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Modeling Co-Occurring Depression and Anxiety in Patients with an Acute Coronary Syndrome: A Dissertation

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MODELING CO-OCCURRING DEPRESSION AND ANXIETY IN PATIENTS WITH AN ACUTE CORONARY SYNDROME

A Dissertation Presented

By

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Thank you to Ruben for loving me and for standing by me during the hard times.

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Abstract

The purpose of the current project is to illustrate the application of advanced statistical techniques to address research questions about depression and anxiety in patients with an acute coronary syndrome (ACS). The first study, using data from 100 patients who were randomized into a clinical trial of cognitive behavioral therapy, used bivariate mixed models to determine trajectories of depression and anxiety after an ACS, to examine the effects of cognitive behavioral therapy (CBT) on depression and anxiety, and to determine if anxiety and depression symptoms change at the same rate with CBT treatment as indicated by joint modeling of these two psychiatric disorders. The findings suggest that depression and anxiety are highly correlated and persistent in patients with an ACS both at baseline and over time. The intervention used in the present investigation does not appear to uncouple the association between anxiety and depression, suggesting that CBT has comparable effects on both psychiatric disorders.

The second study used latent transition analysis to identify symptomatology profiles of depression, anxiety, and functional impairment in patients with an ACS, describe changes over time (two, three and six-month follow-up) in patient's acute symptom profiles, and determine if patients receiving CBT showed signs of remission in depression, anxiety and impaired function earlier than patients that received usual care. A three-class model was selected to identify and describe these acute symptom profiles. One class was characterized by patients with both psychiatric disorders and impaired function, the second by patients with psychiatric disorders but normal function, and the third by patients with anxiety but without depression, and having normal function. There

was moderate improvement in depression, anxiety and functional status for control patients, but this improvement was less evident than in the treatment group. Women showed a better response to CBT than men.

The third study used latent class and latent transition analysis to determine symptom profiles of depression and anxiety in patients with an ACS using the Hospital Anxiety Depression Scale; a secondary study goal was to examine the effects of age and gender on these symptom patterns. A two-class model was selected to describe depression and anxiety symptomatology profiles. Class I (76% of patients at baseline) was labeled as “severe depression and some anxiety” whereas Class II (24% of patients at baseline) was labeled as “mild depression and distress anxiety”. More than 70% of older patients continued to have severe depression and anxiety at follow-up and a large proportion of these patients who reported mild depression and anxiety at baseline showed worsening of symptoms at follow-up. The current study demonstrates that patients with depression and anxiety after an ACS can be identified on the basis of the symptoms that they present. This is particularly important to identifying individuals at potential risk for developing clinical complications after an ACS.

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Preface:

Depression and anxiety in patients with an acute coronary syndrome (ACS) are a significant and growing public health and clinical concern. Very few studies have, however, examined changing patterns of depression and anxiety over time in patients with an ACS. Furthermore, the majority of published studies have failed to examine the joint effects of depression and anxiety. This is particularly important to examine since the majority of patients with an ACS report symptoms of both disorders.

The proposed study is designed to address these gaps, and will longitudinally assess patterns and predictors of depression and anxiety in the six-month period following an ACS event using advanced statistical techniques. The results may allow clinicians to better diagnose and treat anxiety and depression. Determining the prevalence rates of depression and anxiety after hospitalization for an ACS, and factors associated with both mood disorders and their changing patterns over time, should translate into improved long-term outcomes including enhanced medication compliance, better quality of life, and improved daily functioning in patients with an ACS.

Chapter I

The acute coronary syndromes (ACS), including acute myocardial infarction and unstable angina, are a common and prevalent disease, affecting approximately 16 million Americans in the last year [1-4]. Depressive illness, ranging from dysthymia to major depressive disorder (MDD), and anxiety are highly prevalent in chronically, medically-ill individuals, including those with an ACS, than in the general population [1-3, 5]. Patients with an ACS represent a population at increased risk for depression and anxiety, although both psychiatric disorders are often underdiagnosed and less than optimally treated in these high risk patients [6]. The occurrence of depression and anxiety in patients with an ACS presents primary care clinicians with diagnostic and operational challenges. Addressing these challenges is of considerable public health and clinical interest because depression and anxiety have a significant impact on patients with an ACS and are associated with increased morbidity, declines in quality of life and function, and all-cause as well as cardiac related mortality[1].

The majority of research published to date describing the association of an ACS with anxiety and depression has been carried out during a patient's acute hospitalization or during the immediate post-hospitalization period. Few studies have, however, examined changing patterns of depression and anxiety in patients after hospitalization for an ACS and the factors associated with change in these psychiatric disorders over time [7-9]. Furthermore, the majority of published studies have failed to examine the joint effects of depression and anxiety[7-11]. This is particularly important to examine since the majority of patients with an ACS report symptoms of both disorders[11].

The overall goal of this dissertation is to determine and model the joint effects of depression and anxiety, and the factors associated with improvement in the symptoms of these two psychiatric disorders, in patients with an ACS over time**.** Data to support this goal and address study hypotheses (below) will come from a two-arm randomized controlled trial with over 250 observations of patients with an ACS who received phone-based cognitive behavioral therapy to modulate the risk of depression and anxiety. Together, both the counselors and patients identified barriers to adjustment to their medical illness and worked on strategies to address these barriers[16]. In summary, the specific aims of this dissertation include the following:

A. Specific Aims:

Aim 1: Depression and Anxiety after an Acute Coronary Syndrome: a Bivariate Mixed Model Approach: The objectives of this study were to determine trajectories of depression and anxiety after an ACS, to examine the effects of cognitive behavioral therapy (CBT) on depression and anxiety, and to determine if anxiety and depression symptoms change at the same rate with CBT treatment as indicated by joint modeling of these two psychiatric disorders.

Clinical Implications of Aim 1: The estimate for the response to an intervention using CBT will be higher when modeling anxiety and depression separately (conditional growth) than in the latent growth model in which depression and anxiety serve as the indicators of a psychiatric disorder. Although correlated, each of these indicators may provide unique and independent information to the measurement of a psychiatric disorder after modeling the overlapping effects of the two indicators.

Aim 2: Identifying Classes of Response to Treatment of Depression, Anxiety and Function in Patients After an Acute Coronary Syndrome: The objectives of this study were to (1) identify symptomatology profiles of depression, anxiety, and functional impairment among patients with an ACS; (2) describe change over time in symptomatology profile; and (3) determine if patients receiving CBT showed signs of remission in depression, anxiety and impaired function earlier than patients that received usual care. In addition, the association between symptomatology profile and age, gender, and length of stay in the hospital was examined.

Clinical Implications of Aim 2: Examining transitions between symptomatology profiles provides a detailed look at change over time that is difficult to obtain using more traditional data analytic approaches. This statistical approach assists in clarifying periods during which an intervention is most likely to be effective.

Aim 3: Profiling Symptoms of Depression and Anxiety in Acute Coronary Syndrome Patients Using Latent Class and Latent Transition Analysis: To determine the symptom profiles of depression and anxiety in patients with an ACS using the hospital anxiety and depression scale (HADS). A secondary study objective was to examine the effects of age and gender on these symptom patterns.

Clinical Implications of Aim 3: Identifying symptom profiles of depression and anxiety are useful first step towards developing more tailored interventions and improved treatment strategies. The results of the current study stress the importance of the assessment of depression and anxiety and follow-up of patients after an ACS

To accomplish these specific aims, I will conduct an analysis of longitudinal data collected from a randomized controlled trial at two coronary care units at university hospitals in Boston, MA, from September, 2001 to August, 2003.

One hundred English-speaking patients 35 years and older with symptoms of depressive illness or anxiety, as indicated by a score of 7 or higher on either of the subscales of the Hospital Anxiety Depression Scale (HADS), who had not received mental health care in the prior 3 months, psychoactive drug use during the past year, and a diagnosis of substance abuse during the past year were enrolled. The trial intervention consisted of a series of cognitive treatment sessions that helped patients identify and manage the challenges of living with a chronic condition, while patients in the control group received information on coping with cardiac illness (see more details on C.3). In addition, information was collected by telephone interviews for the following scales: the Hospital Anxiety and Depression Scale (HADS), home and work function, and patient's perceptions of their health and state anger. Information was collected at baseline (approximately one month following hospital discharge for an ACS) and at 2, 3 and 6 months after trial enrollment. Information collected from medical records, at baseline only, included demographic characteristics, presence of comorbid conditions, history and characteristics of an ACS, and treatment practices and interventions utilized in patient management (see table 1.2 for details on study sample).

The results of this dissertation will provide insights into the prevalence of depression and anxiety in patients with an ACS over time and other characteristics associated with these disorders. This dissertation will also be utilized to develop tailored

interventions to improve the symptoms of depression and anxiety in patients with an ACS.

B. Background and Significance:

B.1 Overview of acute coronary syndrome (ACS)

The acute coronary syndromes (ACS), including myocardial infarction, and unstable angina, are a major cause of morbidity and mortality worldwide[1–4]. According to recent figures, in the United States approximately 14 million people have a prevalent ACS, with more than 1 million people experiencing an acute myocardial infarction or fatal episode of coronary heart disease each year; more than 466,000 deaths are attributed to an ACS annually[21]. The ACS not only impact morbidity and mortality, but also affects quality of life, functional ability and performance at work [4].

B.2. Overview of depression and anxiety

Major Depressive Disorder (MDD) is a syndrome that includes emotional, cognitive, behavioral and somatic regulation disturbances [28]. It is usually characterized by sadness and anhedonia (inability to experience pleasure), but often includes profound abnormalities on cognition and neurovegetative, or physiological function [27]. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) bases the diagnosis of a mood disorder on the duration of symptoms, the number of symptoms present, and the presumed etiology of the syndrome. Major depressive disorder is characterized by the presence of a depressed mood or the loss of pleasure/interest for most of the day during two weeks, plus clinically significant impairment in at least five of the following areas: appetite or weight disturbance, sleep disturbance, fatigue or loss of energy, psychomotor

agitation or retardation, feelings of worthlessness, poor concentration, and recurrent thoughts of death, including suicidal ideation or attempts that have persisted for at least two weeks[13].

In contrast, dysthymia is reserved for a cluster of symptoms that have persisted over a longer period of time. The number of symptoms (at least two) needed to diagnose dysthymia is less than for MDD, but persistent depressed mood has to be present for at least two years [13]. On the other hand, the diagnosis of a mood disorder, or depressive disorder due to a general medical condition, describes a significant disturbance in mood that is directly related to the presence of a medical condition known to cause depression, as long as the mood symptoms do not meet criteria for other DSM-IV categories of depression [13].

Depressive disorders are relatively common in the general population. The recently completed National Comorbidity Survey Replication survey, an updated version of the National Comorbidity Study, a representative epidemiological study of psychiatric conditions in the general population, reported twelve-month prevalence rates of MDD and dysthymia of 6.7% and 1.5%, respectively in the general population aged 18 years and older [23]. The lifetime prevalence was 16.6% for MDD and 2.5% for dysthymia [24].

Additionally, depression imposes an important economic burden on the United States health care system. Cost-of-illness estimates for the treatment of depression were $ 83 billion in the United States in 2000. Of this amount, 62% were work-related costs (e.g. absenteeism), and one third was attributed to direct medical costs [25].

Anxiety disorders, including panic disorder, generalized anxiety disorder (GAD), specific phobias, and separation anxiety disorder, were the most prevalent lifetime psychiatric disorders reported in the National Comorbidity Survey-Replication survey. A lifetime prevalence rate of 29% for anxiety disorders, in general, and a 6% lifetime prevalence rate for GAD have been estimated [24]; this study also reported a prevalence estimate of GAD within the past 12 months of approximately 3%. The original National Comorbidity survey reported that 58% of respondents with GAD within the past 12 months also met the criteria for MDD within the last 12 months [34]. Generalized anxiety disorder is characterized by feelings of threat, restlessness, irritability, sleep disturbance, tension and symptoms such as palpitations, dry mouth, and sweating [35].

B.3. Depression and anxiety in patients with an ACS

Major depression, minor depressive disorders, and anxiety are all independent risk factors for higher mortality rates and diminished quality of life in patients with an ACS [43, 44]. Moreover, after a myocardial infarction, patients with depression have a 3.5-fold increase in cardiovascular mortality relative to patients without depression [27.] After an ACS episode, depression and anxiety appear to inhibit recovery, decrease medication compliance, and have a negative impact on social functioning and capacity to perform activities of daily living. Additionally, patients with an ACS and symptoms of depression and anxiety experience longer hospital stays and worse symptomatic (physical, mental or both) and social outcomes than those without these conditions[14], increasing the economic burden on the health care system.

Even though most of the studies reported higher mortality rates, higher morbidity and diminished quality of life in patients with an ACS with anxiety and/ or depression, there are some inconsistencies in the literature regarding the association of depression and anxiety as risks factors for increased mortality in patients with an ACS. Some studies clearly demonstrated higher mortality and morbidity rates in patients with an ACS with anxiety and/ or depression whereas a few failed to find an association [8-12]. Two studies reported that the symptoms of depression and anxiety were not associated with higher 12-month mortality in patients with an ACS [8, 12].

On the other hand, there are an extremely limited number of studies that have assessed the joint effects of depression and anxiety in patients with an ACS and the impact of these conditions on ACS related outcomes [9- 11, 17-19.] Most studies have examined the prevalence of depression and anxiety separately. These studies reported a range in the estimated prevalence of depressive symptoms in patients with an ACS from 8 to 47% and a range of clinically diagnosed depression from 11 to 39%. [5-12]. Published estimates of anxiety symptoms in patients with an ACS range from 10 to 25% [33-37]. These broad ranges of depression and anxiety estimates are due to the different instruments used to assess both psychiatric disorders and also due to the different time periods when the disorders were assessed.

In summary, it is important to better understand the joint effects of depression and anxiety, and determine if they are associated with worse outcomes than anxiety and depression alone, in patients with an ACS. It is also of considerable importance to determine the prevalence of depression and anxiety in patients with an ACS and their

joint effects on compliance with medication, morbidity, and mortality in these high-risk patients. Better understanding of these issues can lead to the development of both pharmacological and psychosocial treatments for anxiety and depression among patients with an ACS that can improve patient's prognosis and quality of life [42, 45].

B.3.1. Limitations of previous studies

While it is clear that depression and anxiety are common among patients with an ACS, there are a wide range of estimates of the extent of the problem. The studies reviewed share similar weaknesses. Most studies evaluated patients with an ACS for depression and anxiety during the acute hospitalization period [9, 11, 17]. Prevalence rates of depressive disorders and anxiety are likely to be the highest during this period and decline subsequently over time.

Few studies had prolonged follow-up of their study samples to assess prevalence and changes in the pattern of symptoms of depression and anxiety over time. This is important to evaluate for the following reasons: First, two studies demonstrated that higher sustained levels of anxiety and depression over time are associated with low medication compliance, poorer medical prognosis and increased mortality [5, 36]. Second, the lack of data makes it difficult to estimate the ongoing clinical needs of patients with an ACS and the overall public health impact of depression and anxiety in these high risk patients. Among the few studies that have addressed the longitudinal patterns of anxiety and depression symptoms, inconsistencies have been found. One study followed 37 patients that were admitted into the intensive care unit after a myocardial infarction in the UK during 1998 (mean age: 62 years, 73% men). Researchers assessed these patients for

symptoms of anxiety and depression when they were admitted into the hospital and three months later. The symptoms of depression improved significantly over time, while no changes in anxiety symptoms were apparent [19]. The average HADS anxiety scores decreased by -0.4 points (p-value = 0.69) whereas the average HADS depression scores decreased by -2.13 points (p-value=P <0.05) [19]. Another study in Norway followed more than 23,000 patients from 1995-1997(mean age: 50 years, 45% men). The results suggest that gender differences in the variation of symptoms over time; women showed an increased risk for both anxiety and depression in the first 2 years post-myocardial infarction (MI), followed by a significant reduction in these symptoms. In contrast, the risk for depression in men increased after 2 years post-MI (from 1.36 to 1.61) [11]. No significant trends were found in men (adjusted OR= 1.2, P = 0.3 for depression and adjusted OR=1.03, P = 0.92 for anxiety) [11]. A third study, where 347 patients (mean age: 63 years; 73% men) were assessed for depression and anxiety after a MI in the UK during 1995 has demonstrated that there was an improvement in the depression and anxiety scores at 3 month follow-up, but there was little overall or individual change after that time [10]. Approximately 40 % of patients met the criteria for anxiety during hospital admission and 18% met criteria for depression. There were improvements in mean scores for anxiety and depression between the time of the baseline and 3-month assessments in patients [10]. Finally, in a fourth study, researchers at two general hospitals in the UK assessed 288 MI patients (mean age: 62 years ; 75 % men) for symptoms of depression and anxiety using the Beck Depression Inventory (BDI) and the State–Trait Anxiety Inventory (STAI) in hospital, 2–15 days following MI, and 4 and 12 months

subsequently. The rates of anxiety and depression increased following hospital discharge and remained elevated during the year after the MI occurred, in approximately one third of study participants [12]. During hospitalization, 32 and 26% of the patients reported symptoms of depression and anxiety, respectively. The 4- and 12-month prevalence rates were 38 and 37% for depressive symptoms, and 42 and 40% for anxious symptoms, respectively [12].

All of these studies share a common weakness, which is that they have failed to examine the joint effects of depression and anxiety in patients with an ACS over time. This is particularly important to examine since the majority of patients with an ACS report symptoms of both psychiatric disorders and there is an important overlap of anxiety and depressive symptoms in patients with an ACS over time. An important limitation of the studies reviewed is that none compared profiles of responders vs. non-responders to the behavioral intervention. This information is very important since the response to an intervention is likely to be dependent on the patient's age, gender, level of education and other important factors. My dissertation will specifically address these gaps in the literature to improve the diagnosis and treatment of depression and anxiety in patients with an ACS. These results would translate into improved long- term outcomes including enhanced medication compliance, better quality of life, and improved daily functioning in patients with an ACS.

B.4 Complexity of diagnosing depression and anxiety in patients with an ACS

There are no evidence-based guidelines that specify how to assess depression and anxiety in patients with an ACS, including a lack of recommended assessment scales and

time-frame to conduct these assessments. As evidenced by the wide range of prevalence estimates, diagnosing depression and anxiety in patients with an ACS is a complex task. The diagnosis of depression and anxiety is usually based upon self-reported patient symptoms. Symptoms of an ACS, such as lack of energy or difficulty sleeping, overlap with symptoms of depression and anxiety. Thus, patients with an ACS often have cardiac symptoms that meet diagnostic criteria for depression and/or anxiety [6]. This lack of specificity in symptoms indicates a need for screening and diagnostic assessment tools for use in clinical practice that are able to differentiate between cardiac and psychiatric symptoms. Failure to differentiate the origin of symptoms could result in identifying false positive cases of depression, if the symptoms are incorrectly ascribed to a psychiatric disorder, resulting in unnecessary and even harmful medication treatment in medically complex patients. Improving diagnostic methods for depression and anxiety in patients with an ACS could translate into better treatment for these patients, resulting in improvements in long-term outcomes including enhanced medication compliance, quality of life, and improved functioning.

B.4.1 Common depression and anxiety assessment tools

Several instruments have been used to measure depressive symptoms in patients with an ACS (Table 1). Some of the more common instruments include: the Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (Ham-D), Patient Health Questionnaire (PHQ-9), the Primary Care Evaluation of Mental Disorders (PRIME-MD), Symptom Checklist-90 (SCL-90), Center for Epidemiologic Studies Depression (CES-D), Hospital Anxiety and Depression Scale (HADS) and the Geriatric Depression Scale

(GDS) [30-31]. Common limitations of these scales are, however, that they primarily focus on the somatic symptoms of depression, making it very difficult to differentiate symptoms related to depression from symptoms related to an ACS. The BDI, for example, includes items that focus on somatic symptoms such as lack of energy or difficulty sleeping that may overlap with several cardiac symptoms. While the PHQ-9 is easy to administer, and takes less than five minutes for patients to complete, [31] it also does not differentiate between symptoms. Many of the other measures are quite lengthy and not practical for administration in clinical settings. The best-known anxiety assessment instrument used in research is the Hamilton Rating Scale for Anxiety; this instrument, however, includes information about too many physical symptoms and is not simple to use requiring a trained interviewer to administer the scale [35]. With the exception of the HADS, no survey includes sub-scales to differentiate depression and anxiety.

The HADS overcomes several of the barriers described for measuring anxiety and depression in patients with an ACS. First, it measures both anxiety and depression independently. The HADS is both sensitive and specific in identifying pathological anxiety. The HADS also overcomes the limitation of misdiagnosis with measurement tools that assess somatic depression symptoms, because of shared ACS symptoms, by measuring cognitive depression and anxiety constructs. As such, it has resulted in lower estimated prevalence rates for depression in cardiac patients than the BDI [32]. In addition, it is easily administered in clinical settings, taking five minutes or less to complete.[31]

In summary, there are a wide range of possible scales used to assess depression and anxiety in patients with an ACS. The HADS overcomes many of the limitations of these scales and is an appropriate instrument to measure anxiety and depression in patients with an ACS.

Table 1.1: Instruments utilized to assess depression and anxiety in patients with an ACS

Instrument	Number of items	Time to complete	Items scoring range	Administration	Limitations
HADS	7	5’	0-3 (>8)	Self-report	Does not include DSM-IV criteria
PHQ-9/PRIME-MD	9	5’	0-3 (>10)	Self-report	Designed for primary care use
SCL-90	90	12-15’	0-4	Self-report	Research-oriented - psychiatric & non-psych
HAM-D	17	15-20’	0-2/0-4 (>18)	Trained-interviewer	Items overlap w/ somatic signs.
BDI	21	5-10’	0-3 (>10)	Self-report	Does not include DSM-IV criteria
BAI	21	5-10’	0-3 (>10)	Self-report	Does not include DSM-IV criteria
HAM-A	14	10’	0-4 (>18)	Trained-interviewer	Items overlap w/ somatic signs

The Hospital Anxiety Depression Scale (HADS); Patient Health Questionnaire (PHQ-9), the Primary Care Evaluation of Mental Disorders (PRIME-MD), Symptom Checklist-90 (SCL-90); Hamilton Depression Rating Scale (Ham-D); Beck Depression Inventory (BDI); Beck Anxiety Inventory (BAI); Hamilton Depression Rating Scale (Ham-A)

B.5. Significance of the proposed study

In summary, depression and anxiety in patients with an ACS is a significant and growing public health and clinical concern. The majority of research findings published to date describing anxiety and depression in patients with an ACS were conducted during hospitalization for the ACS event or in the immediate post-hospitalization period. Very few studies have examined changing patterns of depression and anxiety over time in

patients with an ACS [7-9]. Furthermore, the majority of published studies have failed to examine the joint effects of depression and anxiety[7-11]. This is particularly important to examine since the majority of patients with an ACS report symptoms of both disorders[11].

The proposed study is designed to address these gaps, and will longitudinally assess patterns and predictors of depression and anxiety in the six-month period following an ACS event. The results of the proposed study will provide much needed insights into this area of relative neglect by clinical researchers. This information will allow clinicians to better diagnose and treat anxiety and depression. Therefore, it will help to prevent the complications associated with depression and anxiety in patients with an ACS such as increased morbidity, mortality due to cardiovascular illness, and all cause mortality. Determining the prevalence rates of depression and anxiety after hospitalization for an ACS, and factors associated with higher prevalence of both psychiatric disorders and their changing patterns over time will translate into improved long-term outcomes in these high risk patients.

C. Methods:

C.1. Study Design

The proposed study will be a longitudinal analysis of data from a prospective, two-arm, randomized, controlled trial of telephone counseling intervention in patients with depression and anxiety after an ACS supported by funding from the Robert Wood Johnson Foundation. The trial compared the intervention condition, cognitive behavioral therapy (CBT), to usual care for the treatment of psychological distress in patients

surviving a recent ACS. The unit of randomization used in this study was the individual patient. Patients randomized to the CBT arm received the intervention according to a standard protocol. Although the recruitment process began with patient contact in the hospital, recruitment did not occur until one month following hospital discharge to allow for spontaneous resolution of depression and anxiety symptoms. Patients were screened at one month following discharge and those meeting predefined inclusion criteria were consented and assigned randomly to experimental or control status. Baseline survey assessments (within 30 days of hospital discharge) included the Primary Care Evaluation of Mental Disorders (PRIME-MD) and the Hospital Anxiety and Depression Scale (HADS), the primary outcome measure. The HADS and other study instruments were also administered at 2, 3, and 6 months after baseline enrollment. The study design therefore, is a randomized controlled trial with four waves of data corresponding to baseline and three follow-up time points.

C.2. Study Setting and Sample

Patients for this study were recruited from two coronary care units at the Health Centers Division (HCD) of Harvard Pilgrim Health Care, which is one of the largest Health Maintenance Organizations (HMO) in New England, serving nearly 300,000 individuals in and around Boston, MA. Patients were recruited from September, 2001 to August, 2003. The HCD provides medical services to a diverse patient population. Information on race and ethnicity is not uniformly collected, although these variables are recorded for a majority of patients from medical records. According to these data,

approximately three quarters of the patients are Caucasian, 16% African-American, 3% Hispanic, 1% Asian, and 5% other or unknown.

C.2.1 Patient inclusion/exclusion criteria

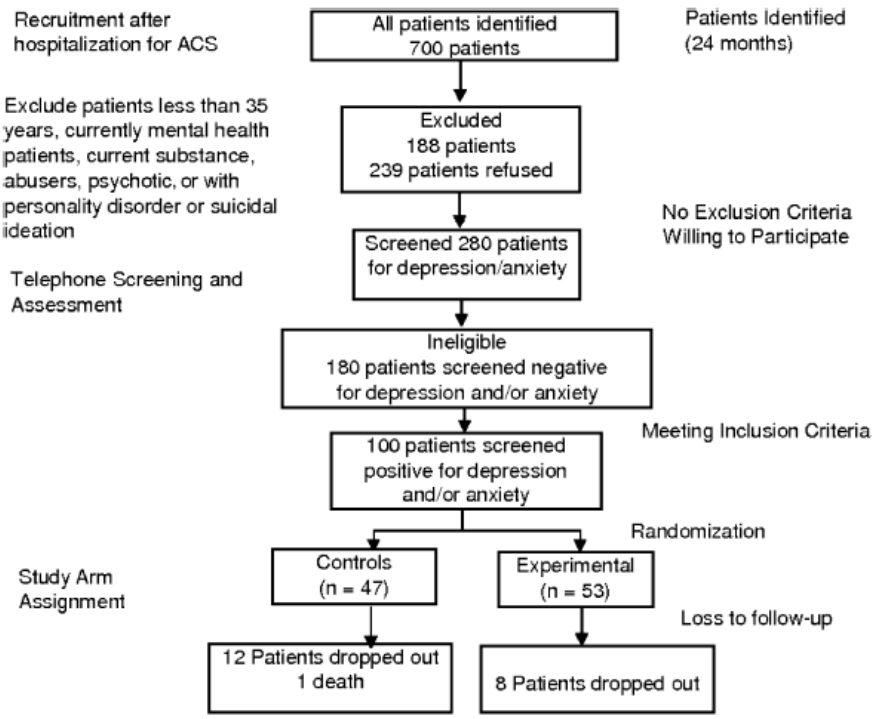
This study targeted for recruitment patients with mild to moderate levels of depression and or anxiety. Patients were eligible for trial entry based on the following eligibility requirements:

- Have an index diagnosis of an ACS, defined as unstable angina pectoris or acute myocardial infarction
- Be between 35 to 64 years of age
- Have a depression and/or anxiety score of 7 to 15 on the HADS, consistent with mild to moderate depression and/or anxiety
- Ability to speak and comprehend English
- Have access to a telephone

Patients were excluded if they met any of the following criteria:

- Exhibit any severe developmental delay or major psychological disorders
- Actively use illegal drugs or consume large amounts of alcohol daily
- Currently receive care from a mental health provider
- Are found to have severe depression or anxiety, indicated by a score of greater than 15 on either the HADS depression or anxiety scale, at time of enrollment phone call.

Figure 1.1: Enrollment and selection of participants



C.2.2. P atient Identification, Recruitment and Informed Consent

Figure 2 describes the patient identification, recruitment and enrollment algorithm for this trial. The study targeted for recruitment patients with mild to moderate levels of depression and/or anxiety who were hospitalized for an ACS. Potentially eligible patients were identified through electronic encounter data and hospital census information. The International Classification of Diseases Ninth Edition (ICD-9) diagnosis codes that were used to identify patients for this study included: 410.xx Myocardial Infarction (all codes 410.1 through 410.9), 411.1 Unstable Angina, and others associated with an ACS.

Patient recruitment began during the index hospitalization at two Boston teaching hospitals. After chart review, the research nurse contacted the patient's attending

physician for permission to approach the patient (Figure 2) with study information. The research nurse then approached the eligible patient during the hospital stay. If the patient expressed interest and chose to participate, the informed consent form was signed at that time. Otherwise, the consent forms and a self-addressed, postage-paid envelope were provided. Informed consent could be obtained for up to 30 days following hospital discharge. Once patients consented, the study coordinator administered the 14-item HADS by phone to assess symptoms of anxiety and depression. Subjects with scores between 7 and 15 on either the anxiety or depression scale were enrolled and randomized to the intervention or usual care. Randomization resulted in balanced intervention and control groups. Participants were largely older patients (mean age patients: 60.7 vs. controls: 59.9) and males (almost 70%), reflecting the descriptive epidemiology of coronary heart disease. The study coordinator was responsible for ensuring that patients met all of the inclusion/exclusion criteria for the study and completed all baseline/screening forms. The institutional review boards of the participating organizations reviewed and approved the study protocol.

C.3. Intervention

C.3.1.Intervention Group

The intervention was a cognitive treatment that helped patients identify and manage the challenges of living with a chronic condition. It was goal oriented, time limited, and issue focused. It was based on other telephone interventions targeted to treat depression by modulating the risk of depression, anxiety, and functional decrements through

improved adjustment to illness [20]. Sessions lasted for approximately 30 minutes and were conducted by doctoral-level clinicians (a psychiatrist, clinical psychologist, and internist). Patients were expected to complete six sessions, but allowed to participate in as few as three if the therapist and patient agreed that all eight issues set forth during treatment were reviewed, and that treatment goals were reached. The first contact reviewed eight fears commonly experienced by those living with chronic medical conditions: loss of control, loss of self-image, dependency, stigma, abandonment, anger, isolation, and fear of death [38]. In sessions two through six, the counselor reviewed progress toward goals with reinforcement and encouragement. A session log tracked the issues reviewed in each session. At weekly meetings, the counselors reviewed cases and notes with the research team to monitor fidelity to the intervention.

C.3.2. Control Group

Patients randomly assigned to the control group received a booklet on coping with cardiac illness typical of those given at hospital discharge and were instructed to contact their primary care physician if they experienced any warning signs of depression. They were advised to continue follow-up with their primary care and specialist physicians.

Table 1.2: Baseline demographics characteristics of study subjects by treatment status

Variable	Control (N=34) Mean (SD)	Intervention (N=45) Mean (SD)
• **Age**	60.7 (9.8)	59.9(10.2)
• **HADS Depression Scores**	6.5 (3.8)	8.5 (3.6)
• **HADS Anxiety Scores**	7.1 (2.9)	8.1 (3.7)
• **Length of stay**	3.1 (4.1)	3.6(3.3)
	Percentage (%)	**Percentage (%)**
• **Cardiac Condition**		
Angina	9	9
Other Ischemic Condition	91	91
• **Major Depression**	29	38
History of Ischemic Heart Disease	47	40
• **Race**		
Black	6	7
White	88	89
Missing	6	4
• **Gender**		
Female	35	31

C.4. Measurements

C.4.1. Longitudinal Data Collection Protocols

A data management and research organization with extensive experience in management of behavioral health data collected survey data at baseline and at 2, 3, and 6 months follow-up using interactive voice recognition (IVR). Interactive voice recognition is an automated telephone system that speaks to a patient and automatically enters

responses into a database by pressing telephone keys indicating their responses to each question. Patients are given written instructions about how and when to call into the IVR system. This approach minimizes the likelihood of contamination of control patients. Those patients who were randomized to the intervention group worked with the study coordinator to schedule the first and follow-up 30-minute calls from their counselor. An aggressive follow-up system consisting of reminder postcards, telephone call reminders, and re-mailing of questionnaires was undertaken to ensure the highest possible degree of complete data. Failure to call into the IVR system to report data triggered a fax to the study coordinator after allowing for a 3-day window for the patient to complete the call. At baseline, measures collected through the IVR included HADS, function at home and work, and self-rated health, and anger. Patients completed only the HADS at each follow-up contact point (2, 3 and 6 months).

C.4.2. Indicators of Psychologic Distress: Depression and Anxiety Symptoms

Depression and anxiety symptoms were assessed with the HADS. As described in section B.4.1., t he HADS overcomes limitations of other assessment tools because it measures depression and anxiety independently, and it assesses cognitive constructs, rather than somatic constructs, which minimizes the likelihood t hat somatic symptoms of an ACS will be attributed to depression. The HADS contains 7 depression and 7 anxiety items rated on 4-point Likert scales. Each scale is scored from 0 to 21, with 0 to 3 considered in the normal range, 4 to 7 subclinical depression, and 8 to 21 ‘‘depressed’’. The same criteria and score are used for anxiety. Patients with a score of 7 or higher on the depression or anxiety subscale at the postdischarge screening were eligible to

participate. The cutoff on the depression and anxiety scales was lenient to maximize inclusion of distressed patients, including the upper end of subthreshold depression or anxiety (upper limit of 15).

C.4.3. Demographic and Illness Variables

Baseline patient demographic and illness information was retrieved from the hospital medical records by the research nurse and study coordinator using a standardized protocol. The period of assessment included up to the point of hospital discharge. Data elements were as follows:

1. **Demographics:** age, gender and race (black, white or missing).
2. **Comorbidities:** history of ischemic heart disease in years
3. **Treatment:** cardiac procedures (coronary angioplasty, catheterization, coronary artery bypass surgery, stent placement, bypass) and use of antidepressants
4. **Severity of Disease:** hospital admission and discharge dates, length of stay, cardiac discharge diagnosis (angina with or without procedure, myocardial infarction with or without procedure and other ischemic heart disease, with or without an accompanying procedure).

C.4.4. Retention Plan

Methods to ensure retention included reminder postcards and telephone call reminders to ensure the highest possible degree of complete data.

C.5. Data Entry and Management

Baseline and follow-up data were collected at 2, 3, and 6 months using IVR. Medical records were reviewed at baseline to collect information on patient's demographics, comorbidities, treatment, severity of disease and clinical diagnosis of depression as described in D.4.3. Data were entered using double data entry into an Access Database specially constructed for the study. Once entered, the data were subject to continuous quality control efforts, thereby ensuring a clean final data set appropriate for study analyses.

C.6 Data Analysis

C.6.1 Power calculations

Latent models are complex due to the multiple partitioning of variance due to autocorrelation in repeated measures, random effects, correlation among predictor variables as well as the high correlation between anxiety and depression[55-57]. Modeling the joint effects of depression and anxiety together will give more information than in the simpler single outcome model. Once we have estimated all means, standard deviations and the random effect estimates, a post-hoc power calculation will be performed to inform the reliability and the strength of the inferences derived from the growth models.

C.6.2 Statistical software

SAS version 9.1.3 software will be used for data analysis. Recently released SAS macros and procedures will be employed for the latent class trajectory models.

C.6.3 Detailed statistical analysis for the different study aims

C.6.3.1: Aim 1: Depression and Anxiety after an Acute Coronary Syndrome: a Bivariate Mixed Model Approach

We compared unconditional means, unconditional growth models (fixed time), and conditional models (fixed time, experimental status, and time by status interaction) to examine the variance parameters of the regression models. Goodness of fit was assessed with Akaike's information criterion. We assumed a linear trend model that provided a better fit than curvilinear models. A bivariate mixed model with an unstructured covariance matrix was employed to estimate correlation coefficients for depression and anxiety over time [58]. Bivariate linear mixed models are useful when analyzing longitudinal data of two or more highly associated variables. Comparison of the correlation coefficients obtained was conducted by calculating z-statistics according to the method of Fisher [58]. We used SAS 9.1.3 software (PROC MIXED) to fit all models [58].

C.6.3.2: Aim 2: **Identifying Classes of Response to Treatment of Depression, Anxiety and Function in Patients After an Acute Coronary Syndrome:**

Latent transition analysis (LTA) was used to identify subgroups of patients with similar patterns of depression, anxiety, and function, and to describe changes over time in these patients groups. Latent transition models describe change over time in outcomes that are not directly observed. That is, the outcomes in latent transition models are inferred based on information from a set of observed variables [54-57]. The latent transition model combines cross-sectional measurement of categorical latent variables and the longitudinal description of change in categories of the latent variable over time. One important

advantage of these models is that they allow investigators to examine the impact of the intervention, CBT in this case, on change in depression, anxiety, and functional symptoms simultaneously.

Selection of the optimal model that considered both goodness of fit and parsimony was based on various statistical fit indices. Statistical indices reported in this investigation included: the Akaike information criterion (AIC), Bayesian information criterion (BIC) and G2. Model selection was also based on: the log-likelihood ratio, and the number of estimated parameters in the model [54-57]. Lower values for the BIC, AIC and G2 indicate better model fit [54-57]. Latent Transition Analysis estimates the proportion of patients in each class at each time point, and the probability of moving from one class to another, conditioned on prior membership status [54-57].

Latent Transition Analysis involves four different types of parameters: the gamma parameters, which are estimates of the proportion of the population in each latent class or subgroup [57]. The delta parameters which are estimates of the proportion of the population in each latent status at each occasion of measurement [57]. The tau parameters which refer to the conditional probability of transitioning from one latent class to another, and lastly the rho parameters, which represent measurement error, are estimates of a particular item response conditional on latent class and latent class membership [57].

C.6.3.3: Aim 3: Profiling Symptoms of Depression and Anxiety in Acute Coronary Syndrome Patients Using Latent Class and Latent Transition Analysis: Latent class analysis (LCA) and latent transition analysis (LTA) were used to identify subgroups of patients with similar patterns of depression and anxiety symptoms, and to describe

change over time in subgroup membership. Latent class analysis identifies a set of mutually exclusive and exhaustive latent classes characterized by similar patterns of responses to manifest items [54-57]. Latent transition analysis is a longitudinal extension of latent class analysis that additionally models change over time in class membership [54-57]. Latent class analysis and latent transition analysis are measurement models meaning that they separate out measurement error from other aspects of the model. Latent class analysis estimates the probabilities of responding to items in different ways given class membership, as well as the distribution of the classes. Latent transition analysis additionally estimates the probabilities of transitioning between classes over time. The 14 items of the HADS were included in the models to measure depression and anxiety symptom profile. The 14 items were re-coded so one represented never or rarely ever experiencing the symptom and two represented experiencing the symptom sometimes or most of the time

C.7: Study limitations

Several limitations of this study must be considered in interpreting my study findings.

- Generalizability: based on subject inclusion criteria, and limitations of the subject selection criteria based on baseline rates of anxiety and depression (scores from 7 to 15 in the HADS)
- Generalizability to sites other than urban, tertiary care centers and possible bias because of exclusion of individuals receiving mental health treatment in the period before the index hospitalization.

- Generalizability: minority and ethnic patients were under-represented (88% white, 6% black and 6% missing)
- Power: sample size=79 , but latent growth model based on number of observations (N=268)
- The study relied upon patient self-reports that needs to be validated with more objective outcome measures to prevent misclassification.
- Patient's dexterity and visual ability to comply with intervention (completing the HADS over the phone)

Despite these limitations, this study will provide several useful insights. This study will longitudinally assess patterns and predictors of depression and anxiety in the 6 months following an ACS event. This information will allow clinicians to better diagnose and treat anxiety and depression.

Chapter II

Depression and Anxiety after an Acute Coronary Syndrome: a Bivariate Mixed Model Approach

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Background: Depression and anxiety inhibit recovery, and have a negative impact on social functioning in patients after an acute coronary syndrome (ACS). Few studies have, however examined patterns of change in anxiety and depression after an ACS

Objectives: Determine trajectories of depression and anxiety after an ACS, to examine the effect of cognitive behavioral therapy (CBT) on depression and anxiety, and examine if anxiety and depression symptoms change at the same rate with CBT treatment as indicated by joint modeling of these two psychiatric disorders.

Participants/Measurements: A total of 100 patients with an ACS with scores on the Hospital and Anxiety Depression Scale (HADS) indicating mild to severe depression and/or anxiety at 1 month post-hospital discharge were enrolled in a randomized trial of CBT and were followed for changes in anxiety and depression at 2, 3, and 6 months post-baseline.

Main Results: The average age of study patients was 60 years and 30% were women. Patients in the intervention group had a 20% of improvement in their HADS scores at the end of the study. Patterns of changes from the joint modeling of both psychiatric disorders were similar in the intervention and control groups; the correlation, however, was significantly higher in the treatment group at all follow-up points.

Conclusions: Our results indicate that depression and anxiety are highly correlated and persistent in patients with an ACS both at baseline and over time. The intervention does not appear to uncouple the association between anxiety and depression, suggesting that CBT has comparable effects on both psychiatric disorders.

Introduction

Acute coronary syndrome (ACS), including acute myocardial infarction and unstable angina, represents common cardiac diseases in the majority of industrialized countries. Acute coronary syndrome is a leading cause of death, and disability, and also significantly impacts patient's quality of life and functional status [1]. In the United States, ACS affects approximately 16 million people [2-4]. Patients with an ACS, like other chronically, medically ill individuals, experience considerable stress in adjusting to living with their illness. Thus, it is not surprising that depression and anxiety are more prevalent in chronically physically ill individuals, including those with an ACS, than in the general population [2-3, 5 -7]. Moreover, depression and anxiety tend to occur together. Recent findings suggest that approximately 60% of depressed patients may have concomitant anxiety [8]. Patients with an ACS and symptoms of depression and anxiety not only show higher long-term morbidity and mortality but also report decreased compliance with medication , slower return to work, a nd worse quality of life than patients without symptoms of those psychiatric disorders [9-10]. Despite the high prevalence of anxiety and depression in patients with an ACS, and their role as predictors of higher morbidity and mortality, both of these common yet serious disorders are often under-diagnosed and under-treated in primary care settings [5, 8, 11]. Because of its public health importance, depression in cardiac patients has been the subject of quality improvement research including intensive and large scale mortality trials aimed at reducing risk of death through treatment of depression [2-4]. Researchers found that CBT was effective for reduction of depressive symptoms, but unfortunately there was not

much information reported about the effect of CBT on the co-occurrence of depression and anxiety and their pattern of change over time [12].

The objectives of this study were to determine the trajectories of depression and anxiety after an ACS, to examine the joint distribution of treatment effects of cognitive behavioral therapy (CBT) on depression and anxiety, and to determine if both psychiatric disorders change at the same rate accompanying CBT treatment using novel bivariate mixed model methods. Data from a previously reported randomized trial of CBT treatment of patients with an ACS were utilized to examine our study hypotheses [13].

Design and Methods:

The study group consisted of 100 patients hospitalized with an ACS in two coronary care units at a university hospital in Boston, MA, between September, 2001 and August, 2003 [13-15]. Patients were 35 years and older at the time of trial entry and had symptoms corresponding to mild to moderate levels of depression and/or anxiety as indicated by a score of seven or higher on either of the subscales of the Hospital Anxiety Depression Scale (HADS). None of the study patients had received mental health care in the prior three months, used a psychoactive drug during the past year; or were diagnosed with substance abuse during the past year. Potentially eligible patients were identified by a research nurse through the review of hospital records and hospital census information. The diagnosis codes used to identify patients for this study included acute myocardial infarction, unstable angina, and ischemic heart disease. Patients were screened at approximately one month after hospital discharge for an ACS and those meeting the predefined study inclusion criteria were randomly assigned to treatment or control status.

Patient recruitment began during the index hospitalization. Once patients consented to trial enrollment, the study coordinator administered the 14-item HADS by phone to assess the symptoms of anxiety and depression. Subjects with scores between 7 and 15 on either the anxiety or depression scale were enrolled into the trial and randomized into the intervention or usual care comparison groups.

The trial intervention consisted of a series of CBT sessions that helped patients identify and manage the challenges of living with a chronic condition [13]. Patients in the control group received information on coping with cardiac disease. Baseline survey assessments (within 30 da ys of hospital discharge) included the Primary Care Evaluation of Mental Disorders (PRIME-MD) and the Hospital Anxiety and Depression Scale (HADS), our primary outcome measure [13]. The HADS was re-administered at two, three, and six months after trial enrollment [13]. The study protocol was reviewed and approved by the institutional review board of the participating hospital.

Intervention

The trial intervention consisted of CBT that helped patients identify and manage the challenges of living with chronic cardiac disease [13]. This intervention was goal-oriented, time-limited, and issue-focused. It was based on other telephone interventions targeted to treat depression by modulating the risk of depression, anxiety, and functional decrements through improved adjustment to illness and has been well-described elsewhere [13]. Individual sessions lasted for approximately 30 minutes and were conducted by doctoral-level clinicians. Patients were expected to complete six sessions, but were allowed to participate in as few as three sessions if the therapist and patient

agreed that all issues set forth during treatment were reviewed and that treatment goals were reached. Patients randomly assigned to the control group received a booklet on coping with cardiac illness, typical of those given to patients with an ACS at the time of hospital discharge, and were instructed to contact their primary care physician if they experienced any warning signs of depression.

Data Collection Protocols

Data were collected at the time of baseline enrollment for the HADS, functional status at home and at work, and a self-rated health and anger questionnaire using interactive voice recognition (IVR) system. Patients completed only the HADS at the time of the two, three, and six month study follow-up visits. An aggressive follow-up system consisting of reminder postcards, telephone call reminders, and re-mailing of questionnaires was undertaken to enhance survey response rates.

Assessment Instrument

The HADS contains seven questions related to depression and seven related to anxiety. Each scale is scored from 0 to 21; scores between 4 and 7 represent subclinical depression whereas patients who scored 8 or higher were classified as being ‘‘depressed’’. The same criteria and scores were used for diagnosing anxiety. It is important to highlight that previous research into the dimensional structure of the HADS reported evidence for a two-factor solution that corresponded almost exactly with the anxiety and depression subscale [16]. A key element of using the HADS is that this scale focuses on cognitive rather than somatic constructs, which minimizes the likelihood that somatic symptoms of an ACS will be attributed to depression.

Data Analysis

Descriptive analyses on baseline patient characteristics were performed; t-tests and chi-square tests, as appropriate, were used to examine possible differences in baseline categorical and continuous variables between patients randomly assigned to the intervention and control groups.

We compared unconditional means, unconditional growth models (fixed time), and conditional models (fixed time, experimental status, and time by status interaction) to examine the variance parameters of the regression models. Goodness of fit was assessed with Akaike's information criterion. We assumed a linear trend model that provided a better fit than curvilinear models. A bivariate mixed model with an unstructured covariance matrix was employed to estimate correlation coefficients for depression and anxiety over time [17]. Comparison of the correlation coefficients obtained was conducted by calculating z-statistics according to the method of Fisher [17]. We used SAS 9.1.3 software (PROC MIXED) to fit all models [18, 19].

Results:

Between September, 2001 and August, 2003, a total of 706 participants were screened for potential trial enrollment. Of these, 38% were excluded based on the trial eligibility criteria, and an additional 34% declined trial participation. Of the 280 patients administered the HADS, 36% met the inclusion criterion by scoring between 7 and 15 on either or both measures. Of these patients, 47 were randomized to control status and 53 to the intervention group. Twenty eight percent of study patients dropped out of the study from the control group, which included one death. Fifteen percent of the patients from the

treatment group dropped out of the study. Dropouts were comparable with participating trial patients on various baseline characteristics as determined by standard t-tests and chi-square tests statistics.

The final cohort consisted of 79 patients (34 in the control and 45 in the intervention group). Of the 79 patients with an ACS, 37 (47%) met the study inclusion criteria for both anxiety and depression; of the remaining 42 patients, 31 met the depression, but not anxiety criterion, and 11 met the anxiety criterion solely.

At the time of randomization, the two groups were well balanced with a predominance of white, older male patients in both groups. Average depression and anxiety scores were slightly higher for the treatment group at baseline (Table 1). In examining possible differences in average depression and anxiety scores at the different study follow-up points, similar trajectories were observed in the treatment and control groups for both psychiatric disorders. There was a significant decline in the mean depression and anxiety scores from baseline that was significantly greater in the intervention group (Figures 1A and B).

Almost half of the patients assigned to the CBT group met the criteria for depression and anxiety at the time of trial enrollment. The prevalence for both psychiatric disorders was lower in the control group at the same time of assessment: 16% of these patients satisfied the criteria for anxiety and depression respectively (Table 2). The two month prevalence rates of depression and anxiety decreased by nearly one half in the treatment group but did not change in the control group. Lastly, the three and six month prevalence for both psychiatric disorders did not change, and approximately one quarter

of the patients met the criteria for depression and anxiety in the treatment and control groups.

Regression results showed a significant decrease in depression scores from baseline in the intervention group (Table 3). The final mean depression score was 1.96 units lower in the treatment group than in controls at six months. Similar results were observed for the analysis of intervention effects on anxiety scores. Regression results indicated a significant decline in the linear trend and a lower score of 2.2 units in the intervention group at six months (Table 3).

Lastly, the correlations coefficients and standard errors for the bivariate model were estimated to examine the extent of the correlation between depression and anxiety at baseline, two, three and six months and determine how these scores change in relation to CBT (Table 4). The results from the bivariate random effects model showed a strong correlation between depression and anxiety in the treatment and control groups. The correlations between anxiety and depression scores followed a similar trajectory in the intervention and control group over time (Figure 2), but the estimated correlation coefficients were higher in the treatment group at the different time points (Table 4). These higher correlation coefficients may be related to the differential effects of the intervention in the treatment group.

Discussion:

The results of this study indicate that symptoms of depression and anxiety are common and persistent in patients with an ACS at baseline and during 6 months of follow-up as documented in other investigations [11, 12, 14]. In the treatment group the

prevalence of anxiety and depression decreased by one-third after two or three months of follow-up, but some symptoms of depression and anxiety persisted even after one year. Both psychiatric disorders are also highly correlated as has been previously observed. But unlike any other studies of which we are aware, we were able to model measures of depression and anxiety symptoms simultaneously in a longitudinal, patient-level research design. We used this approach to examine whether CBT treatment "uncoupled" the well documented co-occurrence of depression and anxiety relative to control patients. Similarly, this approach enabled us to examine whether evidence based CBT treatment of depression in patients with an ACS provided any additional "pay-off" on improving anxiety symptoms. This information is valuable since depression and anxiety may be independent risk factors for morbidity, mortality, diminished quality of life and other outcomes in patients with an ACS [9-10].

Correlation of Anxiety and Depression in Patients with an ACS who Received CBT

Study results showed a strong correlation between depression and anxiety that persisted over time in both the treatment and control groups, although the correlation appears to be slightly lower but with a similar pattern in the control group. Patients who received CBT showed a significant decrease in the mean scores for depression and anxiety and this reduction in scores plus the high correlation for both psychiatric disorders may be explained by the administration of CBT. The intervention does not appear to uncouple this correlation in the experimental group, suggesting that the intervention has comparable effects on both depression and anxiety. These findings then suggest that patients with an ACS and symptoms of depression and anxiety may benefit

from interventions, such as CBT, that target both disorders at the same time. It is also important to emphasize that not only it is recommended that the intervention should address both psychiatric disorders but also the statistical method implemented should allow the researchers to measure the effect of the intervention through joint modeling to obtain a more accurate result.

Prevalence of depression and anxiety in patients with an ACS

Several prior studies have also reported high levels of co-existing depression and anxiety in patients with an ACS over time. In a prospective study in the U.K., 288 hospitalized patients with a myocardial infarction (MI) were assessed for symptoms of depression and anxiety using the Beck Depression Inventory (BDI) and the State–Trait Anxiety Inventory (STAI) between 2–15 days after the occurrence of a MI [20]. These patients were re-assessed for depression and anxiety at 4 and 12 months. During the period of hospitalization, 31% and 26% of patients met the criteria for depression and anxiety, respectively. The 4 and 12 month prevalence rates were 38 % and 37% for depressive symptoms, and 42% and 40% for symptoms of anxiety, respectively [20]. Depression and anxiety were highly associated, with 51% of patients experiencing significant levels of depressive and anxious symptoms at baseline. More than half the patients with complete BDI and STAI data experienced either elevated symptoms of anxiety or depression throughout the year following a MI [20].

In another British prospective study slightly different results were found. The researchers collected demographic and cardiological data for all patients (n=347) from a defined geographical area in the U.K who had had a MI. The mean age of the patients

was 60 years and 70% were males [9]. The patients completed the HADS and the 36-item Medical Outcomes Study short form at baseline, 3 months and 1 year later [9]. Fifteen percent of patients were scored as having symptoms of anxiety or depression. There was an improvement at 3 months, but there was little overall or individual change after that time in symptoms of both psychiatric disorders [9]. An important difference between the results in both British studies and our findings is that the researchers in the U.K. studies examined anxiety and depression as separate psychiatric disorders and did evaluate the joint distribution of these two psychiatric disorders nor did they assess the efficacy of any type of intervention applied to these two psychiatric disorders.

Study strengths and limitations

Further longitudinal studies would benefit from longer follow-up time, expansion of site numbers, and a larger sample. Patients with very severe depression/ anxiety and also patients who had received mental health care in the prior three months or had a diagnosis of substance abuse during the past year were excluded from this study. Thus, our findings may not apply to these high risk individuals. Data gathered on depression and anxiety in our study relied upon self-report.

Conclusions

Joint modeling of related outcomes such as those studied in this investigation promise to be very useful in determining the change over time of one outcome as it is highly related to another [19]. These models are of particular importance in understanding multi-dimensional profiles of psychopathology in patients with mental disorders who typically demonstrate multiple maladaptive behaviors, a variety of

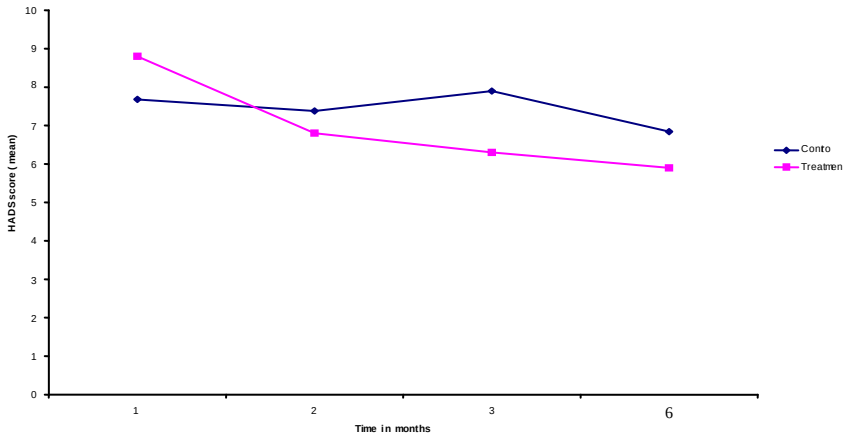
symptoms and decrements in various domains of function all of which are typically correlated. A better understanding of the relative contributions of these various but inter-dependent phenomena in patients' symptoms, function and quality of life could inform appropriate targets for interventions to achieve desired benefits. Even though the implementation of these models could be broadly used and helpful in psychiatry and other medical specialties, they still rarely used. Although this study used bivariate mixed effects models, the conceptual and operational approach to modeling more than two outcomes is the same for higher number of outcomes.

In summary, our results indicate that depression and anxiety are highly correlated in patients with an ACS both at baseline and across six months of follow up. The intervention does not appear to uncouple the correlation between these highly comorbid psychiatric disorders in the experimental group, suggesting that the intervention has comparable effects on both depression and anxiety. Future research needs to investigate the role of anxiety and depression as a joint phenomenon in order to more precisely clarify the effects of these psychiatric disorders on mortality, morbidity and quality of life in patients after an ACS. Additional studies are also needed to compare the effectiveness and cost-effectiveness of CBT and other interventions targeting both psychiatric disorders jointly.

Table 2.1: Characteristics of the study sample according to treatment status

VARIABLE	TREATMENT (N=45)	CONTROL (N=34)
Age (mean, years)	59.9	60.7
Female (%)	31.1	35.3
White (%)	88.9	88.1
History of Ischemic Heart Disease (%)	40.0	47.8
Length of hospital stay (mean, days)	3.6	3.1
Major Depression History (%)	37.8	29.4
HADS Depression Scores (mean)	8.5	6.5
HADS Anxiety Scores (mean)	8.1	7.1

Figures 2.1-A: HADS Depression scores over time



Figures2. 1-B: HADS Anxiety scores over time

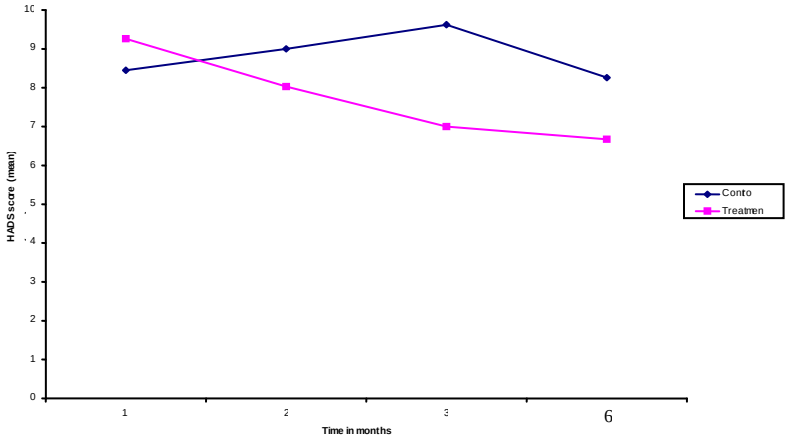


Table 2.2: Prevalence of depression and anxiety according to treatment status

	Treatment (n=45)		Control (n=34)	
	Depression	Anxiety	Depression	Anxiety
Baseline	47%	46%	15%	25%
2 months	24%	29%	16%	27%
3 months	20%	21%	23%	27%
6 months	19%	20%	15%	22%

Table 2.3: Fixed and random effects estimates for the effects of treatment on anxiety and depression

	Depression Estimate (SE)	**Anxiety Estimate (SE)**
Intercept	7.8 (0.7)*	8.93 (0.66)*
Time	-0.08 (0.13)	-0.01 (0.14)
Treatment	-1.96 (0.05)	-2.2 (0.02)
Time*Treatment	-0.38 (0.17)*	-0.39 (0.18)*

*** P-value <0.05**

Figure2. 2: Estimated correlation coefficients for depression and anxiety over time

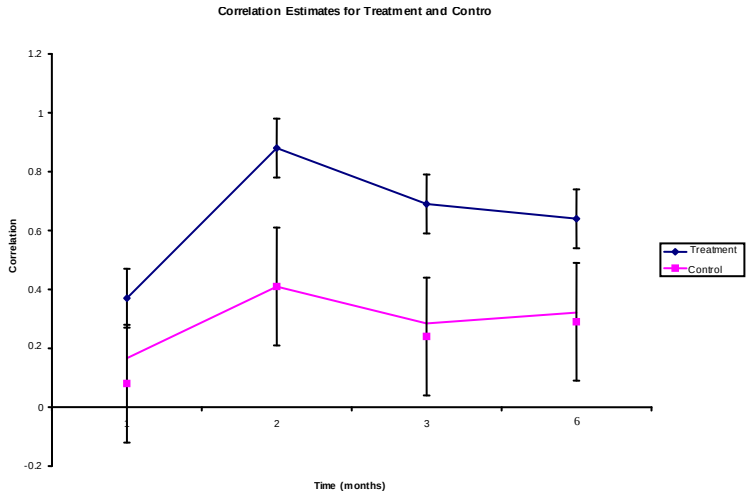


Table 2.4: Correlation estimates, standard errors and confidence intervals by time of assessment

time	Correlation estimate (SE) (CI)		Z-statistic
	Treatment N=45	Control N=34	
Baseline	**0.37** (0.06) (0.25-0.49)	**0.08** (0.22) (-0.36-0.52)	1.29
2 months	**0.88** (0.13) (0.62-1.14)	**0.41** (0.42) (-0.43-1.25)	3.90 *
3 months	**0.69** (0.11) (0.47-0.91)	**0.24** (0.28) (-0.32-0.8)	2.50 *
6 months	**0.64** (0.1) (0.44-0.84)	**0.29** (0.23) (-0.17-0.75)	1.92

*** P-value <0.05**

Chapter III: paper #2

Identifying Classes of Response to Treatment of Depression, Anxiety and Function in Patients After an Acute Coronary Syndrome

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Running title: Depression and anxiety after an acute coronary syndrome

References: XX

Tables: XX Figures: XX

Word count: XX

Background: Depression and anxiety are associated with higher mortality rates and diminished quality of life in patients with an acute coronary syndrome (ACS). While these psychiatric disorders are prevalent in patients with an ACS, they are usually undertreated.

Objectives: The objectives of this study were to (1) identify symptomatology profiles of depression, anxiety, and functional impairment among patients with an ACS, (2) describe change over time in symptomatology profile, and (3) determine if patients receiving cognitive behavioral therapy (CBT) showed signs of remission in depression, anxiety and impaired function earlier than patients that received usual care. In addition, the association between symptomatology profile and age, gender and length of stay in the hospital was examined.

Methods: A total of 100 patients with an ACS and mild to severe depression and/or anxiety at one month post-hospital discharge were enrolled in a randomized trial of CBT. These patients were followed for change in anxiety and depression at two, three, and six months post-baseline enrollment. Latent transition analysis was used to identify patients' symptomatology profiles and to describe changes in those profiles over time.

Results: The average age of study patients was 60 years and 30% were women. The latent transition model specifying a three-class solution was selected to identify and describe symptomatology profiles. One class was characterized by patients with both psychiatric disorders and impaired function, the second by patients with psychiatric disorders but normal function, and the third by patients with anxiety but without depression, and having normal function. As compared to a control group receiving usual

care, patients who received CBT reported higher rates of symptomatology remission (i.e. transition from latent classes I and II to latent class III) between baseline and month-two follow-up. There was moderate improvement in depression, anxiety and function for control patients in latent classes I and II at the three and six-month follow ups, but this improvement was less evident than in the experimental group. Women showed a better response to CBT than men.

Conclusions: Examining transitions between symptomatology profiles provides a detailed look at change over time that is difficult to obtain in more traditional data analysis. This statistical approach thus clarifies periods during which an intervention is most likely to be effective.

Depression and anxiety are highly prevalent disorders in patients after an acute coronary syndrome (ACS) [1-7]. Depression and anxiety appear to inhibit recovery, and have a negative impact on social functioning and capacity to perform activities of daily living in patients who develop an ACS [3, 4, 6, 8-13]. Even though these conditions are prevalent in patients with an ACS, and associated with poorer quality of life, these disorders are not fully recognized and adequately treated in clinical settings.

In the current study, latent transition analysis is used to identify and describe profiles of symptoms that are defined by different patterns of depression, anxiety and function. Second, we examine whether treatment predicts change in symptomatology profile over time. Lastly, we determine if age, gender and length of stay in the hospital predict remission of symptoms. Both psychiatric disorders and impaired function are considered together here, because it has been shown that these negative outcomes are highly prevalent in patients with an ACS, and highly correlated [12]. Latent transition analysis (LTA) provides a different and original approach to determining symptom profiles of depression, anxiety and function in patients after an ACS [14-16]. In LTA, the unit of analysis is an individual's profile of symptoms. Latent transition analysis has several strengths, it combines the cross-sectional measurement and the longitudinal description of change in categories of the latent variable over time and, it has great flexibility in describing progression, stability, and remission of symptoms[14-16].

Data from a randomized controlled trial of patients treated for an ACS at two coronary care units were utilized to examine outcomes over a six-month follow-up period after hospitalization [12, 13].

Design and Methods:

The study sample consisted of 100 patients hospitalized with an ACS in two coronary care units at a university hospital in Boston, MA, between September, 2001 and August, 2003 [12, 13]. Patients were 35 years and older at the time of trial entry and had symptoms corresponding to mild to moderate levels of depression and/or anxiety as indicated by a score of seven or higher on either of the subscales of the Hospital Anxiety Depression Scale (HADS). None of the study patients had received mental health care in the prior three months, used a psychoactive drug during the past year, or had been diagnosed with substance abuse during the past year. Potentially eligible patients were identified by a research nurse through the review of hospital records and hospital census information. The diagnosis codes used to identify patients for this study included acute myocardial infarction, unstable angina, and ischemic heart disease. Patients were screened at approximately one month after hospital discharge for an ACS, and those meeting the predefined study inclusion criteria were randomly assigned to the intervention (i.e. CBT) or control status (i.e. usual care) [12, 13].

Patient recruitment began during the index hospitalization. Once patients consented to trial enrollment, the study coordinator administered the 14-item HADS by phone to assess symptoms of anxiety and depression. Subjects with scores between seven and 15 on either the anxiety or depression scale were enrolled into the trial and randomized into the intervention or usual care comparison groups [12, 13].

The trial intervention consisted of a series of CBT sessions that helped patients identify and manage the challenges of living with a chronic condition [12]. Patients in the

control group received information on coping with cardiac disease. Baseline survey assessments (within 30 da ys of hospital discharge) included the Primary Care Evaluation of Mental Disorders (PRIME-MD), the Work and Social Adjustment Scale (WSAS) and the Hospital Anxiety and Depression Scale (HADS), our primary outcome measure [12]. The HADS and the WSAS were re-administered at two, three, and six months after trial enrollment for purposes of assessing change in depression, anxiety and function at home[12]. The study protocol was reviewed and approved by the institutional review board of the participating hospital.

Intervention

The trial intervention consisted of CBT that helped patients identify and manage the challenges of living with chronic cardiac disease [12]. It has been described in details previously and will only be briefly summarized here. This intervention was goal-oriented, time-limited, and issue-focused. It was based on other telephone interventions targeted to treat depression by modulating the risk of depression, anxiety, and functional decrements through improved adjustment to illness [12]. Individual sessions lasted for approximately 30 minutes and were conducted by doctoral-level clinicians. Patients were expected to complete six sessions, but were allowed to participate in as few as three sessions if the therapist and patient agreed that all issues set forth during treatment were reviewed and that treatment goals were reached. Patients randomly assigned to the control group received a booklet on coping with cardiac illness, typical of those given to patients with an ACS at the time of hospital discharge, and were instructed to contact their primary care physician if they experienced signs of depression.

Data Collection Protocols

Data were collected at the time of baseline enrollment for the HADS, the WSAS, and a self-rated health and anger questionnaire using interactive voice recognition (IVR). Patients completed the HADS and the WSAS at the time of the two, three, and six month study follow-up visits. An aggressive follow-up system consisting of reminder postcards, telephone call reminders, and re-mailing of questionnaires was utilized to enhance survey response rates.

Assessment Instrument

The HADS contains seven questions to assess depression and seven to assess anxiety. Each scale is scored from 0 to 21; scores between four and seven represent subclinical depression whereas patients who scored eight or higher were classified as being ‘‘depressed’’. The same criteria and scores were used for diagnosing anxiety. One important advantage of using the HADS is that this scale focuses on cognitive rather than somatic constructs, which minimizes the likelihood that somatic symptoms of ACS will be attributed to depression.

The work and social adjustment scale (WSAS) was utilized to assess function in this group of patients. The WSAS is a validated measure of self-reported functional impairment at work, home management, social and private leisure, and personal relationships. Each of the five domains is scored from no impairment (zero) to severe impairment (eight), with a score of three to five suggestive of moderate impairment [12, 13].

Depression, anxiety, and function scores were dichotomized for purposes of analysis. Patients who scored below eight on the HADS in any of the two subscales were

classified as non-depressed/non-anxious; patients who scored from eight to fifteen were classified as being depressed or anxious. Patients who scored above 15 in the WSAS were classified as having moderate to severe impairment in function at home and work, and those that scored below 15 were classified as being without functional impairment [12].

Data Analysis

Descriptive analyses of patient baseline characteristics were performed; t-tests and chi-square tests, as appropriate, were used to examine possible differences in baseline variables between patients randomly assigned to the intervention and control groups.

Latent transition analysis (LTA) was used to identify subgroups of patients with similar patterns of depression, anxiety, and function, and to describe changes over time. Latent transition models describe change over time in outcomes that are not directly observed [14-15]. That is, the outcomes in latent transition models are inferred based on information from a set of observed variables [16]. The latent transition model combines cross-sectional measurement of categorical latent variables and the longitudinal description of change in categories of the latent variable over time. One important advantage of these models is that they allow investigators to examine the impact of the intervention, in this case CBT, on change in depression, anxiety, and function symptoms simultaneously.

Selection of the optimal model that considered both goodness of fit and parsimony was based on various statistical fit indices. Statistical indices reported here include: the Akaike information criterion (AIC), Bayesian information criterion (BIC) and G2.Model selection was also based on: the log-likelihood, and the number of estimated parameters

in the model [14-18]. Lower values for the BIC, AIC and G2 indicate better model fit [16-18]. Latent Transition Analysis estimates the proportion of patients in each class at each time point, and the probability of moving from one class to another, conditioned on prior membership status [16-18].

Latent Transition Analysis involves four different types of parameters: the gamma parameters, which are estimates of the proportion of the population in each latent class or subgroup [19]. The delta parameters which are estimates of the proportion of the population in each latent status at each occasion of measurement [19]. The tau parameters which refer to the conditional probability of transitioning from one latent class to another, and lastly the rho parameters, which represent measurement error, are estimates of a particular item response conditional on latent class and latent class membership [19].

Results:

At the time of randomization, the control and intervention groups were well balanced with respect to a variety of patient characteristics (Table 1); both groups were predominantly comprised of white, older males. Average depression and anxiety scores were slightly higher for the intervention group at baseline but the differences were not statistically significant.

Symptomatology Profiles

Latent transition models with two, three, and four latent classes were fit and compared (Table 2). Model identification was checked using 100 sets of random starting values. As shown in Table 2, the three class model had the lowest AIC (499.58), but the two class model had the lowest BIC (613.78). An examination of the two and three class

models revealed the emergence of a latent class characterized by psychiatric disorders but high function in the three class model. Because of the potentially important differences between this class and a class with psychiatric disorders and impaired function, which appeared in both the two and three class models, the three class model was selected as the best at balancing model fit and parsimony in its description of the data.

Profiles of Depression, Anxiety and Function in the Study Sample

Item-response probabilities are one set of parameters estimated in latent transition models and they serve two roles. First, they define the latent classes. In addition, the item-response probabilities reflect measurement precision. Reliable measurement of the latent class variable is reflected in estimates that are close to zero or one. For example, probabilities that are close to zero for having depression and impaired function for members of latent class III, indicates that membership in this latent class (almost) completely determines the response to these manifest items. An estimate that approaches 0.5 indicates an item response that is poorly determined by latent class membership [16-17].

The estimated item-response probabilities for having anxiety, depression and impaired function for the 3-class model are reported in Table 3. The first class was labeled “patients with psychiatric disorders and impaired function”; the second class was labeled “patients with psychiatric disorders and normal function”; and the third class was labeled “patients with moderate anxiety and normal function, but without depression” (Table 3). In latent class I, patients had high probabilities of endorsing each of the three indicators, meaning that patients in latent status I were depressed, anxious and had severe impairment in their function at home; in addition the latent class was well-defined by the

observed psychiatric disorders and function. Patients in latent class II were characterized by high depression and anxiety scores, but they did not have any impairment in function at home. Finally, patients in latent class III were characterized as being without depression or having any impairment in their function at home; they did, however, exhibit moderate symptoms of anxiety.

Latent class membership probabilities are a second set of parameters estimated in latent transition models and they are the expected percentage of patients which each symptomatology profile at each time point of observation [18-19]. The estimated latent class membership probabilities over time are reported in Figures 1 A and B. Patients in the treatment group showed an important decline in the probability of belonging to latent class I (psychiatric disorders and impaired function) over time. In other words, the probabilities of membership in latent classes II and III increased over time, meaning that patients in the treatment group reported reduced impairment of function over time. The control group patients also showed a similar decreasing trend in membership in latent class I over time, but his decrease was less pronounced than in the treatment group.

Transitions between Latent Classes

Transition probabilities are a third and final set of parameters estimated in latent transition models and they describe change over time in class membership. The estimated transition probabilities are reported in Table 4. Each row in Table 4 is row conditional, such that each row sums to one. These probabilities are interpreted as the probability of time t+1 latent class membership (columns), conditional on latent class membership at time t (rows). In the control group, most of the patients remained in the same class

between any two times, with no remission or reappearance of symptoms over time. For those in the intervention group, almost 30% of the patients with depression, anxiety and impairment in their function at baseline showed remission of their symptoms for both psychiatric disorders and function at month two. Among those in latent class II, more than 60% transitioned to latent class III at the time of the two-month follow-up, showing an improvement in their symptoms. There was moderate improvement in depression, anxiety and function for patients in latent classes I and II at the three and six-month follow ups, but this improvement was less significant than had been previously observed. In summary, the effects of the intervention were more evident in the transitions from baseline to two-month follow than in any other follow-up period for all three indicators of the psychiatric disorders and function.

Predictors of Response to the Intervention

In order to consider the effects of different covariates in predicting remission of symptoms of depression, anxiety and impaired function, posterior probabilities were calculated and used to assign patients to a latent class at each point assessed. Although it is possible to incorporate covariates directly into the latent transition model [18], due to the small sample size of the current study, this method was preferred. The quality of latent class assignment was evaluated by examining the average posterior probability of patients assigned to a class at each time point. The average posterior probabilities were high for each latent class at each time point ranging from 0.75 to 0.99. These results indicated a high likelihood of each patient belonging in the class to which he/she was assigned.

Generalized estimating equations were then used to determine if the covariates age, gender and length of stay in the hospital were predictive of the remission of symptoms of both psychiatric disorders and impaired function. The covariates were included one at a time and then combined in the generalized estimating equation models. Gender was the only covariate found to be a statistically significant predictor of remission of symptoms (p-value=0.042). Women showed a significant response to CBT, such that women in the intervention group were more likely than men to transition from latent class I (depression, anxiety and impaired function) and II (depression, anxiety and normal function) to latent class III (moderate anxiety).

Discussion:

The first objective of this study was to identify different symptomatology profiles of depression, anxiety and function in patients with an ACS over time. Our results showed that patients with an ACS could be classified into three different latent classes or profiles. The first class was labeled "Patients with the psychiatric disorders and impaired function"; the second class was labeled "Patients with the psychiatric disorders but normal function" and the third class was labeled "Patients with moderate anxiety, no depression and normal function". The results showed that 80% of patients who were members of latent class I reported depression, 94% reported anxiety, and 84% reported impaired function. Comparatively, in latent class II, 100% of patients reported depression, 75% reported anxiety, and none of them reported any symptoms of impaired function. Lastly, 5% of patients who were members of latent class III reported symptoms of depression, 37% reported symptoms of anxiety, and less than 4% reported signs of

impaired function. In summary, our findings showed that depression and anxiety were highly prevalent disorders in latent classes I and II in this group of patients. The clinical implication of these results is that it is important to assess and consider both disorders in order to better diagnose and treat patients with an ACS.

Change in Symptomatology Profiles

The second objective of this study was to examine change over time in the profiles of depression, anxiety and function among patients with an ACS who were randomized to CBT and usual care treatment. Patients in our study had a high likelihood of belonging to the latent class characterized by depression, anxiety and impaired function at baseline (almost 70% in the control and more than 50% in the treatment group). This probability decreased over time in both the treatment and control group, but decreased more in the treatment group. The treatment group patients were characterized by moderate symptoms of anxiety, no symptoms of depression and normal function at home at the time of the study follow-up visits. This suggests that patients in the treatment group showed important improvements in their symptoms of depression and impaired function at home over time. Patients in the control group showed higher probabilities of belonging to the latent class that reported both psychiatric disorders and impaired function at home (latent class I) and the latent class that reported both psychiatric disorders and normal function at home (latent class II) over time. In summary, when comparing the symptomatology profiles of the treatment and control group, patients in the treatment group showed important improvements in their symptoms of depression and function at home, with moderate persistence of anxiety. These findings showed that symptoms of depression and

impaired function persisted over time in the control group. In this randomized controlled trial this difference between the two groups is likely due to the effect of CBT.

Effects of CBT on Depression and Anxiety in Patients with an ACS

Our results showed a significant effect of CBT in the treatment group, with the highest effect observed between baseline and the second month of follow-up. This effect is important to consider when deciding the type and timing of implementing an intervention in patients with an ACS. Moreover, our results demonstrated that women reported a higher response to CBT showing a more significant remission of symptoms linked to depression, anxiety and function than men. Our findings also demonstrated that women were more likely to transition from latent classes I and II (those that reported depression and anxiety with or without impaired function) to latent class III (moderate anxiety only). These results may be explained by the effect of CBT on depression and function in women.

Prior research has shown that depression, anxiety and function persist over time in patients with an ACS, and treatment response to CBT is still controversial. Results reported from one of the largest studies of patients with an ACS and with symptoms of depression, the ENRICHD trial, were somewhat mixed. Improvement in the assessed depressive symptoms were reported at the six-month evaluation for patients receiving CBT in comparison with the control group, but this improvement did not persist at the 30-month evaluation [11]. Similar results were described in another study conducted by researchers at the Montreal Heart Institute [20]. A group of 1376 post- myocardial infarction (MI) patients (30 % women) were randomly assigned to usual care or a phone-

intervention program which consisted of emotional support, education and practical advice. The intervention was administered monthly for a year period. The goal of this program was to reduce psychological distress that followed the occurrence of myocardial infarction. The authors reported no significant changes on depression and anxiety after one year of follow-up. These researchers reported that women showed a significant negative response to the intervention. Women showed worsening of depressive symptoms in the treatment group when compared to men over time.

It is important to take into account when comparing these two studies to our findings that our sample was smaller, and the follow-up period was shorter than the ENRICHD and the Montreal studies. One important strength of our study is the use of latent transition modeling, which allowed us to conduct modeling of depression and anxiety subscale scores of the HADS and home function jointly. Due to the co-occurrence of these psychiatric disorders and function in patients with an ACS, we believe that combining information from these three indicators may help us to obtain a more accurate assessment of the effectiveness of the intervention in multiple domains, namely remission of symptoms of anxiety, depression and function over time.

Study Strengths and Limitations:

Latent transition models have some important strengths in cases in which it is appropriate to think of the underlying phenomenon of interest in discrete terms. One important strength is that examining the prevalences of the latent classes and the transitions from the one latent class to another provides a detailed look at change over time that is difficult to obtain in continuous data analyses[14-15]. A latent class-based

approach, in particular, can show very clearly whether a given status is particularly prevalent at certain times or for certain subgroups, whether individuals in a certain status are more or less likely to undergo a transition and whether there are qualitative differences between groups [14-15]. From a policy and clinical' point of view, a latent class-based approach can help identify developmental periods in which interventions are most likely to be effective, and what behaviors should be the target of action at different time points.

Future longitudinal studies would benefit from longer duration of follow-up, an increase in the number and variety of sites, and a larger and more representative sample. Patients with very severe depression/ anxiety and also patients who had received mental health care in the prior three months or had a diagnosis of substance abuse during the past year were excluded from this study. Thus, our findings may not apply to these high-risk individuals.

It would also be of importance to examine additional study outcomes such as frequency of re-hospitalizations after an ACS, compliance with medications, workplace performance, and other risk factors that can contribute to depression in patients after an ACS (e.g. social support, family involvement). Future studies examining patterns of change in these psychiatric disorders and function as they are related to clinical outcomes, response to CBT and other meaningful interventions, may provide a better understanding of how to approach and treat patients with an ACS and symptoms of depression and anxiety and impaired function [21].

The implementation of statistical models such as latent transition analysis, that are not frequently used in clinical trials can help us to combine multiple indicators or multiple sources of information into one unique outcome in order to provide a more complete and multidimensional understanding of change over time. In our study, disregarding the high levels of correlation among depression, anxiety and impaired function in patients with an ACS over time may cause important information to be missed which may be crucial to understanding how and when an intervention should be implemented and in which populations to be most effective.

Table 3.1: Patients characteristics

VARIABLE	CONTROL (N=34)	TREATMENT (N=45)
Age (mean, years)	60.7	59.9
Female (%)	35.3	31.1
White (%)	88.1	88.9
History of Ischemic Heart Disease (%)	47.8	40.0
Length of hospital stay (mean, days)	3.1	3.6
Major Depression History (%)	29.4	37.8
HADS Depression Scores (mean)	6.5	8.5
HADS Anxiety Scores (mean)	7.1	8.1
Workplace social adjustment: Work(mean)	3.8	3.6
Workplace social adjustment: Home(mean)	3.0	3.1

Table 3.2: Fit statistics for the latent class models

Model tested	Bayesian Information Criterion (BIC)	Akaike Information Criterion (AIC)	G^2	Log-Likelihood	Degrees of Freedom
2 class	547.09	500.48	460.48	-494.47	8171
3 class	**613.78**	**499.58**	**401.58**	**-465.02**	**8142**
4 class	741.80	532.03	352.03	-440.25	8101

In bold: 3 class model selected for this study

Table 3.3: Item-response probabilities for having anxiety, depression and impaired function for each latent class

	Latent Status I	Latent Status II	Latent Status III
Anxiety	0.79	0.75	0.37
Depression	0.94	1	0.05
Dysfunction	0.84	0	0.05

Latent Status I=Depression, anxiety & dysfunction; Latent Status II=Depression & anxiety; Latent Status III=Anxiety

Figure 3.1-A Membership probabilities for the different latent classes by treatment group at each time point: Control group

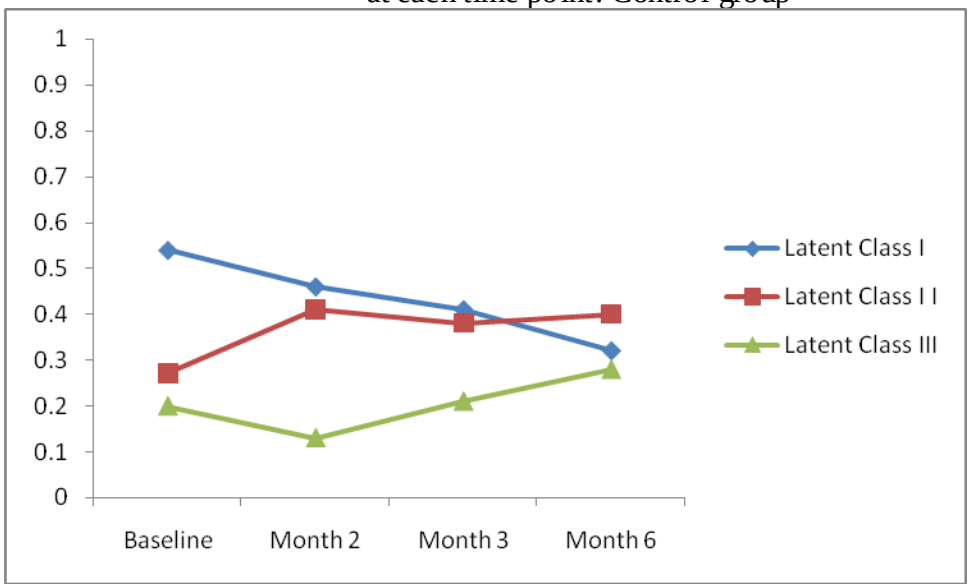

Figure 3.1-B: Membership probabilities for the different latent classes by treatment group at each time point: Treatment group

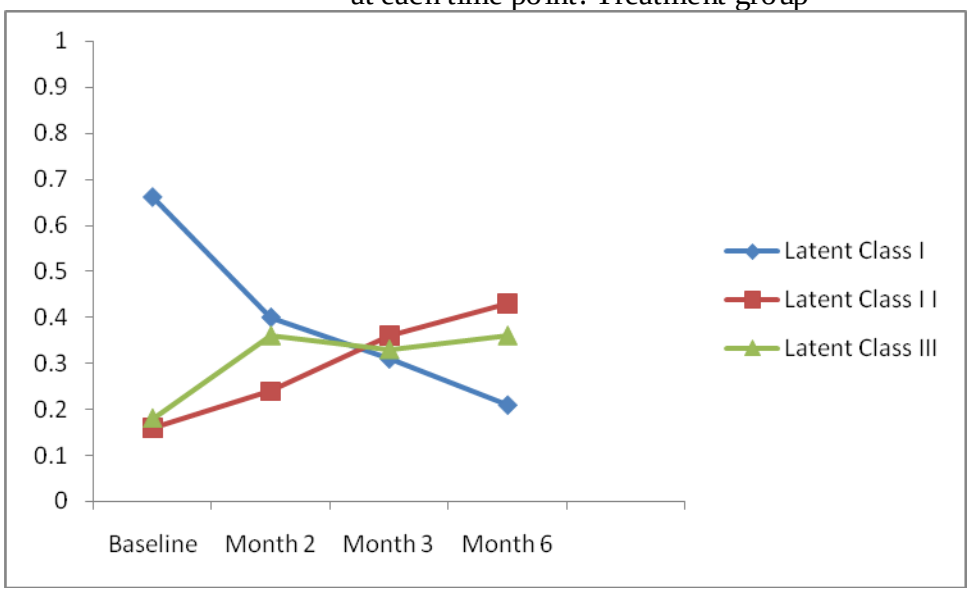

Table 3.4: Transition probabilities by treatment group

	Control				Treatment		
	Month 2						
		Latent Status I	**Latent Status II**	**Latent Status III**	**Latent Status I**	**Latent Status II**	**Latent Status III**
Baseline	**Latent Status I**	0.60	0.39	0	0.59	0.14	0.27
	Latent Status II	0.42	0.47	0.11	0	0.35	0.65
	Latent Status III	0.14	0.34	0.52	0.09	0.50	0.41
	Month 3						
		Latent Status I	**Latent Status II**	**Latent Status III**	**Latent Status I**	**Latent Status II**	**Latent Status III**
Month 2	**Latent Status I**	0.88	0	0.12	0.58	0.36	0.06
	Latent Status II	0.01	0.94	0.05	0.11	0.89	0
	Latent Status III	0	0	1	0.13	0	0.87
	Month 6						
		Latent Status I	**Latent Status II**	**Latent Status III**	**Latent Status I**	**Latent Status II**	**Latent Status III**
Month 3	**Latent Status I**	0.61	0.22	0.17	0.59	0.32	0.09
	Latent Status II	0.19	0.81	0	0.09	0.74	0.17
	Latent Status III	0	0	1	0	0.19	0.81

*Transition probabilities are estimated conditional on the previous time point only; they sum to 1.0 across rows; Latent Status I=Depression, anxiety & dysfunction; Latent Status II=Depression & anxiety; Latent Status III=Anxiety

Chapter IV: paper #3

Profiling Symptoms of Depression and Anxiety in Patients with an Acute Coronary Syndrome Using Latent Class and Latent Transition Analysis

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Running title: Depression and anxiety after an acute coronary syndrome

References: XX

Tables: XX Figures: XX

Word count: XX

Background: Patients with an acute coronary syndrome (ACS) and symptoms of depression and anxiety report a worse quality of life than patients without these disorders. Identifying symptom profiles of patients with depression and anxiety will not only better inform clinical management by improving diagnostic practices but also help to refine treatment strategies in these patients.

Objectives: To determine symptom profiles of depression and anxiety in ACS patients using the hospital anxiety and depression scale (HADS). A secondary study objective was to examine the effects of age and sex on patients' symptom profiles.

Methods: A total of 100 ACS patients with mild to severe depression and/or anxiety at one month post-hospital discharge were enrolled in a randomized trial of cognitive behavioral therapy. Latent class and latent transition analyses were used to identify symptomatology profiles of depression and anxiety.

Results: A two-class solution was selected to describe depression and anxiety symptomatology profiles. Class I (76% of patients at baseline) was labeled "severe depression and some anxiety". Class II (24% of patients at baseline) was labeled "mild depression and distress anxiety". Approximately 25% of patients in the treatment group transitioned to the less severe depression and anxiety class compared to 10% in the control group at the time of the month-two of follow-up; nearly 50% of patients in the control group showed worsening of symptoms as compared to 28% in the treatment group. There were no sex differences in the probability of transitioning from one class to the other. More than 70% of older patients ($\geq$ 60 years old) continued to have severe depression and anxiety at the 2-months follow-up contact.

Conclusions: The results of the current study stress the importance of assessment of depression and anxiety and follow-up of patients after an ACS. Further research should examine the association of depression and anxiety after an ACS with patient's age and determine whether these psychiatric disorders affect subsequent morbidity and mortality in older as compared to younger patients and the reasons for possibly different results

Patients with an acute coronary syndrome (ACS) experience considerable stress in adjusting to living with their illness. Thus, it is not surprising that depression and anxiety are more prevalent in this group of patients than in the general population [1-6]. Patients with an ACS and symptoms of depression and anxiety not only experience higher rates of long-term morbidity and mortality but also report a worse quality of life than patients without symptoms of these psychiatric disorders [3-5]. Due to the clinical and public health significance, as well as the economic burden of depression and anxiety in ACS patients, identifying symptom profiles of these psychiatric disorders will not only better inform clinical management by improving diagnostic practices but will also help to refine the more optimal treatment of these high risk patients. The objectives of this study were to characterize the symptom profiles of depression and anxiety in patients with an ACS using the hospital anxiety and depression scale (HADS). A secondary study objective was to examine the effects of age and sex on these symptom profiles.

This study employed latent class analysis to identify classes of depression and anxiety in patients after an ACS with the goal of improving the diagnosis of symptomatic individuals and better representing the relative severity of diagnostic categories [7].

Design and Methods:

The study sample consisted of 100 patients hospitalized with an ACS in two coronary care units at a university hospital in Boston, MA, between September, 2001 and August, 2003 [8,9]. Patients were 35 years and older at the time of trial entry and had symptoms corresponding to mild to moderate levels of depression and/or anxiety as indicated by a score of seven or higher on either of the subscales of the Hospital Anxiety

Depression Scale (HADS). None of the study patients had received mental health care in the prior three months, used a psychoactive drug during the past year, or were diagnosed with substance abuse during the past year. Potentially eligible patients were identified by a research nurse through the review of hospital records and hospital census information. Patients were screened at approximately one month after hospital discharge for an ACS, and those meeting the predefined study inclusion criteria were randomly assigned to either cognitive behavioral therapy (CBT) or a typical-care control group [8, 9].

Patient recruitment began during the index hospitalization for an ACS. Once patients consented to trial enrollment, the study coordinator administered the 14-item HADS by phone to assess symptoms of anxiety and depression. Subjects with scores between 7 and 15 on either the anxiety or depression scale were enrolled into the trial and randomized into the intervention or usual care comparison groups [8, 9].

The trial intervention consisted of a series of CBT sessions that helped patients identify and manage the challenges of living with a chronic condition [8]. Patients in the control group received information on coping with cardiac disease. Baseline survey assessments (within 30 da ys of hospital discharge) included the Primary Care Evaluation of Mental Disorders (PRIME-MD), the Work and Social Adjustment Scale (WSAS) and the Hospital Anxiety and Depression Scale (HADS), the primary outcome measure [8]. The study protocol was reviewed and approved by the institutional review board of the participating hospital.

Data Collection Protocols

Data were collected at the time of baseline enrollment for the HADS using interactive voice recognition (IVR). Patients completed the HADS at the time of the two, three, and six month follow-up visits. An aggressive follow-up system was used to enhance survey response rates, which consisted of reminder postcards, telephone call reminders, and re-mailing of questionnaires. Data reported for the present study were collected at baseline and at the time of the two-month follow-up. Further analysis was performed on data from the four- and six-month follow-ups, but the results did not differ from those in the two-month follow-up.

Assessment Instrument

The HADS contains seven questions to assess depression and seven to assess anxiety. Each scale is scored from 0 to 21; scores between four and seven represent subclinical depression whereas patients who scored eight or higher were classified as being ‘‘depressed’’. The same criteria and scores were used for diagnosing anxiety. One important advantage of using the HADS is that this scale focuses on cognitive rather than somatic constructs which minimizes the likelihood that somatic symptoms of ACS will be attributed to depression.

In the current study, instead of considering the diagnosis of depression and anxiety as binary indicator, all the 14 items of the HADS were used as indicators of depression and anxiety symptoms. Each item was dichotomized and included individually in the analysis.

Data Analysis

Descriptive analyses on patient's baseline characteristics at the time of trial entry were performed; t-tests and chi-square tests, as appropriate, were used to examine possible differences in baseline continuous and categorical variables between patients randomly assigned to the intervention and control groups.

Latent class analysis and latent transition analysis were used to identify subgroups of patients with similar patterns of depression and anxiety symptoms and to describe changes over time in subgroup membership. Latent class analysis identifies a set of mutually exclusive and exhaustive latent classes characterized by similar patterns of responses [10-11]. Latent transition analysis is a longitudinal extension of latent class analysis that additionally models change over time in class membership[10-11]. Latent class and latent transition analysis are measurement models that separate measurement error from other aspects of the model. Latent class analysis estimates two sets of parameters. Item-response probabilities estimate the probabilities of responding positively and negatively to the HADS items given class membership. Latent class membership probabilities estimate the distribution of the classes. The 14 items of the HADS were used as indicators of depression and anxiety and were re-coded such that one represented never or rarely ever experiencing the symptom whereas the other code represented experiencing the symptom sometimes or most of the time. Thus, because the items were dichotomized and the HADS has 14 indicators, there were more than 16, 000 possible patterns of response (2^{14}= 16384). Statistical indices of goodness of fit included: the Akaike information criterion (AIC), Bayesian information criterion (BIC) and G^2.

Results:

The control and intervention groups were well balanced with respect to a variety of baseline patient characteristics (Table 1); both groups were predominantly comprised of white, older males. Average depression and anxiety scores were slightly higher for the intervention group at baseline but the differences were not statistically significant.

Latent Class Analysis: Fitting and Description of the Classes

Latent class analysis was used to identify the most common anxiety and depression symptom profiles in patients after an ACS. Models with two and three latent classes were fit and compared at baseline; selection of the optimal model considered goodness of fit and parsimony using various statistical fit indices. In order to ensure that the maximum likelihood solution was identified for both models, 100 sets of random starting values were used to examine potential solutions.

Based on the fit indices and stability of the models, a two-class solution was selected (Table 2). Although the AIC was somewhat lower in the three-class model, it was less stable than the two-class model. In addition, the BIC was higher for the three-class model than the two-class model.

Table 3 describes the 14 items assessed by the HADS. In the selected two-class solution, Class I (76% of patients at baseline) was termed “severe depression and some anxiety”; this class was characterized by a pattern of item-response probabilities that indicated many symptoms of depression and some symptoms of anxiety for class members. Class II (24% of patients at baseline) was termed “mild depression and distress anxiety”. This class was characterized by a pattern of item- response probabilities that indicated milder symptoms of depression and symptoms of distress anxiety. To aid

the interpretation of these data, the estimated item-response probabilities are plotted in Figure 1. Class I had higher probabilities of experiencing negative anticipation, panic, lack of enjoyment, and general symptoms of anhedonia. Class II, on the other hand, had higher probabilities of experiencing worrying thoughts but they can still sit and relax, and they did not refer any symptoms related to anhedonia.

Latent class analysis was also used to examine the structure of the classes at the time of the two month follow-up contact. The class structure appeared to be similar, but the distribution of the classes was different, as patients changed class membership over time. Patient change over time is discussed below in the context of the latent transition model.

Latent Transition Analysis: Fitting and Description of the Classes

A Latent transition model was used to examine change over time from baseline to follow-up. Two- and three-class models were fit and compared to confirm that the two classes identified with latent class analysis were adequate. Model identification was again checked using 100 sets of random starting values. Model comparison and confirmation was based on the log-likelihood ratio. The G^2 fit statistic was not computed for this model, because the number of possible response patterns was very large (i.e., 14 items measured at multiple times).

The two-class solution with a log-likelihood of -1032.01 was identified 88% of the time. Estimation of the three-class model was less stable, and the solution with a log-likelihood of - 999.74 was identified only 24 % of the time. The instability of the three-class solution, combined with the results of the latent class analysis discussed above, led

to the selection of the two-class solution as the best at balancing model fit and parsimony in the description of the data.

Class I (55% of patients at baseline and 64% of patients at follow-up) was characterized by a similar pattern of item-response probabilities to the one from the latent class analysis. It was again labeled as “severe depression and some anxiety”. Class II (45% of patients at baseline and 36% of patients at follow-up) was also characterized by a similar pattern of item-response probabilities to the one from the latent class analysis. It was again labeled as “mild depression and distress anxiety”. To aid interpretation, the estimated probabilities are plotted in Figure 2. It should be noted that differences between the latent class and latent transition analysis results may be due to a variety of reasons, including different amounts of power in the two-models and high standard errors of the parameter estimates with the small sample size of the current study.

Latent Transition Analysis: Transitions Between Latent Classes

To examine change over time in patient class membership, latent transition analysis was used to estimate the probabilities of transitioning between classes. About 86% of patients with severe depression and some anxiety at baseline continued to have similar symptoms at the two-month follow-up contact. Among the patients with mild depression and anxiety at baseline, 41% reported a worsening of symptoms to severe depression and some anxiety at the two month follow-up contact.

Latent Transition Analysis: Examining Treatment Related Effects

Treatment group was included in the latent transition analysis as a grouping variable in the follow-up analyses to determine the effects of treatment on change in

patients' symptom profile over time. Patients receiving the intervention showed some improvement in their symptom profile, as approximately 26% of treated patients transitioned from the more severe to the less severe depression and anxiety class. In comparison, less than 10% of the patients in the control group made the transition from more severe depression and anxiety class to less severe class. In addition, 72% of patients in the treatment group remained in the less severe depression and anxiety class over time, compared to 51% of patients in the control group.

Latent Transition Analysis: Examining the Effect of Sex and Age

The effects of sex and age on patients' symptom profiles of depression and anxiety after an ACS were examined in the follow-up analyses. The effect of sex was investigated by including sex into the latent transition analysis as a grouping variable to compare class membership probabilities and transitions for women compared with men. The probabilities of membership in the classes at baseline were non-significantly different for males and females (p-value=0.77) (Table 4) and the intervention was not hypothesized to work differently for males and females.

Similarly, the effect of age was investigated by including age into the latent transition analysis as a grouping variable. Patients were split into two groups, younger (< 60 years old) and older (60 years and older). Table 5 reports the latent class membership probabilities by age group. Baseline differences in the probabilities of latent class membership for younger versus older patients were borderline significant (p-value=0.07).

All younger patients who reported severe depression and some anxiety at baseline remained in the same class at the time of follow-up. In comparison, about 74% of older

patients remained in the severe depression and some anxiety class. In addition, 31% of younger patients with mild depression and distress anxiety transitioned to the more severe depression and anxiety class whereas almost 60 % of older patients made that transition.

Discussion

Two Latent Class Model to Identify More Prevalent Symptoms of Depression and Anxiety

The results of the present study suggest that two clinically relevant classes of symptoms of depression and anxiety in patients with an ACS can be identified. Class I, labeled as "severe depression and some anxiety" had a higher prevalence at baseline and month two of follow-up (55% and 64% respectively) than Class II, labeled as "mild depression and distress anxiety". Moreover, another important finding was that more than 40% of patients who reported "mild depression and distress anxiety" at baseline transitioned to the "severe depression and some anxiety" class at the time of the two-month follow-up visit. These results emphasize the importance of the assessment of depression and anxiety in patients after an ACS not only at the time of their acute event but over a more extended follow-up period.

Regarding the particular items assessed by the HADS, it is important to highlight the presence of anhedonia as a key factor differentiating the two symptom profile classes. Patients that endorsed the "severe depression and some anxiety" class gave a positive answer to all the questions that assessed anhedonia in the HADS, whereas patients that endorsed the "mild depression and distress anxiety" class did not report any major signs of anhedonia.

Other researchers have stressed the importance of anhedonia in patients after an ACS as a predictor of cardiac mortality [12]. The results of one study conducted in 40 hospitals in Ireland investigated the use of the HADS and the Beck depression scale in assessing one-year mortality risk in a national sample of patients after an ACS. Depression, as measured by the HADS, but not by the Beck scale, was associated with an increased risk of dying within one-year [12]. The HADS concentrates on anhedonia, whereas the Beck scale focuses on psychiatric criteria for a major depressive disorder. These findings underline the importance on detecting specific symptoms that are key items, such as anhedonia, in the diagnosis of depression and anxiety in patients after an ACS. Early diagnosis and subsequent treatment of these symptoms may improve morbidity and mortality in this group of high-risk patients [12].

In contrast, items related to anxiety were not as clear as items related to depression in being able to differentiate the two symptoms profile classes. Notably, patients that endorsed the latent class that reported "mild depression and distress anxiety" tended to report more signs of general distress than patients that belonged to the "severe depression and some anxiety" class.

Effects of Treatment on Determining Symptom Profiles of Depression and Anxiety

The inclusion of treatment as a covariate supplied important information for the determination of the effect of treatment in patients' symptom profiles. Patients receiving the intervention showed improvement in their symptom profiles of depression and anxiety at month-two of follow-up; a higher percentage of patients in the treatment group transitioning to the less severe depression and anxiety class as compared to those in the

control group. In addition, an important percentage of patients that received CBT remained in the less severe depression and anxiety class at month-two of follow-up, as compared to the control group. These findings demonstrate the effect of the intervention not only in the improvement of symptoms of depression and anxiety after an ACS but also in the prevention of these symptoms later on in the follow-up period. Considering the important association of depression and anxiety and higher morbidity and mortality in patients after an ACS, CBT should be considered as an important treatment option to improve clinical management in patients after an ACS.

Effects of Age and Sex on Determining Symptom Profiles of Depression and Anxiety

The inclusion of these demographic covariates provided valuable information for the identification of the two classes of symptom profiles. An important association was observed between the "severe depression and some anxiety" class and patients' age. Older patients were more likely to report severe symptoms of depression and anxiety than younger patients both at baseline and over the two-month follow-up. Other researchers have stressed the importance of assessing depression in older patients after an ACS [13]. In a study of more than 100 patients 65 years and older who were released from the hospital a month after an ACS, the Beck and the Standard Clinical Interview for the Diagnostic Statistical Manual of Mental Disorders, Third Edition, Revised (SCID) were completed at the time of baseline enrollment [13]. Older patients with depression were more likely to die during the first four months than older patients without depression [13].

This finding has important implications in terms of allocation of resources for the assessment and treatment of depression and anxiety in older patients after an ACS. Older

patients with symptoms of depression and anxiety after an ACS may benefit from more specified diagnostic and treatment programs. Further research should examine the association of depression and anxiety after an ACS and patient's age and determine whether these psychiatric disorders affect subsequent morbidity and mortality in older as compared to younger patients.

There were no significant differences between the symptoms of depression and anxiety in men and women. A note of caution should be taken here in the interpretation of these results, because the sample was fairly small. Future studies would benefit from an increase in the number and variety of sites, and a larger and more representative sample.

This study also highlights the utility of latent class and latent transition analysis in elucidating symptom profiles of depression and anxiety in patients after an ACS. The results demonstrate that depression and anxiety after an ACS tend to occur together, thus treatment of this group of high-risk patients needs to take into account the interplay of these two psychiatric disorders [12]. The findings also stress the importance of assessment and follow-up of patients after an ACS. An important challenge in clinical practice is to improve the quality of life of patients with a chronic illness such as an ACS. In as much, developing strategies for rapidly detecting and managing those at increased risk is an essential step in overcoming this challenge.

Study Strengths and Limitations

This study has several limitations that must be kept in mind in interpreting the results. Patients with very severe depression/ anxiety, patients who had received mental

health care in the prior three months and those who had a diagnosis of substance abuse during the past year were excluded from this study. Thus, the findings may not apply to these high-risk individuals. Another limitation is the short duration of follow-up and small sample size. Latent class and latent transition analysis have several strengths. They combine the cross-sectional measurement and the longitudinal description of change in categories of the latent variable over time, and have considerable flexibility in describing progression and stability, providing a detailed examination of change over time that is difficult to obtain in continuous data analyses [11]. Identifying symptom profiles of depression and anxiety in patients after an ACS may improve diagnostic practices and refine treatment of these patients

Conclusions

The current study demonstrates that patients with depression and anxiety after an ACS can be identified on the basis of the symptoms that they present. This is particularly important to identifying individuals at potential risk for developing clinical complications after an ACS.

Table 4.1: Characteristics of study participants

VARIABLE	TREATMENT (N=45)	CONTROL (N=34)
Age (mean, years)	59.9	60.7
Female (%)	31.1	35.3
White (%)	88.9	88.1
Major Depression History (%)	37.8	29.4
HADS Depression Scores (mean)	8.5	6.5
HADS Anxiety Scores (mean)	8.1	7.1

Table 4.2: Goodness of fit indices for the latent class analysis for the 2 and 3 class model

	G^2	AIC	BIC	Fqcy
2-class model	480.11	538.11	607.19	100
3-class model	435.57	523.57	628.38	32

Table 4.3: Items of the HADS

QUESTION	Class I	Class II
1-I feel tense or 'wound up' (A)	**0.09**	0.44
3-I get a sort of frightened feeling as if something awful is about to happe n (A)	**0.76**	0.38
5-Worrying thoughts go through my mind (A)	**0.21**	**0.67**
7-I can not sit at ease and feel relaxed (A)	**0.15**	**0.77**
9-I get a sort of frightened feeling like 'butterflies' in the stomach (A)	**0.95**	**0.69**
11-I feel restless as I have to be on the move (A)	0.27	0.55
13-I get sudden feelings of panic (A)	**0.97**	**0.67**
2-I do not enjoy the things I used to enjoy (D)	**0.06**	0.51
4-I can not laugh and see the funny side of things (D)	**0.03**	0.3
6-I do not feel cheerful (D)	**0.09**	0.53
8-I feel as if I am slowed down (D)	0.45	**0.75**
10-I have lost interest in my appearance (D)	**0.96**	**0.85**
12-I do not look forward with enjoyment to things (D)	**0.14**	**0.76**
14-I cannot enjoy a good book or radio or TV program (D)	**0.02**	0.3

Figure 1: Latent class profile plot of the 14-items for the HADS baseline only

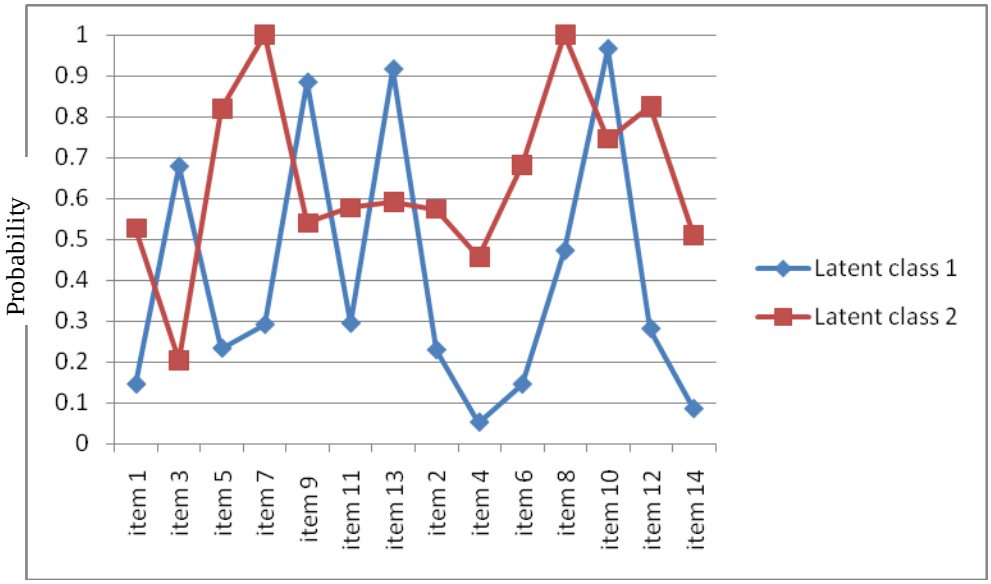

Figure 2: Latent class profile plot of the 14-items for the HADS baseline and month-2

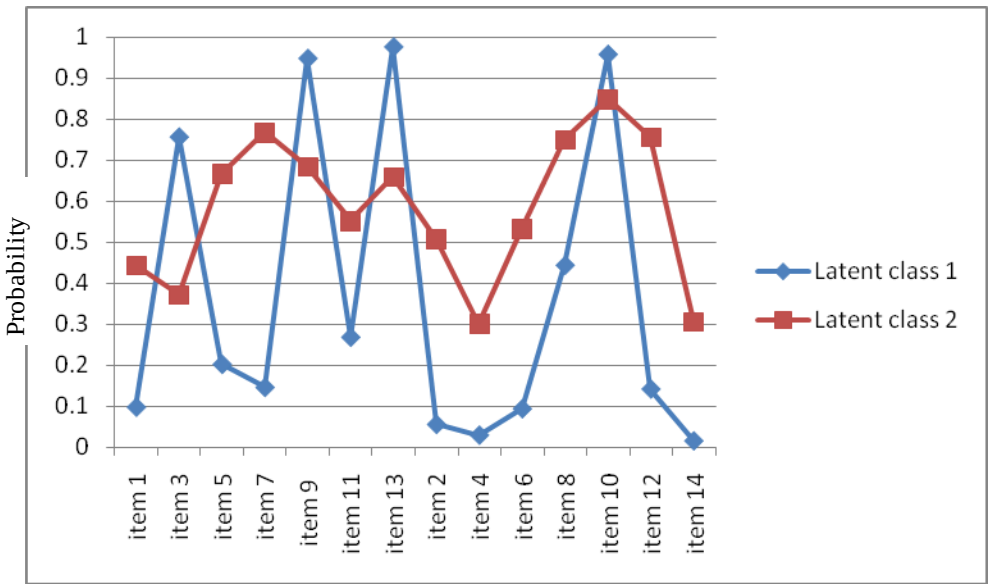

Table 4.4: Membership probabilities by sex at baseline and month-2 of follow-up

	Latent Class I		Latent Class II	
	Male	Female	Male	Female
Baseline	0.578	0.528	0.422	0.471
Month-2	0.643	0.649	0.356	0.350

Table 4.5: Membership probabilities by age at baseline and month-2 of follow-up

	Latent Class I		Latent Class II	
	Younger	Older	Younger	Older
Baseline	0.404	0.742	0.596	0.278
Month-2	0.588	0.700	0.412	0.299

Chapter V

Conclusions

The purpose of the current dissertation was to illustrate the application of advanced statistical techniques to research questions related to depression and anxiety in patients with an ACS.

Chapter II: Depression and Anxiety after an Acute Coronary Syndrome: a Bivariate Mixed Model Approach

The aims of this study were to determine trajectories of depression and anxiety after an ACS, to examine the effects of cognitive behavioral therapy (CBT) on depression and anxiety, and to determine if anxiety and depression symptoms change at the same rate with CBT treatment as indicated by joint modeling of these two psychiatric disorders.

The principal findings of this study suggested that depression and anxiety are highly correlated and persistent in patients with an ACS both at baseline and over the six month follow-up period. The intervention utilized in the parent RCT does not appear to uncouple the association between anxiety and depression, suggesting that CBT has comparable effects on both psychiatric disorders.

Bivariate mixed models are of particular importance in understanding multi-dimensional profiles of psychopathology in patients with mental disorders who typically demonstrate multiple maladaptive behaviors, a variety of symptoms, and decrements in various domains of function, each of which are often highly correlated. A better

understanding of the relative contributions of these various, and inter-dependent, phenomena with regards to patients' symptoms and functionality, could inform appropriate targets for interventions to achieve a better quality of life in patients after an ACS. Future research needs to investigate the roles of anxiety and depression, as well as other indicators of quality of life such as perceived level of stress, and ways of coping with stressful events, as a joint phenomenon in order to more precisely clarify the effects of these psychiatric disorders on mortality, morbidity, and quality of life in patients after an ACS. Additional studies are also needed to compare the effectiveness, and cost-effectiveness of CBT, and other interventions targeting both psychiatric disorders jointly.

Chapter III: Identifying Classes of Response to Treatment of Depression, Anxiety, and Functional Status in Patients After an Acute Coronary Syndrome

The objectives of this study were to (1) identify symptomatology profiles of depression, anxiety, and functional impairment among patients with an ACS; (2) describe changes over time in symptomatology profile; and (3) determine if patients receiving CBT showed signs of remission in depression, anxiety, and impaired function earlier than patients that received usual care. In addition, the associations between symptomatology profile and age, gender, and length of stay in the hospital were examined.

The results of my second paper indicate that a three-class solution was selected to describe symptomatology profiles of patients with an ACS and symptoms of depression and anxiety. One class was characterized by patients with both psychiatric disorders and impaired function (as manifest by the presence of symptoms of anxiety, depression, and impaired function at home), the second by patients with psychiatric disorders but normal

function, and the third by patients with anxiety, but without depression, and having normal function. As compared to a control group receiving usual care, patients who received CBT reported higher rates of symptomatology remission. The results showed a significant effect of CBT in the treatment group, with the highest effect observed between baseline and the second month of follow-up. Latent class and latent transition approach clarifies periods during which an intervention is most likely to be effective in patients with depression and anxiety after an ACS. Moreover, our results suggest that future studies examining patterns of change in these psychiatric disorders and function as they are related to clinical outcomes such as frequency of re-hospitalizations after an ACS, compliance with medications, response to CBT and other meaningful interventions may provide a better understanding of how to approach and treat ACS patients with psychiatric disorders and impaired function [21].

Chapter IV: Profiling Symptoms of Depression and Anxiety in Patients with an Acute Coronary Syndrome Using Latent Class and Latent Transition Analysis

The objectives of this study were to determine the symptom profiles of depression and anxiety in patients with an ACS using the hospital anxiety and depression scale (HADS). A secondary study objective was to examine the effects of age and sex on these symptom patterns.

The results of my third paper indicate that a two-class solution was selected to describe depression and anxiety symptomatology profiles. Models including from two to five latent classes were fit and compared based on the sample size and wellness of fit. Class I was labeled “severe depression and some anxiety”. Class II was labeled “mild

depression and distress anxiety". Regarding the particular items assessed by the HADS, the presence of anhedonia was a key factor differentiating the two symptom profile classes. Patients that endorsed the "severe depression and some anxiety" class gave a positive answer to all the questions that assessed anhedonia, whereas patients that endorsed the "mild depression and distress anxiety" class did not report this symptom. More than 70% of older patients ($\geq$ 60 years old) continued to have severe depression and anxiety at the 2-months follow-up contact.

The results of the current study stress the importance of assessment of depression and anxiety and follow-up of patients after an ACS. Further research should examine the association of depression and anxiety after an ACS with patient's age and determine whether these psychiatric disorders affect subsequent morbidity and mortality in older as compared to younger patients and the reasons for possibly different results. This study also highlights the utility of latent class and latent transition analysis in elucidating the symptom profiles of depression and anxiety in patients after an ACS. This is particularly important in identifying individuals at potential risk for developing clinical complications after an ACS. This finding has important implications in terms of allocation of resources for the assessment and treatment of depression and anxiety in patients after an ACS

Strengths and Limitations of Present Study

This study has several limitations that future longitudinal studies would benefit from. These include the need for a longer duration of follow-up, an increase in the number and variety of participating study sites, and a larger and more representative patient population. Patients with very severe depression/ anxiety, and patients who had

received mental health care in the prior three months or had a diagnosis of substance abuse during the past year, were excluded from this study. Thus, our findings may not apply to these high-risk individuals.

Latent class and latent transition analysis have several strengths. They combine the cross-sectional measurement and the longitudinal description of change in categories of the latent variable (e.g. distress due to a chronic illness) over time, and have considerable flexibility in describing progression and stability of this variable, providing a detailed examination of change over time that is difficult to obtain with more traditional data analyses procedures. Another important advantage of these models is that they allow investigators to examine the impact of the intervention, in this case CBT, on changes in depression and anxiety simultaneously. A latent class-based approach, in particular, can clearly show whether a given status is particularly prevalent at certain times or for certain subgroups, whether individuals in a certain status are more or less likely to undergo a transition, and whether there are significant differences between respective comparison groups.

Final Conclusions

This study highlights the application of advanced statistical techniques in examining depression and anxiety in patients after an ACS. Joint modeling of related outcomes such as those studied in this investigation promise to be very useful in determining the changes over time in an outcome, since these psychiatric disorders are

highly related to each other. The findings also stress the importance of assessment and follow-up of patients after an ACS.

The implementation of statistical models, such as latent transition analysis, that are infrequently used in clinical trials can help us to combine multiple indicators, or multiple sources of information, into a unique composite outcome in order to provide a more complete and multidimensional understanding of changes in relevant factors over time. In the present study, disregarding the high levels of correlation between depression, anxiety, and impaired function in patients with an ACS over time, may result in important information being missed which may be crucial to understanding how and when an intervention should be implemented and in which populations to be most effective.

This study provides support for the idea that patients with depression and anxiety after an ACS can be identified on the basis of the symptoms that they present with. This is particularly important for identifying individuals at high risk for developing clinically significant complications after an ACS such as repeat hospitalizations, as well as poor medication adherence and premature mortality. In addition, the results of the present study illustrate the application and importance of latent class and latent transition analysis in identifying profiles of depression and anxiety in these high risk-patients. Identifying symptom profiles of depression and anxiety in patients after an ACS may improve diagnostic practices and refine the treatment of these patients.

The current study suggests that future research needs to carefully examine, through use of advanced statistical models, how the different aspects of depression and anxiety

after an ACS affect subsequent morbidity and mortality in patients after an ACS. Further prospective studies should focus on the presence of depression and anxiety after an ACS and its association with several clinical outcomes such as recurrent myocardial infarction and other cardiac complications, readmission to the hospital, compliance with cardiac medications, and other factors in the year following the ACS episode and compare the results for the different age groups and gender. An important challenge in clinical practice is to improve the quality of life of patients with a chronic illness such as an ACS. In as much, developing strategies for rapidly detecting and managing these high risk-patients is an essential first step in overcoming this challenge and improving the long-term prognosis and quality of life of these patients.

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Chapter VI

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