each hypothesis. Cox regression analysis is widely used for estimating the effect of depression on survival after adjusting for other explanatory variables. Cox regression assumptions are event-free prior to study, independence of censoring, and event being exclusive/ exhaustive. All participants in the study were event-free (alive and no re-infarction) prior to the start of the study. Independence of censoring means that loss of one subject is independent of loss of other

subjects. Events that are exclusive and exhaustive mean that the subjects either did or did not experience the event; there are no partial events.

The proportional hazards assumption of Cox regression was confirmed by visual examination of log minus log (LML) graphs for each analysis. For the continuous predictors of baseline BDI score and change in BDI score, the cases were divided into three categories according to the predictor and the curves for the three groups compared. For all five analyses (baseline BDI predicts mortality, baseline BDI predicts morbidity, change in BDI predicts mortality, change in BDI predicts morbidity, and treatment resistant depression predicts mortality), the graphs of the subgroups (Figures 3.1-3.5) appeared to be parallel and thus did not appear to violate the proportional hazard assumption.

Figure 3.1 LML function for baseline BDI categories (1=BDI less than 13, 2=BDI 13 to 20, and 3=BDI greater than 20) and mortality after MI

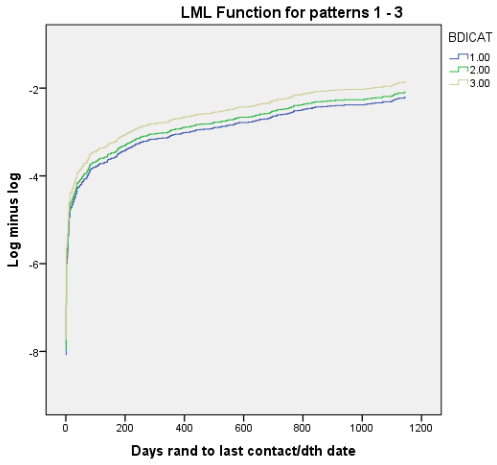


Figure 3.2 LML function for baseline BDI categories (1=BDI less than 13, 2=BDI 13 to 20, and 3=BDI greater than 20) and morbidity after MI

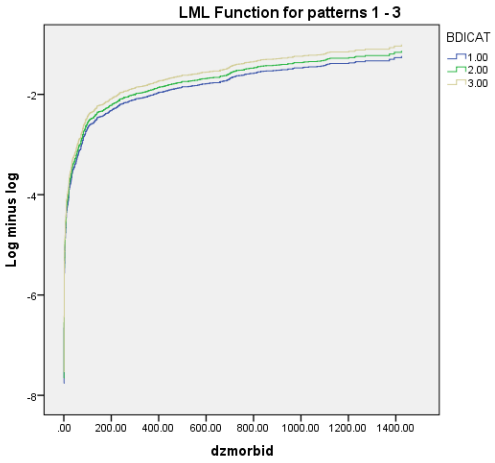


Figure 3.3 LML function for change in baseline BDI categories (1=BDI change less than -11, 2=BDI change -11to -4, and 3=BDI change greater than -5) and mortality after MI

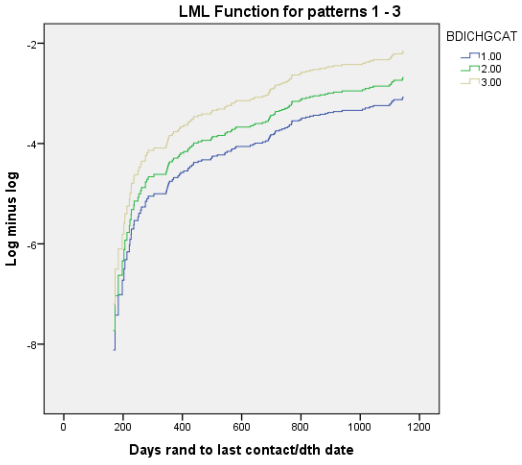


Figure 3.4 LML function for change in baseline BDI categories (1=BDI change less than -11, 2=BDI change -11to -4, and 3=BDI change greater than -5) and morbidity after MI

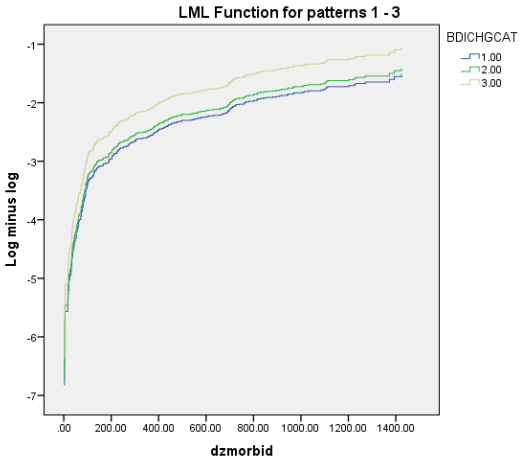
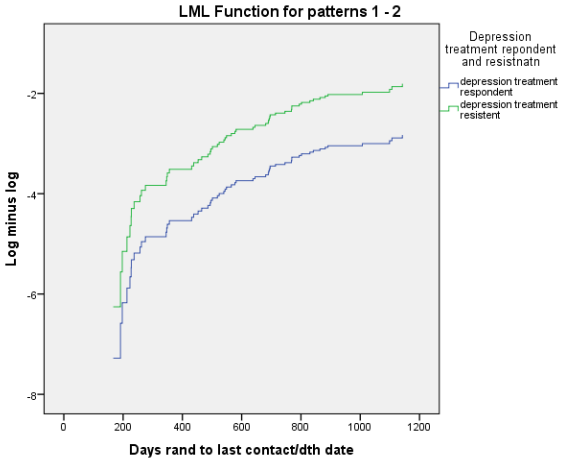


Figure 3.5 LML function for depression treatment resistant and depression treatment respondent participants to mortality after MI



3.7.2 Aim procedures

Aim 1: To examine the contribution of depression symptom severity at baseline to morbidity and mortality in depressed post MI patients after controlling for biological and social factors.

The first hypothesis was that baseline depression severity in depressed post MI patients predicts morbidity and mortality. In other word, higher baseline depression score increases the likelihood of morbidity and mortality after controlling for biological and social factors.

For research aim 1, Separate sets of analyses conducted to examine predictors of morbidity and mortality. For each outcome variable, a model constructed with biological and social factors that affect the dependent variable as well as baseline depression as predictors to control for the contributions of the other factors to the outcome variable. Biological factors that were included as predictors were age, female gender, minority status, and presence of diabetes, history of heart failure, hypertension, prior MI, prior stroke, and current smoking. The social factors that were included as predictors were living alone, perceived social support, and social isolation. Dummy variables used for dichotomous predictor variables. Current smoking categorized as current smoker (coded 1) and current non-smoker (coded 0).

The psychological predictor was the depression score at baseline that was the baseline BDI scores, which was a continuous variable with higher score indicating more severe depression symptoms (see Table 3.5). The outcome variables were morbidity and mortality, which were continuous variables (see Table 3.6). Cox proportional hazards regression analysis was used to examine hypotheses for both mortality and morbidity. For

mortality outcome, the event of interest was death; for morbidity outcome, the event of interest was re-infarction or death, whichever came first. Time to event was calculated as time from study enrollment to the event, either death or re-infarction.

First, separate regression analyses with each individual predictor were analyzed to examine the predictor's contribution to the outcome without controlling for any other variables. The first model combining the biological and social predictors included all variables in the individual prediction models. The final model consists of only predictors with $p< 0.20$ in the first model and other predictors were excluded.

To determine power and required sample size for Cox regression, we need to estimate the smallest outcome group. Based on this study sample size (n=1834), 14% (n=257) died and 24% (n=457) with morbidity. With 10 cases in the smallest outcome group per predictor, the power would be adequate for up to 25 predictors (Vittinghoff & McCulloch, 2007). This study has 10 predictors. The sample size of this study provides sufficient power to conduct these analyses.

Aim 2: To examine the relation of progressive depression symptom severity to mortality and morbidity in depressed post MI patients after controlling for biological and social factors.

The second hypothesis was that worsening depression symptoms from baseline to 6-months in depressed post MI patients predicts mortality and morbidity. In other word, worsening baseline depression score from 6 months increases the likelihood of morbidity and mortality after controlling for biological and social factors.

For research aim 2 (as also indicated in aim 1), separate sets of analyses were conducted to examine predictors of morbidity and mortality. For each outcome variable,

a model constructed with biological and social factors that affect the dependent variable as well as baseline depression as predictors to control for the contributions of the other factors to the outcome variable. Biological and social factors that examined were the same as aim 1.

The psychological predictor was the change of baseline depression score from the depression score at 6 months. This was a continuous variable with zero meaning no change of depression score from baseline, negative values mean that depression symptoms has worsen, and positive values indicates improvement of depression symptomalogy. The change in baseline BDI from 6-months used in these analyses. The dependent variables were morbidity and mortality, which were time from enrollment in the study until the event (morbidity/mortality) (see Table 3.6).

To examine the hypothesis, Cox regression analysis was used. First, separate regression analyses with each individual predictor were analyzed to examine the predictor's contribution to the outcome without controlling for any other variables. The first model combining the biological and social predictors included all variables in the individual prediction models. The final model consists of only predictors with $p < 0.20$ in the first model and other predictors were excluded.

To determine power and required sample size for Cox regression, we need to estimate the smallest outcome group. Based on this study sample size (n=1834), 14% (n=257) died and 24% (n=457) with morbidity. With 10 cases in the smallest outcome group per predictor, the power would be adequate for up to 25 predictors (Vittinghoff & McCulloch, 2007). This study has 11 predictors. The sample size of this study provides sufficient power to conduct these analyses.

Aim 3: To compare mortality between treatment-resistant and treatment respondent depression in depressed post MI patients after controlling for biological and social factors.

The third hypothesis is that depressed post MI patients with TRD have a higher risk of mortality when compared to treatment-respondent patients.

For research aim 3, analyses were conducted to examine predictors of mortality. The participants in this aim consist of participants in the aim 1&2 (N=1834) that received depression treatment in the first 6-months of enrollment in the research study (N=770). Treatment resistant depression (TRD) was defined as less than 50% improvement of 6-months HAM-D score from baseline in patients with 6-months HAM-D greater than 10. For the outcome variable, a model was constructed with biological and psychological, and social factors that affect the dependent variable as predictors to control for the contributions of the other factors to the outcome variable. Biological, psychological, and social factors that examined were the same as aim one.

To examine the hypothesis, Cox regression analysis was used. First, separate regression analyses with each individual predictor were analyzed to examine the predictor's contribution to the outcome without controlling for any other variables. The first model combining the biological, psychological, and social predictors included all variables in the individual prediction models. The final model consists of only predictors with $p< 0.20$ in the first model and other predictors were excluded.

To determine power and required sample size for Cox regression, we need to estimate the smallest outcome group. Based on this study sample size (n=770), 8% (n=62) died. With 10 cases in the smallest outcome group per predictor, the power would

be adequate for up to six predictors (Vittinghoff & McCulloch, 2007). This study has six predictors. The sample size of this study provides sufficient power to conduct these analyses.

3.8 Limitation and Strengths

This study was a secondary data analysis of an existing trial. This places limitation to this study regarding control over the variable definition, measurement, data collection and other crucial aspects of the study design. With this study we were not able to establish causality of depression symptom severity, worsening of depression symptoms and treatment-resistant depression with mortality and mortality. The study findings were only able to provide evidence towards the associations between the variables. Despite the limitations of this study, the strengths outweigh the limitations of the study. Using an existing database, this study has the advantage of providing a large representative sample rather than a small convenience sample. The database was comprehensive including questionnaires and medical history. ENRICHD included detailed questionnaire development, data collection procedures, and data management and quality control measures.

3.9 Summary

In Chapter 3, research design, data source, sample selection, and data files were described. This study was a secondary data analysis using longitudinal data from ENRICHD randomized trial. This study has 3 aims. The first aim was to examine the contribution of baseline depression symptom severity to mortality and morbidity in depressed post MI patients after controlling for biological and social factors. To examine

this aim, Cox regression analysis was used. This study met all assumptions of Cox regression and had sufficient power and sample size to do the analysis.

The second aim was to examine the contribution of progressively worsening depression symptoms from baseline on mortality and morbidity in depressed post MI patients after controlling for biological and social factors. To examine this aim, Cox regression analysis was used. This study met all assumptions of Cox regression and had sufficient power and sample size to do the analysis.

The third aim is to compare mortality between TRD and treatment respondent depression in depressed post MI patients after controlling for biological and social factors. The analytical approach used to investigating this aim was Cox regression. This study met all the assumptions of Cox regression and had sufficient power and sample size to do the analysis.

CHAPTER 4: DATA ANALYSIS

The purpose of this study is to examine the contribution of depression severity at baseline to depressed post MI patients' outcomes, investigate the contributions of progressively worsening depression symptoms (from baseline to 6 months) to depressed post MI patients' outcome and compare mortality rate between treatment resistant and treatment respondent depression in depressed post MI patients after controlling for biological and social factors.

This chapter provides the statistical results of the data analysis that examined the research hypotheses of the study. The participants' characteristics were described in the first section and the Statistical Package of the Social Sciences (SPSS) 20 was utilized for data analyses.

4.1 Participants

A total of 1834 patients were enrolled in the ENRICHD randomized trial from 73 participating clinical sites. All participants were admitted for acute MI and diagnosed with depression within the first 28 days after MI. Table 4.1 reports the demographic characteristics of the participants. The demographical and biological variables described in the study were age, gender, minority, participants' education, presence of diabetes, history of heart failure, hypertension, prior MI, prior stroke, and current smoker. The social factors were living status, perceive social support, and social isolation.

The mean age of the patients was 60.2 years, with a standard deviation (SD) of 12.3. Almost half the patients were female (n=849, 46%) and over two-third were white (n=1239, 67.6%). A majority of the patients (52%) had a high school diploma with no college degree. Clinical history included 35% diabetes, 14% heart failure, 60% hypertension, 28% with prior MI, and 10% stroke. About 42% of the participants lived

alone and almost half the patients reported social isolation (47%). One-third were current smokers (32%), and two-thirds were former or non-smokers (68%). A majority of the patients were diagnosed with major depression (n=955, 52%), 44% with minor depression (n=814) and less than 4% with dysthymia (n=65).

4.2 Descriptive Statistics

Descriptive statistics were evaluated for each variable. The dependent variables were morbidity (non-fatal re-infarction or death before re-infarction) and mortality. Independent variables were biological, social and psychological factors. All continuous independent variables were examined for missing data, outliers and normality.

4.2.1Dependent variables

Dependent variables consist of mortality and morbidity data.

Mortality data

Of the 1834 participants, there were 257 (14%) deaths. All participants followed up for minimum of 18 months and maximum of 4.5 years with an average of 29 months. The time to event variable were used in the Cox regression mortality analyses. Time was in days from enrollment in the study to time of death or until last follow up. Time to death had ranged 0 days and to 1634 days.

Morbidity data

The dependent variable, morbidity was defined as the days from enrollment to non-fatal MI or death, whichever came first. Of the 1834 participants, 24.9%(n= 457) were either diagnosed with recurrent MI or died during the follow-up period. Mortality contributed 55 percent and non-fatal MI contributed 45 percent to the morbidity.

Table 4.1: Baseline Demographical & Biological, Social, and Psychological Characteristics of Participants in the Study Sample (n=1834)

Characteristics		**Mean (SD)**	**N (%)**
Demographics & Biological Characteristics:			
	Age (years) (Range, 34 to 85)	60.2 (12.3)	
	Gender, female		849 (46.3)
	Ethnicity, minority		595 (32.4)
	Education:		
	Basic or no HS degree		494 (26.9)
	HS without college degree		959 (52.3)
	Advanced education		328 (17.9)
	Body Mass Index (Range, 15 to 50)	29.2 (6.3)	
	Diabetes		633 (34.5)
	History of heart failure		265 (14.4)
	History of hypertension		1105 (60.3)
	Prior MI		495 (27.7)
	Prior stroke		186(10.3)
	Smoking, Current		579 (31.6)
Social Characteristics:			
	Live alone		778 (42.4)
	Perceived Social Support (baseline ESSI score) (Range, 8 to 24)	24.28(6.54)	
	Social Isolation		855 (46.6)
Psychological characteristics:			
	Major Depression		955 (52.1)
	Minor Depression		814(44.4)
	Dysthymia		65 (3.5)
Psychological measures:			
	Baseline Depression symptom severity (baseline BDI) (Range, 0 to 50)	17.9 (7.9)	
	Progression of Depression symptom severity* (Range, -48 to 25)	-7.27(9.15)	

*A large value for progression of depression (BDI) indicates a greater worsening of symptoms.

BDI Beck Depression Inventory
ESSI ENRICHD Social Support Inventory
HS High School
TRD Treatment Resistant Depression

4.2.2 Predictor variables

Predictor variables used in the study were biological, psychological and social factors.

Biological data

Age (mean=60.2 years, SD= 12.3, range 34-85) was continuous predictors. Gender (female coded 1 & male code 0) (n=849, 46.3%) and Ethnicity (minority coded 1 & white coded 0) (n=595, 32.4%) were dichotomous predictors.

The biological factors of diabetes (n=633, 34.5%), history of heart disease (n= 265, 14.4%), hypertension (n=1105, 60.3%), prior MI (n=495, 27.7%), prior stroke (n=186, 10.3%), and current smoker (n=579, 31.6%) were scored as dichotomous (yes=1and no=0).

Social data

Live alone (n=778, 42.4%) and social isolation (n=855, 46.6%) were dichotomous predictors (yes=1 and no=0) and perceived social support (mean=24.28, SD 6.54, range 8-34) was a continuous predictor.

Psychological data

To evaluate baseline depression symptom severity, baseline BDI score was utilized. Baseline BDI score (mean=17.9, SD=7.9, range 0-50) was a continuous predictor. There were 838 (45.7%) with mild depression, 595 (32.5%) with moderate depression, and 387 (21.1%) with severe depression. According to DSM-IV depression categories, there were 955 (52.1%) with major depression, 814(44.4%) with minor depression, and 65(3.5%) with dysthymia.

To examine worsening of depression symptom from baseline the change in 6 months BDI score from baseline was used. Value of 0 indicated no change in depression severity symptom from baseline. Negative values were indicative of improvement and positive values correlated with worsening of depression symptoms from baseline. Change in depression symptom severity (mean= -7.27, SD=9.15, range -48 to 25) was a continuous variable.

4.3 Data Analyses

Cox regression analyses were used to address the hypotheses for all research aims.

4.3.1 Research Aim 1

Aim 1: To examine the relation of depression symptom severity at baseline to morbidity and mortality in depressed post MI patients after controlling for biological and social factors.

Hypothesis 1: Depression symptom severity in depressed post MI patients predicts morbidity and mortality after controlling for biological and social factors.

Separate sets of analyses were conducted to examine predictors of morbidity and mortality. For research aim 1 with each outcome, a model was constructed with biological and social factors that affect the dependent variable as well as baseline depression as predictors to control for the contributions of the other factors to the outcome variable. Biological factors that were included as predictors were age, female gender, minority status, and presence of diabetes, history of heart failure, hypertension, prior MI, prior stroke, and smoking status. The social factors that were included as predictors were living alone, perceived social support, and social isolation. First, separate

regression analyses with each individual predictor were analyzed to examine the predictor's contribution to the outcome without controlling for any other variables. Dummy variables were used for dichotomous predictor variables. Smoking was categorized as current smoker (coded 1) and current non-smoker (coded 0).

Aim 1(a): Predicting Mortality

The results of the individual Cox regression analyses for each predictor (see Table 4.2) demonstrate that the biological factors age ($p < 0.001$), female gender ($p = 0.009$), diabetes ($p < 0.001$), history of heart failure ($p < 0.001$), hypertension ($p < 0.001$), prior MI ($p < 0.001$) , prior stroke ($p < 0.001$), and smoking($p < 0.001$) were significant predictors of mortality. Minority status ($p = 0.604$) was not significant or potentially influential ($p < 0.20$) contributor to mortality. The social factors live alone ($p = 0.034$) and social isolation ($p = 0.038$) were significant predictors of mortality. Perceived social support ($p = 0.180$) contributed to mortality at $p < 0.20$ and thus was retained for inclusion in models with multiple predictors. Without controlling for any other variables, the psychological factor, depression symptoms at baseline ($p = 0.152$) was not a significant predictor of mortality.

Table 4.2: Results of separate Cox regression analyses to examine the contributions of each biological, social and psychological predictors to mortality among depressed post MI patients (N=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.055	.005	100.014	<.001	1.056
	Female Gender	.327	.125	6.833	.009	1.387
	Minority Status	-.07	.134	.269	.604	.933
	Diabetes	.807	.126	41.040	<.001	2.242
	Heart Failure	1.614	.131	152.251	<.001	5.022
	Hypertension	.515	.141	13.371	<.001	1.673
	Prior MI	.910	.127	51.176	<.001	2.485
	Prior Stroke	.990	.152	42.587	<.001	2.691
	Current Smoker	-.591	.153	14.821	<.001	.554
Social Factors:						
	Live Alone	.265	.125	4.482	.034	1.303
	Perceived Social Support	.013	.010	1.798	.180	1.013
	Social Isolation	-.264	.127	4.325	.038	.768
Psychological Factor:						
	Baseline depression symptom severity	.011	.008	2.053	.152	1.011

It was hypothesized that baseline depression symptoms would predict mortality after controlling for biological and social predictors. The first model combining the biological and social predictors included all variables in the individual prediction models with $p< 0.20$ in the individual models and baseline depression symptoms. In the first combined Cox regression model (see table 4.3), biological factors of age ($p< 0.001$), diabetes ($p= 0.010$), history of heart failure ($p< 0.001$), prior MI ($p= 0.21$), and prior stroke ($p= 0.023$) were significant independent predictors of mortality. Female gender ($p= 0.688$), minority status ($p= 0.925$), hypertension ($p= 0.954$), and current smoker ($p= 0.846$) were not independent predictors of mortality at $p< 0.20$ and thus were not included in the next model. In the first combined Cox regression model, none of the social factors were significant predictors of mortality at $p< 0.20$ and were not retained in the next model. Baseline depression symptoms also was not a significant contributor ($p= 0.247$) to mortality after controlling for the influence of all of the other predictors.

Table 4.3: Model 1: Results of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social and psychological predictors to mortality among depressed post MI patients (N=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.047	.007	50.194	<.001	1.048
	Female Gender	-.060	.149	.162	.688	.942
	Minority Status	.014	.151	.009	.925	1.014
	Diabetes	.383	.148	6.656	.010	1.466
	Heart Failure	1.137	.152	55.636	<.001	3.117
	Hypertension	-.009	.156	.003	.954	.991
	Prior MI	.337	.146	5.290	.021	1.400
	Prior Stroke	.380	.167	5.197	.023	1.462
	Current Smoker	-.034	.174	.038	.846	.967
Social Factors:						
	Live Alone	.106	.153	.481	.488	1.112
	Perceived Social Support	.003	.018	.020	.887	1.003
	Social Isolation	-.237	.225	1.110	.292	.789
Psychological Factor:						
	Baseline Depression Symptom Severity	.010	.009	1.338	.247	1.010

The second model combining the biological and social predictors included all variables with $p < 0.20$ in the first combined prediction models and baseline depression symptoms. In the second combined Cox regression model (see Table 4.4), biological factors of age ($p < 0.001$), diabetes ($p = 0.001$), history of heart failure ($p < 0.001$), prior MI ($p = 0.018$), and prior stroke ($p = 0.012$) were significant independent predictors of mortality. In model 1, none of the social factors were significant predictors of mortality at $p < 0.20$ and were not retained in model 2. Baseline depression symptoms also was not

a significant contributor (p= 0.408) to mortality after controlling for the influence of all of the other predictors.

Table 4.4: Model 2: Results of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social and psychological predictors to mortality among depressed post MI patients (n=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.048	.006	61.297	<.001	1.049
	Diabetes	.447	.139	10.331	.001	1.564
	Heart Failure	1.134	.150	57.182	<.001	3.108
	Prior MI	.337	.142	5.634	.018	1.400
	Prior Stroke	.412	.164	6.326	.012	1.509
Social Factors:						
	None					
Psychological Factor:						
	Baseline Depression Symptom Severity	.007	.009	.685	.408	1.007

Based on prior research showing differences between men and women in reporting depression (Kessler et al., 1993; Nolen-Hoeksema, 2001), the interaction of baseline depression and female gender was added to the model (see Table 4.5). In this analyses, both the interaction between female gender and baseline depression symptoms (p= 0.049) and the baseline depression symptoms (p= 0.038) were significant predictors of mortality.

Table 4.5: Model 3a: Results of the combined simultaneous Cox regression analysis to examine the independent contributions of biological, social, and psychological predictors, in addition to interaction between female gender and baseline depression symptoms, to mortality among depressed post MI patients (n=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.048	.006	59.892	<.001	1.049
	Female	.588	.340	2.994	.084	1.800
	Diabetes	.456	.140	10.686	.001	1.578
	Heart Failure	1.150	.150	58.627	<.001	3.158
	Prior MI	.318	.144	4.911	.027	1.375
	Prior Stroke	.415	.163	6.443	.011	1.514
Social Factors:						
	None					
Psychological Factor:						
	Baseline Depression Symptom Severity	.025	.012	4.324	.038	1.026
Interaction factor:						
	Baseline Depression symptom by Female	-.033	.017	3.876	.049	.967

Similarly, based on prior research showing differences between minorities and non-minorities in reporting depression (Ghafoori et al., 2012), the interaction of baseline depression with minority status was added to the prior model (see Table 4.6). Neither minority (p= 0.551) nor the interaction of minority status and baseline depression (p= 0.572) made an influential contribution (p= 0.572) to mortality. Thus, the model including the interaction of baseline depression symptoms and female gender was the final model.

Table 4.6: Model 3b: Results of the Cox regression analyses to examine the contributions of biological, social, and psychological predictors, in addition to the interaction between minority status and baseline depression symptoms, to mortality among depressed post MI patients (n=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.047	.006	59.058	<.001	1.049
	Minority	-.218	.365	.356	.551	.804
	Diabetes	.454	.141	10.342	.001	1.575
	Heart Failure	1.133	.150	57.175	<.001	3.105
	Prior MI	.339	.142	5.690	.017	1.404
	Prior Stroke	.418	.164	6.507	.011	1.519
Social Factors:						
	None					
Psychological Factor:						
	Baseline Depression Symptom Severity	.003	.011	.076	.782	1.003
Interaction factor:						
	Baseline Depression symptom by Minority	.010	.017	.320	.572	1.010

Age and baseline depression symptoms scores were re-centered on the lowest age in the study (34) and the lowest symptom score for depression (10), for ease of interpretation of the interaction. The final model was re-run with the centered variables. The contributions of the significant independent predictors to mortality among post MI patients who are depressed are: for every year increase in age, mortality risk increases by 4.9%; patients with diabetes have 57.8% greater risk of mortality than those without diabetes; patients with heart failure have 3.16 times the risk as those without heart failure; patients with a history of stroke have 51.4% greater risk of mortality than those without

that history; patients with a prior MI have 37.5% greater risk of mortality than those without one.

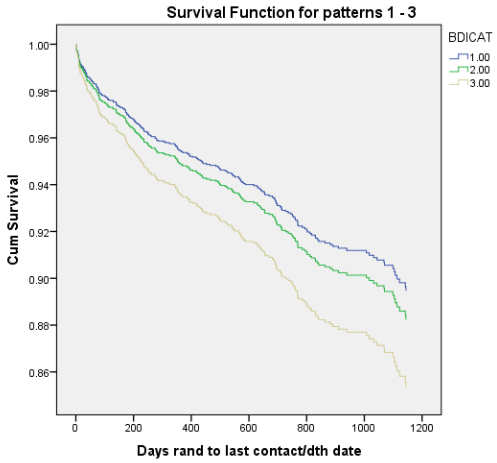
Table 4.7: Final Model: Results of a Cox regression analysis to examine the contributions of biological, social, and psychological predictors, in addition to the interaction between female gender and baseline depression symptoms, to mortality among depressed post MI patients using the centered age and centered baseline depression symptoms values (n=1834)

	B	SE	Wald	Sig.	HR	95% CI for HR	
						Lower	Upper
Biological Factors:							
Centered Age*	.048	.006	59.892	<0.001	1.049	1.04	1.06
Female	.588	.340	2.994	0.084	1.800	0.93	3.50
Diabetes	.456	.140	10.686	0.001	1.578	1.20	2.08
Heart Failure	1.150	.150	58.627	<0.001	3.158	2.35	4.24
Prior MI	.318	.144	4.911	0.027	1.375	1.04	1.82
Prior Stroke	.415	.163	6.443	0.011	1.514	1.10	2.09
Social Factors:							
None							
Psychological Factor:							
Centered Baseline Depression Symptom Severity **	.025	.012	4.324	.038	1.026	1.001	1.050
Interaction factor:							
Baseline Depression symptom by Female	-0.03	0.02	3.88	0.049	0.967	0.936	1.00

*Age re-centered on the lowest age in the study 34

** Baseline Depression Symptom Severity re-center to the lowest score of 10

Figure 4.1 Survival function for baseline BDI categories (1=BDI less than 13, 2=BDI 13 to 20, and 3=BDI greater than 20) and mortality after MI



Based on the significant interaction between gender and baseline depression symptom score, the contribution of baseline depression symptoms and gender to mortality depend upon each other. Table 4.8 includes the computed hazard ratio for male and female post MI patients with low depression symptom scores (BDI = 10) compared with those with higher depression symptoms scores (BDI= 24). Among depressed post MI patients, men with more symptoms of depression have a 42% greater risk of mortality than men with fewer symptoms of depression, women with fewer symptoms have an 80% greater risk of mortality than men with fewer symptoms of depression, women with more symptoms of depression have a 61% greater risk of mortality than men with fewer symptoms of depression. Depression was associated with increased risk of mortality for men but not for women.

Table 4.8: Estimated hazard ratio of mortality for an individual who is depressed post MI according to gender and severity of depression symptoms† with all other predictors (age, diabetes, heart failure, prior MI and prior stroke) at their average levels.

Gender	**Depression Symptoms†**	**Hazard Ratio**
Male	Low	1
Male	High	1.42
Female	Low	1.80
Female	High	1.61

†Low depression symptoms: BDI 10 the lower limit of mild depression symptom severity; high depression symptoms: BDI = 24 the lower limit of severe depression symptom severity.

Hypotheses 1(a) was partially supported with regard to mortality. Baseline depression symptoms predicted mortality, but the contribution of these symptoms to mortality depended upon the gender of the depressed post MI patient. Among depressed post MI patients, depression symptoms were associated with increased risk of mortality for men but not for women.

Aim 1(b): Predicting Morbidity

The aim 1(b) was to examine the contribution of baseline depression symptom severity to morbidity in depressed post MI patients after controlling for biological and social factors. Separate sets of analyses were conducted to examine predictors of morbidity.

The results of the individual Cox regression analyses for each predictor (see Table 4.9) demonstrated that the biological factors age ($p< 0.001$), diabetes ($p< 0.001$), history of heart failure ($p< 0.001$), hypertension ($p< 0.001$), prior MI ($p< 0.001$), prior stroke ($p< 0.001$), and current smoking status ($p< 0.001$) were significant predictors of morbidity. Female gender ($p= 0.052$) was a potentially influential ($p< 0.20$) contributor to morbidity.

Minority status (p= 0.957) was not a significant or potentially influential (p< 0.20) contributor to morbidity. The social factor live alone (p= 0.028) was a significant predictor of morbidity. Perceived social support (p= 0.763) and social isolation (p= 0.325) were not significant or influential (p< 0.20) contributors to morbidity. Without controlling for any other variables, the psychological factor, baseline depression symptom severity was a significant predictor of morbidity (p= 0.001).

Table 4.9: Results of separate Cox regression analyses to examine the contributions of each biological, social and psychological predictors to morbidity among depressed post MI patients (N=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.033	.004	71.832	<.001	1.034
	Female	.182	.094	3.782	.052	1.200
	Minority	.005	.100	.003	.957	1.005
	Diabetes	.620	.094	43.132	<.001	1.858
	Heart Failure	1.095	.105	107.865	<.001	2.990
	Hypertension	.392	.103	14.546	<.001	1.480
	Prior MI	.808	.097	70.061	<.001	2.243
	Prior Stroke	.799	.122	42.622	<.001	2.224
	Current Smoker	-.506	.111	20.609	<.001	.603
Social Factors:						
	Live Alone	.206	.094	4.828	.028	1.229
	Perceived Social Support	.002	.007	.091	.763	1.002
	Social Isolation	-.093	.094	.969	.325	.911
Psychological Factor:						
	Baseline depression symptom severity	.018	.005	11.243	.001	1.019

It was hypothesized that Baseline Depression Symptom Severity would predict morbidity after controlling for biological and social predictors. The first model combining the biological and social predictors included all variables in the individual prediction models and baseline depression symptoms. In the first combined Cox regression model (see table 4.10), biological factors of age ($p < 0.001$), diabetes ($p = 0.001$), history of heart failure ($p < 0.001$), prior MI ($p < 0.001$), prior stroke ($p = .010$) were significant independent predictors of morbidity. Current smoking status ($p = 0.193$) was an influential contributor to morbidity with $p < 0.20$ and was included in the next model. Female gender ($p = 0.255$) and minority status ($p = 0.953$) were not independent predictors of morbidity at $p > 0.20$ and thus were not included in the next model. In the first combined Cox regression model, none of the social factors were significant or influential predictors of morbidity at $p < 0.20$ and were not retained in the next model. Baseline depression symptoms was a significant contributor ($p = 0.020$) to morbidity after controlling for the influence of all of the other predictors.

Table 4.10: Model 1: Results of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social and psychological predictors to morbidity among depressed post MI patients (N=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.026	.005	31.524	<.001	1.027
	Female Gender	-.125	.110	1.295	.255	.883
	Minority Status	-.007	.112	.003	.953	.993
	Diabetes	.363	.110	10.904	.001	1.438
	Heart Failure	.640	.122	27.451	<.001	1.897
	Hypertension	-.007	.114	.004	.948	.993
	Prior MI	.458	.110	17.296	<.001	1.581
	Prior Stroke	.345	.135	6.581	.010	1.412
	Current Smoker	-.163	.126	1.691	.193	.849
Social Factors:						
	Live Alone	.138	.115	1.422	.233	1.147
	Perceived Social Support	-.001	.014	.003	.954	.999
	Social Isolation	-.174	.167	1.091	.296	.840
Psychological Factor:						
	Baseline Depression Symptom Severity	.015	.006	5.433	.020	1.015

The second model combining the biological and social predictors included all variables with p< 0.20in the first combined prediction models and baseline depression symptoms. In the second combined Cox regression model (see table 4.11), biological factors of age (p< 0.001), diabetes (p= 0.001), history of heart failure (p< 0.001), prior MI (p< 0.001), and prior stroke (p= 0.010) were significant independent predictors of morbidity. Current smoker(p=.163) remained an influential contributing (p< 0.20)

predictor to morbidity In model 1, none of the social factors were significant or influential predictor for morbidity at p< 0.20 and were not retained in model 2. Baseline Depression Symptom Severity was a significant contributor (p= 0.033) to morbidity after controlling for the influence of all of the other predictors.

Table 4.11: Model 2: Results of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social and psychological predictors of morbidity among depressed post MI patients (n=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.027	.005	35.694	<.001	1.027
	Diabetes	.360	.106	11.638	.001	1.434
	Heart Failure	.627	.121	26.754	<.001	1.872
	Prior MI	.485	.107	20.359	<.001	1.623
	Prior Stroke	.342	.133	6.554	.010	1.407
	Current Smoker	-.173	.124	1.944	.163	.841
Social Factors:						
	None					
Psychological Factor:						
	Baseline depression symptom severity	.013	.006	4.526	.033	1.013

Based on prior research showing differences between men and women in reporting depression (Kessler et al., 1993; Nolen-Hoeksema, 2001), the interaction of baseline depression and female gender was added to the model (see Table 4.12). In this analysis, neither the interaction between female gender and Baseline Depression Symptom Severity (p = 0.798) nor the baseline depression symptom severity (p= 0.083) was a significant predictor of morbidity.

Table 4.12: Model 3a: Results of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social, and psychological predictors, in addition to interaction between female gender and baseline depression symptom severity to morbidity among depressed post MI patients (n=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.028	.005	36.125	<.001	1.028
	Female	-.021	.250	.007	.933	.979
	Diabetes	.369	.106	12.066	.001	1.447
	Heart Failure	.633	.122	27.137	<.001	1.883
	Prior MI	.472	.109	18.881	<.001	1.603
	Prior Stroke	.344	.133	6.655	.010	1.411
	Current Smoker	-.176	.124	2.011	.156	.839
Social Factors:						
	None					
Psychological Factor:						
	Baseline depression symptom severity	.015	.009	2.998	.083	1.016
Interaction Factor:						
	Baseline Depression symptom by Female	-.003	.012	.065	.798	.997

Similarly, based on prior research showing differences between minorities and non-minorities in reporting depression (Ghafoori et al., 2012), the interaction of baseline depression with minority status was added to the prior model (see Table 4.13). Neither minority (p= 0.476) nor interaction of minority status and baseline depression (p= 0.528) made an influential contribution (p= 0.528) to morbidity. They were not included in the final model.

Table 4.13: Model 3b: Results of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social, and psychological predictors, in addition to interaction between minority status and baseline depression symptom severity to morbidity among depressed post MI patients (n=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.027	.005	34.379	<.001	1.027
	Minority	-.190	.266	.509	.476	.827
	Diabetes	.367	.107	11.836	.001	1.444
	Heart Failure	.625	.121	26.572	<.001	1.868
	Prior MI	.487	.108	20.487	<.001	1.628
	Prior Stroke	.345	.134	6.686	.010	1.412
	Current Smoker	-.169	.124	1.863	.172	.844
Social Factors:						
	None					
Psychological Factor:						
	Baseline depression symptom severity	.010	.008	1.497	.221	1.010
Interaction factor:						
	Baseline Depression symptom by Minority	.008	.012	.398	.528	1.008

Since there were no significant interaction between gender/minority and baseline depression symptom score, the final model selected was model 2. Age and baseline depression symptom scores were re-centered on the lowest age in the study (34) and the lowest symptom score for depression (10) for ease of interpretation. The final model was re-run with the centered variables (Table 4.14). The contributions of the significant independent predictors to morbidity among depressed post MI patients were: for every year increase in age, morbidity risk increases by 2.7%; patients with diabetes have 43.4% greater risk of morbidity than those without diabetes; patients with heart failure have

87.2% greater risk of morbidity than those without heart failure; patients with a prior MI have 62.3% greater risk of morbidity than those without one; patients with a history of stroke have 40.7% greater risk of morbidity than those without that history; for every unit increase in baseline depression symptom score, morbidity risk increases by 1.3%.

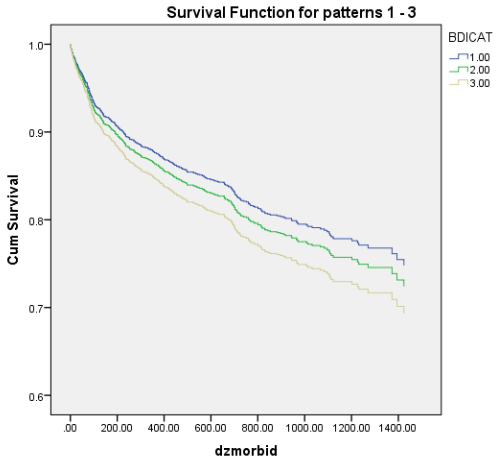
Table 4.14: Final Model: Results of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social, and psychological predictors to morbidity among depressed post MI patients using centered age and centered baseline depression symptoms values

		B	SE	Wald	Sig.	HR	95% CI for HR	
Biological Factors:							Lower	Upper
	Centered Age*	.027	.005	35.694	<.001	1.027	1.018	1.037
	Diabetes	.360	.106	11.638	.001	1.434	1.166	1.763
	Heart Failure	.627	.121	26.754	<.001	1.872	1.476	2.374
	Prior MI	.485	.107	20.359	<.001	1.623	1.315	2.004
	Prior Stroke	.342	.133	6.554	.010	1.407	1.083	1.828
	Current Smoker	-.173	.124	1.944	.163	.841	.660	1.073
Social Factors:								
	None							
Psychological Factor:								
	Centered Baseline Depression Symptom Severity**	.013	.006	4.526	.033	1.013	1.001	1.026

*Age re-centered on the lowest age in the study 34

** Baseline Depression Symptom Severity re-center to the lowest score of 10

Figure 4.2 Survival function for baseline BDI categories (1=BDI less than 13, 2=BDI 13 to 20, and 3=BDI greater than 20) and morbidity after MI



Hypotheses 1(b) was supported with regard to morbidity. Baseline depression symptoms predicted morbidity after controlling for biological and social factors.

It was noted that over 50% of the morbidity was due to death. Thus, there was the potential that predictors of mortality were overly influential in their contributions to morbidity. therefore a second analysis was performed to examine the contributions of the final model predictors to re-infarction only in the subgroup of patients who did not die (n= 1121). One hundred forty two (12.7%) of these patients experienced re-infarction.

Results of this analysis revealed that baseline depression severity was a significant independent predictor of morbidity in this subgroup. The predictors of morbidity were not overshadowed by the deaths (see Table 4.15).

Table 4.15: Final Model Without Mortality Data: Results of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social, and psychological predictors to re-infarction among depressed post MI patients who did not die prior to re-infarction using centered age and centered baseline depression symptoms values (n=1121)

	B	SE	Wald	Sig.	HR	95% CI for HR	
Biological Factors:						Lower	Upper
Centered Age*	.008	.007	1.276	.259	1.008	.994	1.021
Diabetes	.314	.159	3.910	.048	1.369	1.003	1.869
Heart Failure	-.068	.233	.084	.771	.934	.592	1.476
Prior MI	.610	.161	14.420	<.001	1.840	1.343	2.522
Prior Stroke	.344	.228	2.271	.132	1.411	.902	2.206
Current Smoker	-.266	.178	2.226	.136	.766	.540	1.087
Social Factors:							
None							
Psychological Factor:							
Centered Baseline Depression Symptom Severity**	.018	.009	4.300	.038	1.019	1.001	1.037

*Age re-centered on the lowest age in the study 34
** Baseline Depression Symptom Severity re-center to the lowest score of 10

4.3.2 Research Aim 2

Aim 2: To examine the relation of progressively worsening depression symptoms from baseline to morbidity and mortality in depressed post MI patients after controlling for biological and social factors.

Hypothesis 2: Worsening of baseline depression symptoms at 6 months predicts morbidity and mortality in the depressed post MI patients after controlling for biological and social factors.

For research aim 2 with each outcome, a model was constructed with biological and social factors as well as baseline depression, in order to control for the contributions of the other factors to the outcome variable. Biological factors examined were age, gender, minority status, and the presence of diabetes, history of heart failure, hypertension, prior MI, prior stroke and current smokers. Social factors examined were living alone, perceived social support, and social isolation. First, separate regression analyses with each individual predictor were used to examine the predictor's contribution to the outcome without controlling for any other variables. Dummy variables were used for dichotomous predictor variables. Smoking was categorized as current smoker (coded 1) and current non-smoker (coded 0).

Aim 2(a): Predicting Mortality

The results of the individual Cox regression analyses for each predictor (see Table 4.16) demonstrated that the biological factors age ($p < 0.001$), gender ($p = 0.009$), diabetes ($p < 0.001$), history of heart failure ($p < 0.001$), hypertension ($p < 0.001$), prior MI ($p < 0.001$), prior stroke ($p < 0.001$), and current smoking status ($p < 0.001$) were significant predictors of mortality. Minority status ($p = 0.604$) was not a significant or influential ($p < 0.20$) contributor to mortality. The social factors live alone ($p = 0.034$) and social isolation ($p = 0.038$) were significant predictors of mortality. Perceived social support ($p = 0.180$) contributed to mortality at $p < 0.20$ and was retained for inclusion in final models with multiple predictors. Without controlling for any other variables, the psychological factor, baseline depression symptom severity ($p = 0.152$) was not a significant predictor and the progression of depression symptoms from baseline ($p = 0.007$) was a significant predictor of mortality in depressed post MI patients.

Table 4.16: Results of separate Cox regression analyses to examine the contributions of each biological, social and psychological predictor to mortality among depressed post MI patients (N=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.055	.005	100.014	<.001	1.056
	Female	.327	.125	6.833	.009	1.387
	Minority Status	-.07	.134	.269	.604	.933
	Diabetes	.807	.126	41.040	<.001	2.242
	Heart Failure	1.614	.131	152.251	<.001	5.022
	Hypertension	.515	.141	13.371	<.001	1.673
	Prior MI	.910	.127	51.176	<.001	2.485
	Prior Stroke	.990	.152	42.587	<.001	2.691
	Current Smoker	-.591	.153	14.821	<.001	.554
Social Factors:						
	Live Alone	.265	.125	4.482	.034	1.303
	Perceived Social Support	.013	.010	1.798	.180	1.013
	Social Isolation	-.264	.127	4.325	.038	.768
Psychological Factors:						
	Baseline depression symptom severity	.011	.008	2.053	.152	1.011
	Progression of Depression Symptoms from Baseline to 6 Months*	-.027	.010	7.324	.007	.973

*A large value for progression of depression (BDI) indicates a greater worsening of symptoms

It was hypothesized that progressively worsening depression symptoms from baseline would predict mortality after controlling for biological and social predictors. The first model combining the biological and social predictors included all variables in the individual prediction models and the psychological predictors. In the first combined Cox regression model (see Table 4.17), biological factors of age ($p= 0.001$), diabetes ($p< 0.001$), and history of heart failure ($p< 0.001$) were significant independent predictors of mortality. Prior MI ($p= 0.179$) and prior stroke ($p= 0.20$) were influential contributors to mortality ($p< 0.20$) and were included in the next model. Female gender ($p= 0.416$), minority status ($p= 0.484$), hypertension ($p= 0.748$), and current smoking status ($p= 0.349$) were not independent predictors or influential predictors ($p< 0.20$) of mortality and hence were not included in the next model. In the first combined Cox regression model, none of the social factors were significant predictors of influential contributors to ($p< 0.20$) mortality and were not retained in the next model. Baseline depression symptom severity was not a significant or influential contributor ($p= 0.230$) to mortality after controlling for the influence of all of the other predictors. Progression of depression symptom severity from baseline ($p= 0.013$) was a significant predictor to mortality after controlling for the influence of other predictors.

Table 4.17: Model 1: Results of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social and psychological predictors to mortality among depressed post MI patients (N=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.035	.010	11.784	.001	1.035
	Female Gender	-.187	.230	.662	.416	.829
	Minority Status	.161	.230	.490	.484	1.175
	Diabetes	.850	.236	13.011	<.001	2.340
	Heart Failure	1.226	.236	27.083	<.001	3.407
	Hypertension	-.081	.254	.103	.748	.922
	Prior MI	.301	.224	1.804	.179	1.352
	Prior Stroke	.337	.266	1.603	.205	1.400
	Current Smoker	-.264	.281	.879	.349	.768
Social Factors:						
	Live Alone	.024	.239	.010	.921	1.024
	Perceived Social Support	.010	.029	.121	.728	1.010
	Social Isolation	-.324	.354	.840	.359	.723
Psychological Factors:						
	Baseline depression symptom severity	.019	.015	1.439	.230	1.019
	Progression of Depression Symptoms from Baseline*	.030	.012	6.130	.013	1.031

*A large value for progression of depression (BDI) indicates a greater worsening of symptoms

The second model combining the biological and social predictors included all variables with $p < 0.20$ in the first combined prediction models and baseline depression symptom severity. In the second Cox regression model (see Table 4.18), biological factors of age ($p < 0.001$), diabetes ($p < 0.001$), and history of heart failure ($p < 0.001$) were significant independent predictors of mortality. Prior MI ($p = 0.160$) and prior stroke ($p = 0.129$) were influential contributors ($p < 0.20$) to mortality. In model 1, neither social factors nor baseline depression symptom severity was a significant or influential ($p <$

0.20) predictor of mortality; they were not included in model 2. Progression of depression symptoms from baseline was a significant contributor (p= 0.036) to mortality after controlling for the influence of all other predictors.

Table 4.18: Model 2: Results of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social and psychological predictors to mortality among depressed post MI patients (n=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.033	.009	12.733	<.001	1.033
	Diabetes	.960	.216	19.792	<.001	2.613
	Heart Failure	1.228	.227	29.265	<.001	3.415
	Prior MI	.303	.216	1.976	.160	1.354
	Prior Stroke	.388	.255	2.303	.129	1.473
Social Factors:						
	None					
Psychological Factor:						
	Progression of Depression Symptoms from Baseline	.023	.011	4.379	.036	1.023

*A large value for progression of depression (BDI) indicates a greater worsening of symptoms

Based on prior research showing differences between men and women in reporting depression (Kessler et al., 1993; Nolen-Hoeksema, 2001), the interaction of progression of depression symptom severity and female gender was added to the model (see Table 4.19). In this analysis, the interaction between female gender and progression of depression symptoms from baseline (p= 0.154) was not a significant predictor of mortality and was not retained in the final model.

Table 4.19: Model 3a: Results of combined simultaneous Cox regression analysis to examine the independent contributions of biological, social, and psychological predictors, in addition to the interaction between female gender and progression of depression symptoms from baseline to mortality among depressed post MI patients (n=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.033	.009	12.798	<.001	1.034
	Female	-.279	.241	1.339	.247	.757
	Diabetes	.977	.219	19.798	<.001	2.655
	Heart Failure	1.231	.227	29.364	<.001	3.424
	Prior MI	.309	.217	2.031	.154	1.362
	Prior Stroke	.359	.257	1.956	.162	1.432
Social Factors:						
	None					
Psychological Factor:						
	Progression of Depression Symptoms from Baseline to 6 months	.037	.015	6.000	.014	1.038
Interaction Factor:						
	Progression of Depression from Baseline by Female*	.031	.022	2.032	.154	1.031

*A large value for progression of depression (BDI) indicates a greater worsening of symptoms

Similarly, based on prior research showing differences between minorities and non-minorities in reporting depression (Ghafoori et al., 2012), the interaction of progression of depression symptom severity (from baseline to 6 months) with minority status was added to the prior model (see Table 4.20). The interaction of minority status and progression of depression symptoms made a significant contribution (p= 0.001) to mortality and was included in the final model.

Table 4.20: Model 3b: Results of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social, and psychological predictor, in addition to interaction between minority status and progression of depression symptoms from baseline to mortality among depressed post MI patients (n=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.035	.009	14.525	<.001	1.036
	Minority	-.336	.263	1.638	.201	.715
	Diabetes	.938	.220	18.193	<.001	2.554
	Heart Failure	1.226	.227	29.265	<.001	3.408
	Prior MI	.344	.216	2.519	.112	1.410
	Prior Stroke	.311	.258	1.457	.227	1.365
Social Factors:						
	None					
Psychological Factor:						
	Progression of Depression Symptoms from Baseline	.052	.014	13.710	<.001	1.053
Interaction Factor:						
	Progression of Depression from Baseline by Minority*	.070	.022	10.306	.001	1.072

*A large value for progression of depression (BDI) indicates a greater worsening of symptoms

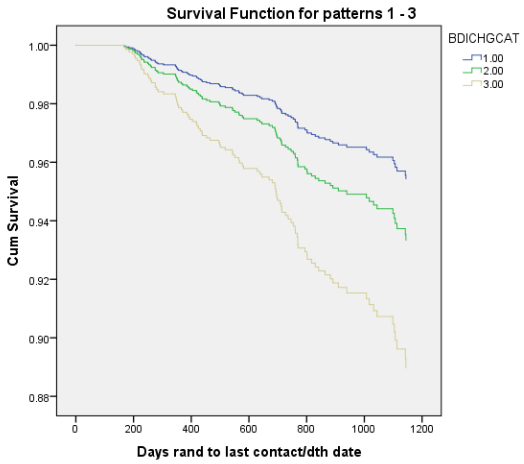
Age and progression of depression symptom severity from baseline were re-centered on the lowest age in the study (34) and the lowest depression symptom score change from baseline (-48) for ease of interpretation. The final model was re-run with the centered variables (see Table 4.21). The contributions of the significant independent predictors to mortality among depressed post MI patients were: for every year increase in age, mortality risk increases by 3.6%; patients with diabetes have 2.55 times the risk as those without diabetes; patients with heart failure have 3.41 times the risk as those without heart failure.

Table 4.21: Final Model: Results of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social, and psychological predictors, in addition to interaction between minority status and progression of depression symptoms from baseline to mortality among depressed post MI patients (n=1834) using the centered age and progression depression symptoms

	B	SE	Wald	Sig.	HR	95% CI for HR	
Biological Factors:						Lower	Upper
Centered Age*	.036	.009	15.055	<.001	1.036	1.018	1.055
Minority	-.350	.263	1.779	.182	.704	.421	1.179
Diabetes	1.000	.217	21.221	<.001	2.718	1.776	4.159
Heart Failure	1.252	.221	32.010	<.001	3.497	2.266	5.396
Prior MI	.366	.214	2.922	.087	1.442	.948	2.195
Social Factors:							
None							
Psychological Factor:							
Centered Progression of Depression symptoms from Baseline to 6 months**	.047	.014	11.610	.001	1.049	1.020	1.077
Interaction Factor:							
Progression of Depression from Baseline by Minority***	-.065	.022	9.141	.002	.937	.898	.977

*Age re-centered on the lowest age of 34
** Progression of depression symptom severity from baseline re-centered on lowest depression score change of -48
***A large value for progression of depression (BDI) indicates a greater worsening of symptoms.

Figure 4.3 Survival function for change in baseline BDI categories (1=BDI change less than -11, 2=BDI change -11to -4, and 3=BDI change greater than -5) and mortality after MI



Based on the significant interaction between minority and progression of depression, the contribution of progression of depression and minority to mortality depended upon each other. Table 4.22 includes the computed hazard ratio for minority and non-minority post MI patients with no change in depression symptom (centered BDI change = 0) compared with those with higher depression symptoms scores (centered BDI change = 20). Whites with high depression worsening had 2.83 times the risk of mortality when compared to whites with no depression change. Minority with no depression change had a 29% reduction in mortality than whites with no depression change. Minority participants with high depression worsening were 8.20 times more at risk of mortality when compared to whites with no depression change. Progression in depression symptom severity from baseline was associated with more drastic increased risk of mortality for minorities than for whites.

Table 4.22: Estimated hazard ratio of mortality for an individual who is depressed post MI according to progression of depression symptoms and minority status with all other predictors (age, diabetes, heart failure, prior MI and prior stroke) at their average levels

	Progression of Depression Symptoms†	**Hazard Ratio**
White	No	1
White	High	2.83
Minority	No	0.71
Minority	High	8.20

†No progression of depression symptoms: BDI change of 0; high progression of depression symptoms: BDI change of 20.

Hypothesis 2(a) was partially supported with regard to mortality. Progression of depression symptoms from baseline predicted mortality, based on minority status. Among depressed post MI patients, the contribution of progression of depression symptom from baseline was greater in minority than in whites.

Aim 2(b): Predicting Morbidity

Aim 2(b) was to examine the contribution of progression of depression symptoms from baseline to morbidity in depressed post MI patients after controlling for biological and social factors.

The results of the individual Cox regression analyses for each predictor (see Table 4.23) demonstrated that the biological factors age ($p< 0.001$), diabetes ($p< 0.001$), history of heart failure ($p< 0.001$), hypertension ($p< 0.001$), prior MI ($p< 0.001$), prior stroke ($p< 0.001$), and current smoking status ($p< 0.001$) were significant predictors of morbidity. Female gender ($p= 0.052$) was an influential ($p< 0.20$) contributor to morbidity. Minority status ($p= 0.957$) neither was a significant nor an influential ($p< 0.20$) contributor to

morbidity. The social factor live alone (p= 0.028) was a significant predictor of morbidity. Perceived social support (p= 0.763) and social isolation (p= 0.325) were not significant or potentially influential (p< 0.20) contributors to morbidity. The psychological factor baseline depression symptom severity (p= 0.001) was a significant contributor to morbidity. Without controlling for any other variables, progression of depression symptoms from baseline (p= 0.143) was an influential contributor (p< 0.20) to morbidity in depressed post MI patients.

Table 4.23: Results of separate Cox regression analyses to examine the independent contributions of each biological, social and psychological predictors to morbidity among depressed post MI patients (N=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.033	.004	71.832	<.001	1.034
	Female Gender	.182	.094	3.782	.052	1.200
	Minority Status	.005	.100	.003	.957	1.005
	Diabetes	.620	.094	43.132	<.001	1.858
	Heart Failure	1.095	.105	107.865	<.001	2.990
	Hypertension	.392	.103	14.546	<.001	1.480
	Prior MI	.808	.097	70.061	<.001	2.243
	Prior Stroke	.799	.122	42.622	<.001	2.224
	Current Smoker	-.506	.111	20.609	<.001	.603
Social Factors:						
	Live Alone	.206	.094	4.828	.028	1.229
	Perceived Social Support	.002	.007	.091	.763	1.002
	Social Isolation	-.093	.094	.969	.325	.911
Psychological Factor:						
	Baseline Depression Symptom Severity	.018	.005	11.243	.001	1.019
	Progression of Depression symptom from Baseline to 6 months*	.010	.007	2.145	.143	1.010

*A large value for progression of depression (BDI) indicates a greater worsening of symptoms.

It was hypothesized that progressively worsening depression symptom from baseline would predict morbidity after controlling for biological and social predictors. The first model combining the biological and social predictors included all variables in the individual prediction models including baseline depression symptom severity and progression of depression symptoms. In the first combined Cox regression model (see Table 4.24), biological factors of age ($p< 0.008$), diabetes ($p= 0.001$), history of heart failure ($p= 0.006$), prior MI ($p< 0.001$), and stroke ($p= 0.010$) were significant independent predictors of morbidity. Female gender ($p= 0.095$) and current smoking status ($p= 0.169$) were influential contributors ($p< 0.20$) to morbidity and were included in the next model. Minority status ($p= 0.789$) and history of hypertension ($p= 0.936$) were not predictors of morbidity at $p< 0.20$ and were excluded from the next model. In the first combined Cox regression model, none of the social factors were predictors of morbidity at $p> 0.20$; they were not included in the next model. After controlling for biological and social factors, baseline depression symptom severity ($p= 0.054$) and progression of depression symptoms from baseline ($p= 0.066$) tended to contribute to morbidity.

Table 4.24: Model 1: Results of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social and psychological predictors to morbidity among depressed post MI patients (N=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.016	.006	7.024	.008	1.016
	Female	-.239	.143	2.793	.095	.788
	Minority Status	.038	.143	.072	.789	1.039
	Diabetes	.493	.143	11.937	.001	1.637
	Heart Failure	.460	.169	7.406	.006	1.584
	Hypertension	.012	.150	.006	.936	1.012
	Prior MI	.516	.143	13.052	<.001	1.676
	Prior Stroke	.466	.180	6.718	.010	1.593
	Current Smoker	-.223	.162	1.891	.169	.800
Social Factors:						
	Live Alone	.140	.152	.856	.355	1.151
	Perceived Social Support	-.004	.018	.059	.808	.996
	Social Isolation	-.195	.219	.790	.374	.823
Psychological Factors:						
	Baseline Depression Symptom severity	.018	.009	3.716	.054	1.018
	Progression of Depression Symptoms from Baseline to 6 months*	.015	.008	3.384	.066	1.015

*A large value for progression of depression (BDI) indicates a greater worsening of symptoms.

The second model combining the biological and social predictors included all variables with $p < 0.20$ in the first combined prediction models and the baseline depression symptom severity and progression of depression symptoms from baseline to 6 months. In the second combined Cox regression model (see Table 4.25), biological factors of age ($p = 0.005$), diabetes ($p < 0.001$), history of heart failure ($p = 0.011$), prior MI ($p < 0.001$), prior stroke ($p = 0.009$) were significant independent predictors of morbidity. Female gender ($p = 0.183$) and current smoking status ($p = 0.111$) were

influential contributor (p< 0.20) to morbidity. In model 1, none of the social factors were not predictors of morbidity at p> 0.20; they were not included in model 2. Both baseline depression symptom severity (p= 0.029) and progression of depression symptoms from baseline (p= 0.041) were significant contributors to morbidity after controlling for the influence of all other predictors.

Table 4.25: Model 2: Result of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social and psychological predictors of morbidity among depressed post MI patients (n=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.017	.006	7.813	.005	1.017
	Female	-.179	.135	1.769	.183	.836
	Diabetes	.519	.138	14.095	<.001	1.680
	Heart Failure	.429	.168	6.536	.011	1.536
	Prior MI	.521	.141	13.672	<.001	1.683
	Prior Stroke	.461	.177	6.774	.009	1.586
	Current Smoker	-.255	.160	2.545	.111	.775
Social Factors:						
	None					
Psychological Factor:						
	Baseline Depression Symptom Severity	.019	.009	4.795	.029	1.019
	Progression of Depression Symptoms from Baseline*	.016	.008	4.162	.041	1.016

*A large value for progression of depression (BDI) indicates a greater worsening of symptoms.

Based on prior research showing differences between men and women in reporting depression (Kessler et al., 1993; Nolen-Hoeksema, 2001), the interaction of progression of depression symptoms and female gender was added to the model (see Table 4.26). In this analyses, the interaction between female gender and progression of

depression symptoms (p= 0.526) was not a significant or influential predictor of morbidity; it was not included in the final model.

Table 4.26: Model 3a: Results of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social, and psychological predictors, in addition to interaction between female gender and progression of depression symptom from baseline to morbidity among depressed post MI patients (n=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.017	.006	7.862	.005	1.017
	Female	-.237	.163	2.108	.147	.789
	Diabetes	.519	.138	14.103	<.001	1.681
	Heart Failure	.430	.168	6.583	.010	1.538
	Prior MI	.524	.141	13.846	<.001	1.688
	Prior Stroke	.452	.178	6.478	.011	1.572
	Current Smoker	-.256	.160	2.566	.109	.774
Social Factors:						
	None					
Psychological Factor:						
	Baseline Depression Symptom Severity	.019	.009	4.647	.031	1.019
	Progression of Depression Symptoms from Baseline*	.020	.010	3.939	.047	1.020
Interaction factor:						
	Progression of Baseline Depression Symptoms *by Female	.009	.014	.402	.526	1.009

*A large value for progression of depression (BDI) indicates a greater worsening of symptoms.

Similarly, based on prior research showing differences between minorities and non-minorities in reporting depression (Ghafoori et al., 2012), the interaction of progression of depression symptoms from baseline with minority status was added to model 2 (see Table 4.27). The interaction of minority status and progression of

depression symptom from baseline made an influential contribution (p= 0.079) to morbidity and was included in the final model.

Table 4.27: Model 3b: Results of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social, and psychological predictors, in addition to interaction between minority status and progression of baseline depression symptoms to morbidity among depressed post MI patients (n=1834)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.017	.006	8.262	.004	1.017
	female	-.179	.136	1.754	.185	.836
	Minority	-.152	.173	.780	.377	.859
	Diabetes	.517	.139	13.811	<.001	1.677
	Heart Failure	.436	.168	6.771	.009	1.547
	Prior MI	.533	.141	14.214	<.001	1.704
	Prior Stroke	.436	.178	5.976	.015	1.546
	Current Smoker	-.236	.160	2.184	.139	.790
Social Factors:						
	None					
Psychological Factor:						
	Baseline Depression Symptom Severity	.019	.009	4.594	.032	1.019
	Progression of Depression Symptoms from Baseline*	.025	.009	7.288	.007	1.026
Interaction factor:						
	Progression of Baseline Depression Symptoms* by Minority	.025	.014	3.089	.079	1.025

*A large value for progression of depression (BDI) indicates a greater worsening of symptoms.

Since there were an influential interaction between minority and progression of depression symptom, the final model selected was model 3b. Age and baseline depression symptom scores were re-centered on the lowest age in the study (34) and the lowest progression of depression symptom from baseline (-48) for ease of interpretation. The final model was re-run with the centered variables (Table 4.28). The contributions of the

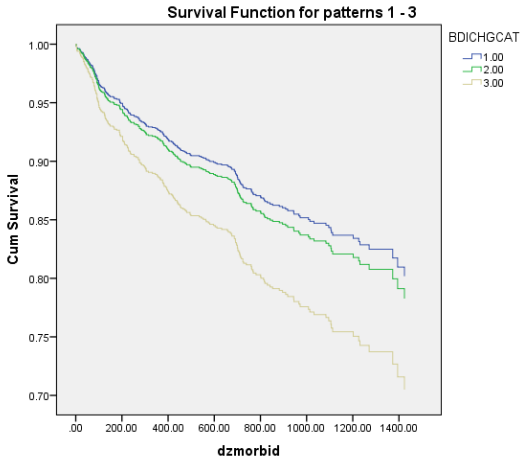
significant independent predictors to morbidity among depressed post MI patients were: for every year increase in age, morbidity risk increases by 1.7%; patients with diabetes have 68% greater risk of morbidity than those without diabetes; patients with history of heart failure have a 54.7% greater risk of morbidity than those without; patients with prior MI have a 70.4% greater risk of morbidity than those with no prior MI; patients with prior stroke have a 54.6% greater risk than those without; for every unit increase in baseline depression symptoms, morbidity risk increases by 1.9%; for every unit increase in progression of depression symptoms, morbidity risk increases by 2.6%.

Table 4.28: Final Model: Results of combined simultaneous Cox regression analysis to examine the independent contributions of biological, social, and psychological predictors, in addition to interaction between minority status and progression of baseline depression symptoms to morbidity among depressed post MI patients (n=1834)

	B	SE	Wald	Sig.	HR	95% CI for HR	
Biological Factors:						Lower	Upper
Centered Age*	.02	.01	8.26	.004	1.02	1.005	1.03
female	-.18	.14	1.75	.185	.84	.64	1.09
Minority	-.15	.17	.78	.377	.86	.61	1.20
Diabetes	.52	.14	13.81	<.001	1.68	1.28	2.20
Heart Failure	.44	.17	6.77	.009	1.55	1.11	2.15
Prior MI	.53	.14	14.21	<.001	1.70	1.29	2.25
Prior Stroke	.44	.18	5.98	.015	1.55	1.09	2.19
Current Smoker	-.24	.16	2.18	.139	.79	.58	1.08
Social Factors:							
None							
Psychological Factor:							
Baseline Depression Symptom Severity	.02	.01	4.59	.032	1.02	1.00	1.04
Centered Progression of Depression Symptoms from Baseline to 6months**	.03	.01	7.29	.007	1.03	1.01	1.04
Interaction factor:							
Progression of Baseline Depression Symptoms*** by Minority	-.03	.01	3.09	.079	.98	.95	1.00

*Age re-centered on the lowest age of 34
** Progression of depression symptom severity from baseline re-centered on lowest depression score change of -48
***A large value for progression of depression (BDI) indicates a greater worsening of symptoms.

Figure 4.4 Survival function for change in baseline BDI categories (1=BDI change less than -11, 2=BDI change -11to -4, and 3=BDI change greater than -5) and morbidity after MI



Hypothesis 2(b) was supported with regard to morbidity. Progression of depression symptoms from baseline predicted morbidity after controlling for biological, social, psychological factors.

It was noted that over 50% of the morbidity was due to death. Thus there was the potential that predictors of mortality were overly influential in their contributions to morbidity. Therefore, a second analysis was performed to examine the contributions of the final model predictors to re-infarction only in the subgroup of patients who did not die. In this analysis, change in symptoms of depression was not an independent predictor of re-infarction. This analysis suggests that the relationship of worsening of depression symptoms to mortality may have been responsible for the relationship of the worsening symptoms to morbidity as indicated above (see Table 4.29).

Table 4.29: Final Model Without the Mortality Data: Results of combined simultaneous Cox regression analysis to examine the independent contributions of biological, social, and psychological predictors, in addition to interaction between minority status and progression of baseline depression symptoms to re-infraction among depressed post MI patients who did not die prior to re-infarction (n=1121)

	B	SE	Wald	Sig.	HR	95% CI for HR	
Biological Factors:						Lower	Upper
Centered Age*	.009	.008	1.296	.255	1.009	.994	1.024
female	-.192	.178	1.168	.280	.825	.582	1.169
Minority	-.057	.227	.062	.803	.945	.606	1.473
Diabetes	.322	.182	3.119	.077	1.380	.965	1.972
Heart Failure	-.205	.277	.551	.458	.814	.474	1.400
Prior MI	.644	.182	12.585	<.001	1.904	1.334	2.718
Prior Stroke	.576	.244	5.593	.018	1.779	1.104	2.869
Current Smoker	-.204	.197	1.077	.299	.815	.554	1.199
Social Factors:							
None							
Psychological Factor:							
Baseline Depression Symptom Severity	.024	.011	4.335	.037	1.024	1.001	1.047
Centered Progression of Depression Symptoms from Baseline to 6m**	.009	.012	.553	.457	1.009	.985	1.034
Interaction factor:							
Progression of Baseline Depression Symptoms*** by Minority	.001	.018	.003	.955	1.001	.966	1.037

*Age re-centered on the lowest age of 34
** Progression of depression symptom severity from baseline re-centered on lowest depression score change of -48
***A large value for progression of depression (BDI) indicates a greater worsening of symptoms.

4.3.3 Research Aim 3

Aim 3: To compare mortality and morbidity between treatment-resistant and treatment respondent depression in depressed post MI patients. The third hypothesis is that depressed post MI patients with treatment-resistant depression have a higher risk of mortality when compared to treatment-respondent patients.

In aim 3, subjects were limited to depressed post MI patients in ENRICHD trial who received treatment for depression regardless of their assigned group placement. Aim 3 participants received cognitive behavior treatment (CBT) (n=469, 60.9%), or antidepressant medication (n=85, 11%), or both (n=216, 28.1%). Patients were classified as treatment resistant depression (TRD) when total HAM-D score is not decreased more than 50% from baseline with a total HAM-D score above 10 after completing depression treatment. Treatment respondent depression were patients with 6-months HAM-D of less than 10 or greater than 50% decrease in their 6-months HAM-D from baseline.

A total of 770 in ENRICHD participants received depression treatment. Treatment resistant depression was present in 103 (13.9%) of the patients who were treated for depression. Patients with TRD were significantly younger in age ($p= 0.04$) and more likely to be female gender ($p= 0.031$). Patients with TRD were significantly more likely to have hypertension ($p= 0.033$) and more likely to be a current smoker ($p= 0.007$). Two thirds of the TRD patients were diagnosed with major depression at initial assessment compared to half of the treatment respondent depressed patients ($p< 0.001$). Patients with TRD reported significantly higher depression symptom severity at baseline than those without TRD ($p< 0.001$). Patients with TRD had a significantly lower baseline perceived social support when compared to those without TRD. There were no significant differences in minority status ($p= 0.995$), education level ($p= 0.153$), body mass index ($p= 0.444$), diabetes ($p= 0.120$), history of heart failure ($p= 0.258$), prior MI ($p= 0.524$), prior stroke ($p= 0.180$), living alone ($p= 0.570$) or reported social isolation ($p= 0.176$) between TRD and non TRD patients (see Table 4.30).

Table 4.30: Comparison of Demographic Biological, Social, and Psychological Characteristics of Depressed Post MI Patients with treatment resistant and non treatment resistant depression (n=770)

Characteristics	**TRD n=103 N (%)***	**Non TRD n=667 N (%)***	
Demographics & Biological Characteristics:			
Age, mean (SD), years	57.0 (11.7)	59.5 (12.0)	t= -2.07, p= .04
Gender, female	59 (57.3)	306 (45.9)	X^2 (1)= 4.65, p=.031
Ethnicity, minority	32 (31.1)	207 (31.0)	X^2 (1)= .0, p= .995
Education:			X^2 (2)=3.76, p= .153
Basic or no HS degree	25 (24.3)	162 (24.3)	
HS without college degree	64 (62.1)	355 (53.2)	
Advanced education	13 (12.6)	133 (19.9)	
Body Mass Index, mean (SD)	29.7 (6.3)	29.2 (6.1)	t= .77, p= .444
Diabetes	42 (40.8)	222 (33.3)	X^2 (1)= 2.41, p= .120
History of Heart Failure	17 (16.5)	84 (12.6)	X^2 (1)= 1.28, p= .258
Hypertension	70 (68.0)	388 (58.2)	X^2 (1)= 4.56, p= .033
Prior MI	22 (21.4)	165(24.7)	X^2 (1)= .41, p=.524
Prior Stroke	13 (12.9)	57 (8.7)	X^2 (1)= 1.80, p=.180
Current Smoker	46 (44.7)	208 (31.2)	X^2 (1)=7.34, p= .007
Social characteristics:			
Live alone	46(44.7)	276 (41.4)	X^2 (1)= .32, p= .570
Social Support	54(52.4)	302(45.3)	X^2 (1)= 1.84, p=.176
Psychological characteristics:			X^2 (2)= 16.7,p> .001
Major Depression	69 (67.0)	329 (49.3)	
Minor Depression	28 (27.2)	320(48.0)	
Dysthymia	6 (5.8)	18 (2.7)	
Psychosocial measures:			
Baseline Depression Symptom Severity (BDI), mean (SD)	22.4 (9.3)	17.0 (7.4)	t= 6.62, p< 0.001
Baseline Perceived Social Support (ESSI), mean (SD)	22.9 (7.0)	24.7 (6.3)	t= -2.74, p= .006
Baseline Depression symptom (HAM-D), mean (SD)	20.9 (6.5)	17.4 (6.1)	t= 5.07, p< .001

*** Except where SD is noted**
BDI Beck Depression Inventory
ESSI ENRICHD Social Support Inventory
HAM-D Hamilton Depression Rating Scale
HS High School
TRD Treatment Resistant Depression

Descriptive Statistics

Descriptive statistics were evaluated for each variable. The dependent variable was mortality. All continuous independent variables were examined for missing data, outliers and normality. Normality of distributions was examined by computing skewness and kurtosis; no variables had extreme values that needed transformation (Tabachnick & Fidell, 2007). Missing data was less than five percent thus there was not a need to examine patterns of missing data (Tabachnick & Fidell, 2007). All inferential tests conducted at the 0.05 level of significance.

Dependent Variable

Mortality data

Of the 770 participants, there were 13 deaths, (13%) in the TRD group and 49 deaths (7%) in the non-TRD group. All participants followed minimum of 18 months and maximum of 4.5 years with an average of 29 months. The time to event variable used in the Cox regression mortality analyses was time enrolled in the study to time to death or to last follow-up.

Independent Variables

Demographical and Biological Data

Patients with TRD and without TRD were compared (see Table 4.30). Patients with TRD were significantly younger (p= 0.04) (mean=57.0 years, SD=11.7) than those without TRD (mean=59.5, SD= 12.0). There was a significantly [X^2 (1) =4.65, p= 0.031] higher percentage of female, with TRD (57.3%) when compared to non-TRD (45.9%). There was no significant difference in the percentage of minorities in TRD (31.1%) and non-TRD (31.0%) (p= 0.995). Biological factors used in the study were age, gender,

minority, presence of diabetes, history of heart failure, hypertension, prior MI, prior stroke, and current smoking status.

There was a significantly [X^2 (1) = 4.56, p= 0.033] higher percentage of hypertension in patients with TRD (68%) than those without TRD (58%). There were significantly more current smokers with TRD (45%) than without TRD (31%) [$X^2_{(1)}$=7.34, p= 0.007].

There were no significant differences in diabetes (p= 0.120), history of heart failure (p= 0.258), prior MI (p= 0.524), and prior stroke (p= 0.180) between patients with TRD and those without TRD.

Social Data

Social factors utilized in this study were live alone, perceived social support and social isolation. There were no significant differences in the percentage of participants who lived alone in the TRD (44.7%) compared to those without TRD (41.4%) (p= 0.570) or in the percentage of participants that reported social isolation in the TRD group compared to those without TRD (p= 0.176).

Perceived social support was significantly lower in patients with TRD (mean=22.9, SD=7.0) than those without TRD (mean=24.7, SD=6.3) [t= -2.74, p= 0.006].

Psychological Data

Depression diagnosis was determined at initial assessment via diagnostic interview as part of the eligibility criteria. Major depression was significantly more common among patients with TRD (67.0%) then those without TRD (49.3%)

[$X^2_{(2)}$=16.7,p> .001]. The frequency of TRD was examined according to gender and minority status. Sixteen percent of females (n=59) had TRD compared to 11% of males (n=44). Thirteen percent of minority (n=32) patients and 13% of non-minority (n=71) patients had TRD.

Baseline depression symptom severity was a continuous variable using BDI (Beck Depression Inventory) scale. TRD (mean= 22.4, SD=9.3) participants had a significantly higher baseline depression symptom severity when compared to non-TRD (mean=17.0, SD=7.4) participants [t= 5.07, p< 0.001].

Research Aim 3: Hypotheses

Hypothesis 3: Depressed post MI patients with TRD have a higher risk of mortality than treatment–respondent patients after controlling for biological, social, and psychological factors.

The results of the individual Cox regression analysis for each predictor (see Table 4.31) demonstrated that the biological factors age (p< 0.001), female gender (p= 0.005), diabetes (p< 0.001), history of heart failure (p< 0.001), hypertension (p= 0.002), prior MI (p< 0.001), prior stroke (p< 0.001), and current smoker (p= 0.002) were significant predictor of mortality. Minority status (p= 0.943) was not an influential (p< 0.20) contributors to mortality. The social factors live alone (p= 0.032) was a significant predictor of mortality. Perceived social support (p= 0.279) and social isolation (p= 0.446) were not significant or potentially influential contributors to mortality at p< 0.20. Baseline depression symptoms (p= 0.978) was not an influential contributor (p< 0.20) to mortality. Without controlling for any other variables, TRD (p= 0.087) had a tendency (p< 0.20) to contribute to mortality in treated depressed post MI patients.

Table 4.31: Results of separate Cox regression analyses to examine the contributions of each biological, social and psychological predictor to mortality among treated depressed post MI patients (N=770)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.048	.011	19.205	<.001	1.050
	Female Gender	.741	.266	7.791	.005	2.098
	Minority Status	.020	.272	.005	.943	1.020
	Diabetes	1.448	.272	28.401	<.001	4.255
	Heart Failure	1.495	.275	29.507	<.001	4.461
	Hypertension	1.002	.322	9.675	.002	2.723
	Prior MI	.961	.261	13.533	<.001	2.616
	Prior Stroke	1.165	.306	14.496	<.001	3.207
	Current Smoker	-1.128	.361	9.781	.002	.324
Social Factors:						
	Live Alone	.552	.258	4.591	.032	1.737
	Perceived Social Support	.022	.020	1.172	.279	1.022
	Social Isolation	-.197	.258	.582	.446	.822
Psychological Factor:						
	Baseline Depression Symptom Severity	<.001	.016	.001	.978	1.000
	Treatment Resistant Depression	.534	.312	2.927	.087	1.705

It was hypothesized that TRD predicts mortality after controlling for biological, social, and psychological predictors. The first model combined biological, social, and psychological predictors into an individual prediction model. In the first combined Cox regression model (see Table 4.32), biological factors of age (p= 0.025), diabetes (p= 0.012), and history of heart failure (p= 0.002) were significant independent predictors of mortality. Current smoking status (p= 0.143) was an influential contributor (p< 0.20) to mortality and was included in the next model. Female gender (p= 0.315), minority status (p= 0.917), history of hypertension (p= 0.303), prior MI (p= 0.501), and prior stroke (p= 0.263) were not influential predictors of mortality at p< 0.20 and were excluded from the next model. In the first combined Cox regression model, none of the social factors were influential predictors (p< 0.20) of mortality; they were excluded from the next model.

Similarly, baseline depression symptom severity was not a significant contributor (p= 0.249) to mortality. After controlling for all other factors, TRD (p= 0.076) had a tendency to contribute (p< 0.20) to mortality in treated depressed post MI patients.

Table 4.32: Model 1: Results of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social and psychological predictors to mortality among treated depressed post MI patients (N=770)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.030	.013	4.995	.025	1.030
	Female Gender	.326	.325	1.009	.315	1.386
	Minority Status	-.032	.312	.011	.917	.968
	Diabetes	.805	.319	6.359	.012	2.236
	Heart Failure	.983	.323	9.230	.002	2.672
	Hypertension	.368	.358	1.059	.303	1.446
	Prior MI	.209	.310	.453	.501	1.232
	Prior Stroke	.392	.350	1.254	.263	1.480
	Current Smoker	-.637	.434	2.150	.143	.529
Social Factors:						
	Live Alone	.253	.322	.619	.431	1.288
	Perceived Social Support	.036	.040	.794	.373	1.037
	Social Isolation	.066	.440	.023	.880	1.068
Psychological Factor:						
	Baseline Depression Symptom Severity	-.024	.021	1.326	.249	.976
	Treatment Resistant Depression	.712	.401	3.152	.076	2.038

The second model combined the biological, social, and psychological predictors with p< 0.20 from the first combined prediction model. In the second combined Cox regression model (see Table 4.33), biological factors of age (p= 0.004), diabetes (p<

0.001), and history of heart failure (p= 0.001) were significant independent predictors of mortality. Current smokers (p= 0.087) was an influential contributor (p< 0.20) to mortality. Treatment resistant depression was a significant (p= 0.046) contributor to mortality after controlling for the influence of all other predictors.

Table 4.33: Model 2: Results of a combined simultaneous Cox regression analysis to examine the independent contributions of biological, social and psychological predictors to mortality among treated depressed post MI patients (n=770)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.035	.012	8.280	.004	1.036
	Diabetes	1.069	.294	13.243	<.001	2.912
	Heart Failure	1.007	.290	12.089	.001	2.736
	Current Smoker	-.690	.403	2.932	.087	.502
Social Factors:						
	None					
Psychological Factor:						
	Treatment Resistant Depression	.691	.347	3.967	.046	1.995

Based on prior research showing differences between men and women in reporting depression (Kessler et al., 1993; Nolen-Hoeksema, 2001), the interaction of TRD and female gender was added to the model (see Table 4.34). In this analysis, the interaction between female gender and TRD (p = 0.467) was not a significant predictors of mortality and was not included in the final model.

Table 4.34: Model 3a: Results of combined simultaneous Cox regression analysis to examine the independent contributions of biological, social, and psychological predictors, in addition to interaction between female gender and TRD to mortality among treated depressed post MI patients (n=770)

		B	SE	Wald	Sig.	HR
Biological Factors:						
	Age	.034	.012	7.542	.006	1.034
	Female	.472	.331	2.039	.153	1.603
	Diabetes	1.011	.297	11.563	.001	2.748
	Heart Failure	.967	.290	11.130	.001	2.630
	Current Smoker	-.706	.403	3.071	.080	.494
Social Factors:						
	None					
Psychological Factor:						
	Treatment Resistant Depression	1.012	.579	3.058	.080	2.752
Interaction Factor:						
	Treatment Resistant Depression by Female	-.517	.710	.530	.467	.596

Similarly, base on prior research showing differences between minorities and non-minorities in reporting depression (Ghafoori et al., 2012), the interaction of baseline depression with minority status was added to the prior model (see Table 4.35). The interaction of minority status and TRD made an influential contribution (p= 0.119) to mortality and was included in the final model.

Table 4.35: Model 3b: Results of combined simultaneous Cox regression analysis to examine the independent contributions of biological, social, and psychological predictors, in addition to interaction between minority status and TRD to mortality among treated depressed post MI patients (n=770)

	B	SE	Wald	Sig.	HR
Biological Factors:					
Age	.035	.012	8.251	.004	1.036
Minority	.129	.320	.162	.687	1.138
Diabetes	1.064	.298	12.735	<.001	2.897
Heart Failure	1.021	.295	12.023	.001	2.777
Current Smoker	-.559	.407	1.888	.169	.572
Social Factors:					
None					
Psychological Factor:					
Treatment Resistant Depression	1.024	.378	7.317	.007	2.783
Interaction Factor:					
Treatment Resistant Depression by Minority	-1.717	1.102	2.426	.119	.180

Age was re-centered on the lowest age in the study (34) for ease of interpretation. The final model was re-run with the centered variable (see Table 4.36). The contributions of the significant independent predictors to mortality among treated depressed post MI patients were: for every year increase in age, mortality risk increases by 3.6%; patients with diabetes have 2.90 times the risk of those without diabetes; patients with heart failure have 2.78 times the risk of those without heart failure; patients with TRD have 2.78 times the risk of patients without TRD.

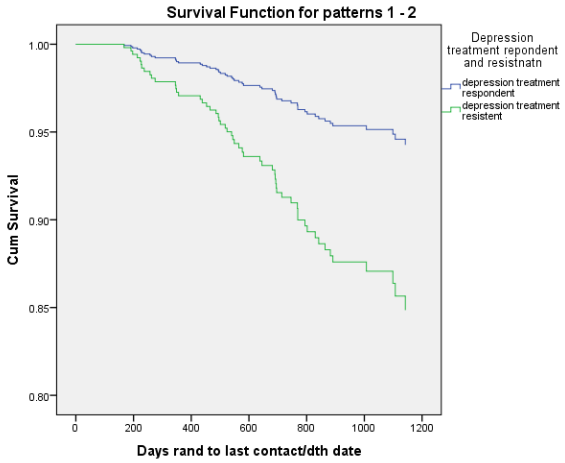
Table 4.36: Final Model: Results of combined simultaneous Cox regression analysis to examine the independent contributions of biological, social, and psychological predictors, in addition to interaction between minority status and TRD to mortality among treated depressed post MI patients using centered age (n=770)

	B	SE	Wald	Sig.	HR	95% CI for HR	
Biological Factors:						Lower	Upper
Centered Age*	.035	.012	8.251	.004	1.036	1.011	1.061
Minority	.129	.320	.162	.687	1.138	.607	2.131
Diabetes	1.064	.298	12.735	<.001	2.897	1.615	5.195
Heart Failure	1.021	.295	12.023	.001	2.777	1.559	4.947
Current Smoker	-.559	.407	1.888	.169	.572	.257	1.269
Social Factors:							
None							
Psychological Factor:							
TRD	1.024	.378	7.317	.007	2.783	1.326	5.843
Interaction factor:							
TRD by Minority	-1.72	1.102	2.426	.119	.180	.021	1.558

*Age re-centered on the lowest age of 34

TRD Treatment Resistant Depression

Figure 4.5 Survival function for depression treatment resistant and depression treatment responsive participants to mortality after MI



Hypothesis 3 was supported with regard to mortality. Treatment resistant depression predicted mortality after controlling for biological and social factors.

4.4 Summary

The three aims of the study were examined with the Cox regression analyses. The first aim was to examine the contribution of depression symptom severity at baseline to morbidity and mortality in depressed post MI patients after controlling for biological and social factors. The biological factors that were examined were age, gender, minority status, presence of diabetes, history of heart failure, hypertension, prior MI, prior stroke, and current smoker. The social factors that were examined were living alone, perceived social support, and social isolation. Separate sets of analyses were conducted to examine predictors of morbidity and mortality. According to the final model for mortality, depression symptom severity in depressed post MI patients partially predicts mortality depending on gender after controlling for biological and social factors. The controlling factors in the final model were age, gender, presence of diabetes, history of heart failure, prior MI, and prior stroke. Among depressed post MI patients, depression was associated with increased risk of mortality for men but not for women.

According to the final model for morbidity, depression symptom severity in depressed post MI patients significantly predicts morbidity after controlling for biological and social factors. The controlling factors in the final model were age, presence of diabetes, history of heart failure, prior MI, prior stroke, and current smoker. Among depressed post MI patients, higher depression symptom severity was associated with increased (HR= 1.013) risk of morbidity (see Table 37).

The second aim of the study was to examine the contribution of progressively worsening depression symptoms from baseline to 6 months to the mortality and morbidity in depressed post MI patients after controlling for biological and social factors. Separate sets of analyses were conducted to examine predictors of morbidity and mortality. According to the final model for mortality, worsening of depression symptoms from baseline in depressed post MI patients predicts mortality after controlling for biological and social factors. The controlling factors in the final model were age, minority, presence of diabetes, history of heart failure, prior MI, prior stroke, and the interaction of progression of baseline depression by minority. Among depressed post MI patients, worsening of depression symptom was associated with increased risk of mortality in minorities but not in whites.

The first model for morbidity combined the biological and social predictors in addition to baseline depression symptom severity. Predictors with significant or influential contribution were included in model 2. In the second model, age, diabetes, history of heart failure, prior MI, prior stroke, and baseline depression symptom severity were significant independent predictors of morbidity. An influential interaction between minority and progression of depression symptom was included in the final model. No significant interaction between gender and progression of depression symptom and was not included in the final model. According to the final model, progressively worsening of depression symptom in depressed post MI patients significantly predicts morbidity after controlling for biological, social, and psychological factors. The contributing factors in the final model were age, gender, minority, presence of diabetes, history of heart failure, prior MI, prior stroke, current smoker, baseline depression symptom severity, and

interaction of progression of baseline depression symptom by minority. Among depressed post MI patients, worsening depression symptom severity from baseline was associated with increased risk of morbidity (HR= 1.026) (see Table 37).

Cox regression analyses were used to examine the third aim. The third aim was to examine the mortality differences between TRD and non-TRD in depression treated depressed post MI patients after controlling for biological, social, and psychological factors. The first model for mortality combined the biological and social predictors in addition to baseline depression symptom severity. Predictors with significant or influential contribution were included in model 2. In the second model, age, diabetes, and history of heart failure were significant independent predictors of mortality. In the next model, the interaction of minority and TRD was added to the model. In this analysis, the interaction was an influential predictor of mortality and was included in the final model. There was no significant interaction between gender and TRD; therefore it was not included in the final model. According to the final model, TRD significantly predicts mortality after controlling for biological and social factors. The controlling factors in the final model were, age, minority, presence of diabetes, history of heart failure, current smoker, and the interaction of TRD by minority. Among depression treated depressed post MI patients, TRD was associated with increased risk of mortality when compared to patients without TRD (HR= 2.783).

It was noted that over 50% of the morbidity was due to death. Thus, there was the potential that predictors of mortality were overly influential in their contributions to morbidity. Therefore a second analysis was performed to examine the contributions of the final model predictors to re-infarction only in the subgroup of patients who did not

die (n= 1121). One hundred forty two (12.7%) of these patients experienced re-infarction. Results of the second analysis revealed that baseline depression severity was a significant independent predictor of morbidity in this subgroup of patients. The predictors of morbidity were not overshadowed by the deaths. However, the results of the second analysis performed to examine the contributions of the final model predictors for progression of depression symptoms revealed that re-infarction is not a predictor in this subgroup of patients who did not die. In this analysis, change in symptoms of depression was not an independent predictor of re-infarction. This analysis suggests that the relationship of worsening of depression symptoms to mortality may have been responsible for the relationship of the worsening symptoms to morbidity.

Table 4.37: Result Summary of baseline depression symptoms, progression of baseline depression symptoms, and treatment resistant depression final models to morbidity and mortality

	Mortality HR(95%CI)	**Morbidity HR[95%CI]**
Baseline Depression Symptom Severity	1.026(1.001-1.050)	1.013(1.001-1.026)
Progression of Depression Symptoms from Baseline to 6 months*	1.049(1.020-1.077)	1.026 (1.007-1.044)
Treatment Resistant Depression	2.783 (1.326-5.843)	----

*A large value for progression of depression (BDI) indicates a greater worsening of symptoms.

All hypotheses were either totally or partially supported by this study. Among depressed post MI patients, baseline depression and progression of depression predicted morbidity after controlling for biological and social factors. Among depressed post MI patients, baseline depression predicted mortality depending on gender and progression of depression of symptom predicted mortality depending on minority status after controlling for biological, psychological, and social factors. Among treated depressed post-MI

patients, TRD was a significant independent predictor of mortality after controlling for biological and social factors.

CHAPTER 5: DISCUSSION

5.1 Summary

The purpose of this study was to 1) examine the contribution of depression severity at baseline to depressed post MI patients' outcomes, 2) investigate the contributions of progressively worsening depression symptoms from baseline to 6 months in depressed post MI patients' outcomes, and 3) compare mortality rate between treatment resistant and treatment respondent depression in depressed post MI patients to patient's outcomes after controlling for biological and social factors. This study was conducted using a Limited Access Database (NHLBI, 2011) from the Enhancing Recovery in Coronary Heart Disease (ENRICHD), clinical trial. The ENRICHD trial examined mortality and morbidity in enrolled post MI patients who were diagnosed with depression and/or low perceived social support. It examined mortality and morbidity in those who were treated with psychosocial intervention compared to those receiving usual care. The ENRICHD trial started in 1995 and was completed in 2005. Patients were recruited over a 36 month period and the follow-up was continued until all patients completed 18 months of follow-up (average of 29 months).

Data from a subset of patients enrolled in ENRICHD were used as the sample for this study. The current study included only participants who were diagnosed with only depression. Participants in ENRICHD with the diagnoses of perceived low social support but without depression were not included in the current study (aim 1 and 2). The third aim addressed treatment resistant depressions (TRD). This aim was examined in the subset of depressed patients who received depression treatment. Depressed patients who did not receive any depression treatment were excluded from the sample used to examine aim 3.

The Biopsychosocial holistic model for cardiovascular health as advanced by Dr. Thomas (2008) was used to direct this study. This model provided a conceptual framework appropriate for studying the effect of depression on mortality after MI. It has a multi-dimensional approach toward health; health is the dynamic interaction of biological, social, and psychological influences as triadic reciprocally. The advantage of using this model is to view a person as a holistic entity and incorporate all factors that impact a person's health. The biological variables included in this study were age, gender, minority status, presence of diabetes, history of heart failure, prior MI, prior stroke, and current smoker. The social variables were live alone, perceived social support, and social isolation. Psychological variables were baseline depression symptom severity and progression of depression symptom severity from baseline to 6-months. In the final aim, TRD was an additional psychological factor that was examined.

The study outcomes were mortality and morbidity. Mortality was defined as the time to death or censor and morbidity was defined as the time to event or censor. Morbidity event was defined as the occurrence of non-fatal MI or death, whichever came first. The independent variables were biological, social, and psychological variables. The psychological and social variables were assessed with the BDI and ESSI scale respectively. Psychosocial measures were completed at baseline and follow-up visits. Data were analyzed using Cox regression to control for the contribution of other factors.

5.2 Participants

A total of 1834 patients enrolled in the (ENRICHD) randomized trial from 73 participating clinical sites. They had been admitted to a hospital with an acute MI and had been diagnosed with depression. The mean age of the patients was 60.2 (SD=12.3)years.

Almost half the patients were female (n=849, 46%) and over two-third were white (n=1239, 67.6%). A majority (52%) of the patients had a high school diploma with no college degree. The patient's clinical history included 35% diabetes, 14% heart failure, 60% hypertension, 28% prior MI, and 10% prior stroke. About 42% of the patients lived alone and almost half the patients reported isolation (47%). One-third of the patients were current smokers (32%), and two-thirds were former or non-smokers (68%). A majority of the patients were diagnosed with major depression (n=955, 52%), 44% with minor depression (n=814) and less than 4% with dysthymia (n=65). There were 257 deaths (14%) in the depressed patients.

In aim 3, subjects were limited to depressed post MI patients in ENRICHD trial who received treatment for depression regardless of their assigned group placement. Aim 3 participants received cognitive behavior treatment (CBT) (n=469, 60.9%), or antidepressant medication (n=85, 11%), or both (n=216, 28.1%). Patients were classified as treatment resistant depression (TRD) when total HAM-D score is not decreased more than 50% from baseline with a total HAM-D score above 10 after completing depression treatment. Treatment respondent depression were patients with 6-months HAM-D of less than 10 or greater than 50% decrease in their 6-months HAM-D from baseline.

Aim 3 study participants consisted of 770 patients that received depression treatment of which 13.4% (n=103) had treatment resistant depression (TRD) and 86.6% (n=667) were non-TRD. The TRD patients were significantly younger in age ($p= 0.04$) and more likely to be female ($p=0.031$), to have hypertension ($p=0.033$), and to be current smokers ($p=0.007$). Two thirds of the TRD patients were diagnosed with major depression compared to half of the treatment respondent depressed patients ($p< 0.001$).

Patients with TRD reported significantly higher depression symptom severity than patients without TRD ($p < 0.001$). Patients with TRD had a significantly lower baseline perceived social support when compared to patients without TRD. There were no significant differences for minority status ($p = 0.995$), education level ($p = 0.15$), body mass index ($p = 0.44$), diabetes ($p = 0.12$), history of heart failure ($p = 0.26$), prior MI ($p = 0.52$), prior stroke ($p = 0.180$), living alone ($p = 0.57$), and reported social isolation ($p = 0.176$) between TRD and non TRD patients.

5.3 Discussion

5.3.1 Aim 1

Aim 1: To examine the relation of depression symptom severity at baseline to morbidity and mortality in depressed post MI patients after controlling for biological and social factors.

The contributions of recent studies show that psychological factors, such as depression, are predictors of morbidity and mortality in patients after myocardial infarction (MI) (Carney et al., 2004; Huffman et al., 2008; Lane, Carroll & Lip, 2003). Among post MI patients, diagnoses of depression is associated with a 2 to 2.5 fold increased risk of mortality (van Melle, 2004). CHD patients with depression have a higher morbidity and mortality than CHD patients without depression (Rugulies, 2002). Based on Geerlings et al (2002)'s Aging Study, the severity of depression increases the chances of mortality. This study shows that both high baseline depression symptoms and increasing depression symptoms from the baseline are predictors of mortality in older adult patients.

Penninx et al. (2001) documented a relationship between the level of depression symptom severity and 4-year cardiac mortality among 2847 older community residents. The risk for cardiac mortality was 1.6 times increased in minor and 3 times increased in major depression patients when compared to non-depressed participants. The baseline depression symptom severity was examined in Lesperance et al. (2002) study. This study revealed that the level of depression symptom during hospital admission for MI is more predictive of long-term survival than the level at 1year. Lesperance study found that higher baseline depression symptom severity is associated with higher 5-year death rate. This is also seen in The Cardiovascular Health Study (2000) evaluating 5201 subjects with a follow-up of 6 years. This study found that higher baseline depressive symptoms were associated with higher mortality compared to lower baseline depression in older adults (Schulz et al, 2000). This has not been widely examined in depressed post MI patients. The relationship between the level of depression and cardiac outcome is limited. In the current study, the contribution of baseline depression symptom severity to mortality and morbidity in depressed post MI patients after controlling for other risk factors was examined.

In the current study the interaction between gender and baseline depression was a significant predictor of mortality. The finding of the study suggested that baseline depression symptom severity in depressed post MI patients partially predicts mortality after controlling for biological and social factors. The significant independent predictors of mortality were age, diabetes, history of heart failure, prior MI and prior stroke. Among depressed post MI patients, depression was associated with increased risk of mortality for men but not for women. The association between depression and mortality may be gender

related; however, this has rarely been examined. The finding of this study have been consistent with Zheng, et al. (1997) longitudinal study of 57,897 adults that shows an increase of all cause of mortality in patients with major depression, predominantly among men. One possible explanation may be that women are culturally more prone to report depressive complaint that may result in higher depression score than men. In other word, the same depression score in men and women may not represent the same degree of depression symptom severity. Future studies needed to explore the relationship between depression symptom severity and gender differences.

The finding of the study suggested that baseline depression symptom severity in depressed post MI patients significantly predicts morbidity after controlling for other factors. Significant independent predictors for morbidity in depressed post MI patients were age, diabetes, history of heart failure, prior MI and prior stroke. Among depressed post MI patients, higher depression symptom severity was associated with increased risk of morbidity. Studies that examined the baseline depression symptom severity morbidity in post-MI patients are limited and no comparable study was found to be contrast to this current study.

Over 50% of the morbidity was due to death. Thus, there was the potential that predictors of mortality were overly influential in their contributions to morbidity. Therefore, another analysis was performed to examine the contributions of baseline depression symptom severity on re-infarction using the variable in the final model. Results of this analysis revealed that baseline depression severity was a significant independent predictor of morbidity in this subgroup. The predictors of morbidity were not overshadowed by the deaths.

5.3.1 Aim 2

Aim 2: To examine the relation of progressively worsening depression symptoms from baseline to morbidity and mortality in depressed post MI patients after controlling for biological and social factors.

Although there are increasing evidence that depression is related to mortality in post MI patients (Geerlings et al., 2002; Kouzis et al., 1995; Pulska et al., 1998; Schoevers et al., 2000; Zheng et al., 1997; Zubenko et al., 1997), limited studies have examined the contribution of worsening of depression symptoms to mortality. Based on Geerlings et al (2002)'s Aging Study, increasing depression symptoms from baseline were predictors of mortality in older adult patients. The seven-year SADHART follow-up study suggested that failure to improve depression symptom during the 6 months following MI predicted more than doubling of mortality over 6 years of follow-up and persistent depression increased mortality in post MI patients (Glassman, Bigger & Gaffney, 2009). The present study aim was to examine the contribution of progressively worsening depression symptoms from baseline to mortality and morbidity in depressed post MI patients after controlling for biological and social factors. Progression of depression symptoms was defined as the change in the BDI score from baseline to 6 months. According to the current study, worsening of depression symptom from baseline in depressed post MI patients partially predicts mortality depending on minority status after controlling for biological and social factors. There was a significant interaction between minority and progression of depression symptom. The study showed that the significant independent predictors for mortality were age, diabetes, and history of heart failure. Among depressed post MI patients, worsening of depression symptom was

associated with increased risk of mortality that was greater in minorities than in whites. There are limited studies that show minority differences in progression of depression symptoms mortality. That may due to the reason that minority includes many different racial and ethnic groups with diverse mixed backgrounds. They have their own histories, spiritual practices and cultures that may affect the way they interpret and report their depression symptoms. Cultural influences may lead to under reporting of depression symptom among minority. Future studies are need for developing culturally sensitive tools for minority patients to ensure accurate depression symptom measurement in these patients. Genetic factors may also have a role in outcome differences in depressed post-MI minority patients. Future studies are needed to address race and ethnic disparities in depressed post MI patients and to understand the underlying causes that lead to this disparity.

The finding of this study suggested that progressively worsening of depression symptom in depressed post MI patients significantly predicts morbidity after controlling for biological, social, and psychological factors. The significant predictors of morbidity were; age, diabetes, history of heart failure, prior MI, prior stroke, and baseline depression symptoms. Among depressed post MI patients, worsening of depression symptoms was associated with increased risk of morbidity. Studies that examined the progression of depression symptom morbidity in post-MI patients are limited and no comparable study was found to be contrast to this current study.

Over 50% of the morbidity was due to death. Thus, there was the potential that predictors of mortality were overly influential in their contributions to morbidity. Therefore, another analysis was performed to examine the contributions of progression of

depression symptom severity on re-infarction using the variable in the final model. Results of this analysis revealed that worsening of depression symptom severity was not a significant independent predictor of morbidity in this subgroup. This analysis suggests that the relationship of worsening of depression symptoms to mortality may have been responsible for the relationship of the worsening symptoms to morbidity.

5.3.3 Aim 3

Aim 3: To compare mortality between treatment-resistant and treatment-respondent depression in depressed post MI patients after controlling for biological and social factors.

The third aim was examined in the subgroup of study participants who received depression treatment. Recent clinical studies show that not all depressed patients respond adequately to treatment, and their depression does not improve significantly with current depression treatments. These depressed patients are treatment resistant (Fava et al. 1996). Presently, there is limited study that shows improved outcomes of acute myocardial infarction by treating depression (Berkman et al., 2003; Glassman et al., 2002; Van Mille et al., 2002). One explanation of this may be that previous studies of post MI patients included a subgroup of patients with TRD who may have impacted the results. The presence of the TRD sub-group may cause a failure in the study's ability to show improved survival in the intervention group.

The third aim of the study was to examine the differences in mortality between patients with TRD and those without TRD in depression treated depressed post MI patients after controlling for other factors. According to the finding of this study, significant predictors for mortality among depressed post MI patients whose depression

was treated were; age, diabetes, and history of heart failure. The study findings suggested that TRD significantly predicts mortality after controlling for other factors (HR= 2.783). Among depression treated depressed post MI patients, TRD was associated with an increased risk of mortality when compared to non-TRD patients. This finding is consistence with the 7-year follow-up analysis of the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART). The SADHART was a randomized trial that examined the effect of antidepressant medication (sertraline) on depressed patients with heart disease (Glassman et al., 2002). Initial finding of the study revealed a non-significant reduction in re-current MI and death (RR=0.77;95% CI=0.51-1.16). At this time, they did not examine the difference between survival in respondent and non-respondent to depression treatment. The 7-year follow-up analysis of the SADHART trial found that patients who responded to treatment with sertraline had a reduction in mortality versus non-responders (15.6% vs. 28.4%; HR, 2.39) (Glassman, Bigger & Gaffney, 2009).

5.4 Strengths and Limitations

This study was a secondary data analysis of an existing trial. This places limitation to this study regarding control over the variable definition, measurement, data collection and other crucial aspects of the study design. With this study we were not able to establish causality of the contributions of depression symptom severity, worsening of depression symptoms or treatment-resistant depression for mortality or morbidity. The study findings were only able to provide evidence of the associations between the variables. Despite the limitations of this study, the strengths outweigh the limitations of the study. Using an existing database, this study has the advantage of providing a large

representative sample rather than a small convenience sample. Women and minorities were well represented in the ENRICHD data. The database is comprehensive including questionnaires, medical history, and the results of physical examination. ENRICHD included detailed questionnaire development, data collection procedures, data management, and quality control measures. The use of ENRICHD dataset provided an opportunity to use high quality dataset without the high cost and effort of obtaining this type and amount of data.

5.5 Human Subjects Protection

There were no human subject concerns in this study because secondary data analysis was used with data provided in a de-identified format. The University of Maryland Internal Review Board (IRB) reviewed and approved this study with full IRB review. The data files were retrieved from NBLHI after IRB approval was documented.

5.6 Implications for Nursing Practice & Future Research

This study provided this new evidence that psychological factors such as baseline depression symptom severity and progression of depression symptom from baseline predicts mortality and morbidity in depressed post MI patients. Therefore, the importance of screening and follow-up with these patients is invaluable to nursing practice. Since the risk of morbidity and mortality increased with depression, depressed patients should be recognized as a high risk population. Prevention and treatment of depression may be one of the most effective targets for interventions aimed at reducing the risk for mortality. The ability of advanced practice nurse to detect depression and follow the patient

regarding their progression of depression symptoms may have a favorable impact on patient's outcome. This is extremely important, knowing that not all depressed patients respond adequately to treatment (Fava, 1996).

The findings of this study provided evidence that depressed patients with TRD have more than triple the risk of mortality when compared with patients whose depression is effectively treated. This sub-group of depressed patients with TRD did not improve their depression symptom with their current depression treatment and are in desperate need for more efficacious depression treatment. Closer follow-ups of depression symptoms, aggressively treating other modifiable risk factors, and modifying risky health behaviors may lead to a better chance of survival in depressed post MI patients. This knowledge may assist primary care providers regarding clinical decision making that provides a better treatment options for patients.

As shown in this current study, depression is a risk factor for both mortality and morbidity among depressed post MI patients. Yet the question remains how to best treat it. The result of ENRICHD trial indicated that cognitive behavioral therapy was not effective in reducing rates of depression and mortality and the improvement in depression symptom was rather modest. The SADHART trial finding did show evidence that SSRIs modestly alleviate depression symptoms, but did not improve cardiac outcome. Future research needed to address the development of effective treatment for depression. Both ENRICHD and SADHART trials reported small effect size using current depression interventions, this suggest a need to increase efficacy of current interventions for depressed post MI patients. The results of the present study accentuate the need for future research for drug development and effective interventions to alleviate depression

symptoms in order to improve cardiac outcomes. Until more effective depression treatments are developed, future clinical trials should point out whether more holistic and integrated care for depressed persons may prevent fatal cardiac events.

The potential mechanisms linking depression and impaired cardiovascular prognosis are still poorly understood and remain an area that is in need of more research. Future studies are needed to give insights and provide evidence that will direct us toward a future in which we, health providers, are able to help and improve survival in post MI patients suffering from depression.

5.7 Conclusion

This study provided evidence that depression symptom severity and worsening of depression are independent contributors to the risk of mortality and morbidity in depressed post MI patients. TRD is also associated with increased mortality in depressed patients whose depression is treated. It is important to continue to monitor depression among post MI patients whose depression is treated. Since, TRD post-MI patients are at higher risk for mortality, closer follow-up and more aggressive risk factor modification needed to improve patients' outcomes. This may lead to an integrated treatment strategy that may decrease risk of morbidity and mortality in post MI patients.

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