

A Hearty Issue: Association of Stress, Anger, and Anxiety with Three Year Heart Failure
Outcomes

by

Andrew J. Dimond

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Name of Candidate: Andrew J. Dimond
Doctor of Philosophy Degree
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DISSERTATION AND ABSTRACT APPROVED:

DATE:

[Redacted Signature]

6/27/18

Dr. Andrew J. Waters
DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY
Committee Chairperson

[Redacted Signature]

6/27/18

Dr. David S. Krantz
DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY
Dissertation Advisor

[Redacted Signature]

6/27/18

Dr. Jeffrey Goodie
DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY
Committee Member

[Redacted Signature]

6/27/18

Dr. Cara Olsen
DEPARTMENT OF PREVENTIVE MEDICINE & BIOSTATISTICS
Committee Member

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DEDICATION

With this I lay my small brick in the foundation of empirical inquiry, I wish to dedicate this work to those who came before in building our knowledge through curiosity and toil. I also wish to dedicate it to those who will come after and continue building upon that foundation. May we continue to reach greater and greater heights from which we can see how our world works just a little better than we could previously.

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Andrew J. Dimond

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ABSTRACT

A Hearty Issue: Association of Stress, Anger, and Anxiety with Three Year Heart Failure Outcomes

Andrew J. Dimond, Ph.D., 2019

Dissertation directed by: David S. Krantz, Ph.D., Professor, Department of Medical and Clinical Psychology

Background. Heart failure negatively impacts the health and quality of life of millions of individuals worldwide. Previous studies have identified stress, anger, and anxiety as psychosocial factors associated with incidence and exacerbation of coronary heart disease and CHF. However, stress, anger, and anxiety often are associated with one another, and the extent to which these characteristics overlap in the degree to which they contribute to CHF exacerbations is unclear. **Methods.** This study involved secondary analyses of the Project BETRHEART dataset, which examined the longitudinal predictors of heart failure exacerbations over a 3 year period. Anger (Weekly Anger Inventory), anxiety (State-Trait Anxiety Scale-State Anxiety), stress (Perceived Stress Scale) and their prospective relationships to all-cause, cardiovascular, and CHF hospitalizations and self-reported CHF symptoms and health status (Kansas City Cardiomyopathy Scale-KCCQ) were examined at baseline, 3 months, and subsequent 6 month intervals over a period of 39 months using marginal models and generalized marginal models. Results yielded between-subjects “chronic” and within-subjects “acute” effects consisting of changes over time in relation to the subjects’ own mean scores. **Results.** There was a predictive relationship between anger and reduced KCCQ, but not between anger and hospitalizations. Anxiety was similarly predictive of KCCQ scores, but was additionally

predictive of CHF and all-cause hospitalizations. Perceived stress was also predictive of KCCQ scores and all-cause and cardiovascular hospitalizations. Analyses of individual predictors controlling for the other two independent variables indicated that acute anger was independently associated with health status, and chronic anger was unexpectedly associated with decreased CHF hospitalization rate. Acute anxiety was independently associated with KCCQ-Clinical Summary scores. Chronic anxiety was independently associated with both CHF and all-cause hospitalizations. Stress was independently associated with KCCQ health status at the acute and chronic levels. Stress was also independently associated with all-cause hospitalizations at the acute level only. Summary measures from the KCCQ produced significant associations at the acute and chronic level with all three types of hospitalizations, except for an acute level effect for KCCQ-Clinical Summary and CHF hospitalizations. When controlling for anger, anxiety, and stress, both KCCQ measures were significantly associated with all three types of hospitalizations.

Conclusion. All three psychosocial risk factors were associated with measures of CHF worsening. Chronic measures of anxiety and stress were significantly associated with more CHF outcomes and stronger relationships compared to acute measures of anxiety and stress. However, when controlling for each other, they each had a unique pattern of association with CHF outcomes, with stress and anxiety having the strongest association with hospitalizations. Mechanisms for these associations may involve changes in health behaviors and physiological activation. Consequently, psychological interventions intended to reduce the significant cost related to CHF re-hospitalizations may benefit most from targeting stress and anxiety and/or the mechanisms linking stress and anxiety to CHF outcomes.

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CHAPTER 1: Introduction

Heart failure, an inability of the heart to pump sufficient blood for the body's needs, reduces quality of life and leads to significant morbidity and mortality. There are many psychosocial risk factors that are known to predict outcomes in heart failure. Anger, anxiety, and stress are three psychosocial risk factors for heart failure that can overlap, but the overlap between them is rarely studied in relation to heart failure. This study used a novel mixed model approach to explore the unique and common predictive power of anger, anxiety, and stress to heart failure outcomes over a 39 month period. The following review will address: the nature of heart failure; biological and psychosocial risk factors for heart failure; theories of emotion; the nature of anger, anxiety, and stress, along with their relationships to cardiovascular disease; the problem of construct overlap amongst anger, anxiety, and stress; racial differences in cardiovascular diseases and emotions, and the difference between current frequently used epidemiological statistical techniques and a mixed model approach.

HEART FAILURE

Congestive heart failure (CHF) is a chronic disease that produces high rates of recurrent hospitalizations, reduces quality of life, and leads to high mortality rates. Heart failure is a progressive disease that often begins with dysfunction of the endothelium (blood vessel lining) and atherosclerosis (arterial fatty plaque formation; 68). Other causes of CHF may include high blood pressure, smoking, alcohol use, and cocaine use. Systolic CHF is characterized by the heart being unable to pump sufficient blood to meet the needs of the rest of the body. Common symptoms of CHF include breathlessness,

fatigue, and fluid overload (89). CHF produces a significant health impact on individuals' lives.

CHF produces a heavy burden both on individual patients and on healthcare systems. CHF is estimated to be present in approximately six million members of the U.S. population (104). A study by Cowie et al (19) found that in a cohort of newly diagnosed CHF patients that 62% died within 1 year of being first diagnosed. Up to 35% of CHF patients are re-hospitalized within 30 days of being released from the hospital (24), and up to 50% are re-hospitalized after 6 months (21). A study by Wexler et al (137) found that 44% percent of a population of 65 year old or younger patients diagnosed with CHF experienced re-hospitalizations within 6 months of hospital discharge. These frequent hospitalizations pose a major disruption in the lives of CHF patients and cost the U.S. healthcare system and Medicare billions of dollars each year (48). Wexler et al. estimated that each re-hospitalization of CHF patients on average incurred a cost of \$7,174. Wexler et al. concluded that interventions producing even slight reductions in re-hospitalizations rates would greatly reduce the financial impact CHF currently produces.

Biological Risk Factors for Heart Failure

Considerable research has been conducted on the biological and behavioral risk factors for CHF deterioration and on the long-term predictors of CHF outcomes (26; 40; 44; 101). Any factor that weakens the heart or increases how hard the heart has to work to pump blood may increase an individual's risk for developing CHF. Currently known common risk factors include high blood pressure, a history of myocardial infarctions (heart attacks), coronary artery disease (CAD), obesity, smoking, alcohol use, and sleep

apnea (82). The current approach to treating CHF often includes prescribing the patient a mix of various medications to reduce the patient's heart rate, improve heart muscle contractility, and reduce blood volume (83). Consequently, the patient's level of compliance with taking medications becomes another risk factor for heart failure worsening. Another behavioral risk factor is diet. A diet containing high amounts of fat can potentiate atherosclerosis and high salt content in a person's diet may lead to increased blood pressure.

Measures of CHF Severity

There are several ways in which the progression of a patient's CHF can be measured and tracked. Common categories include functional status, adverse events, signs, and symptoms.

Functional status is generally concerned with how well the individual is able to complete tasks and activities of daily living, such as grooming, eating, and moving on their own power. Information about a patient's functional status can be collected from self-report information, family report, and/or objective measures, such as observing how far a patient can walk in six minutes (50). Another commonly used index of functional status is the NY Heart Association (NYHA) classification system. It is used to categorize CHF patients into one of four classes of functional status based on their symptoms and functioning (130). Patients in NYHA Class I do not experience any limitations in functional ability. Patients in NYHA Class II experience slight limitation in functional ability, such as being fatigued or short of breath following ordinary physical activity. Patients in NYHA Class III experience marked limitations in functional ability, such as even minor physical activity causing fatigue or heart palpitations. Finally, patients in

NYHA Class IV are severely impaired in their functional ability and experience discomfort from heart failure symptoms even while at rest.

An adverse event refers to any sudden decline in patient health that requires hospitalization or leads to death. The number and frequency of hospitalizations can be seen as one possible proxy of CHF progression.

Signs are indicators of a disease process that are observable by another individual. Signs in CHF patients include things such as rapid weight gain, extreme fluid overload, and shortness of breath after light exertion.

Symptoms are unobservable experiences reported by the patient that may be indicative of a disease process. Examples of possible symptoms reported with CHF include fatigue, mental confusion (sometimes caused by changes in blood flow to the brain), and lack of appetite (caused by changes in blood flow to the digestive tract).

Measuring Self-Report CHF Health Status

Other ways of monitoring CHF include using self-report measures that capture multiple domains of functioning and symptoms. The Kansas City Cardiomyopathy Questionnaire (KCCQ) is one such measure, which assesses domains such as symptoms, treatment self-efficacy, CHF knowledge, social interference caused by CHF, and quality of life (49). As opposed to clinical markers disease progression, the KCCQ also measures aspects of how the patient's various functions of daily life are impaired and also the patient's self-perceived health status. Both of these factors impact a patient's health related quality of life. The proposed study will use the KCCQ scales assessing functional status as well as an overall clinical summary score including symptoms, physical limitations, social limitations, and quality of life. The Functional Status scale has been

associated with NYHA functional status classifications and also to subsequent death or hospitalizations (49). The Clinical Summary Score was chosen because of its ability to predict CHF hospitalizations (49). For example, a study comparing nine measures of CHF change (including multiple health status instruments, physician-assessed functional class, an exercise test, patient weight, and a biomarker) found that the KCCQ-Clinical Summary scale, of the compared measures, was the most predictive of cardiologist judged clinical changes in patients (72). There is also evidence that the KCCQ-Clinical Summary scale is predictive of risk for CHF related hospitalizations and/or mortality (36).

Although the focus of the proposed study will be on the symptom and functional components of the KCCQ. There is evidence that patient perceived health related quality of life is in some cases just as, if not more, valued by CHF patients than actual duration of survival. A study of CHF patients asked the participants to review a series of hypothetical treatments that had different profiles of outcome goals regarding increasing survival time or improving the patient's quality of life, by reducing symptoms (122). Approximately 65% of the participants demonstrated an overall preference for treatments improve their health related quality of life. Based on these results and those of other studies (46), there is evidence that it is important for health professionals to consider and assess both physical status and quality of life in CHF patients.

Psychosocial Risk Factors for Heart Disease

There are a number of psychosocial risk factors that are associated with the development of CHF and other cardiovascular illnesses. There are four main mechanisms that have been proposed by which psychosocial factors could contribute to the

development of heart disease: activation of the autonomic nervous system and hypothalamic-pituitary-adrenal axis, serotonergic dysfunction, secretion of proinflammatory cytokines (cell signaling proteins), and blood platelet activation (35). Some of the psychosocial elements that are related to heart disease include anger, hostility, anxiety, stress, depressive symptomology, and a low level of social support (35; 60; 93; 99).

Depression has been well documented to contribute to CHF outcomes. A meta-analysis of studies found that depression significantly increases the risk of cardiac events and death in CHF patients (109). The same meta-analysis also found that clinically significant depression was observed in at least 20% of the pooled 5,053 participants across the studies. There is also evidence that depression is associated with significant reductions in quality of life among CHF patients (94).

Social support has been examined in relation to CHF in numerous studies and there is evidence that poor social support contributes to hospitalizations and mortality in CHF patients (79). A study of CHF patients also found evidence that negative changes in social support were predictive of reductions in health related quality of life (6). There is also evidence that depression and low social support can have an additive effect in producing increased risk of hospitalization or death (14).

A more acute form of psychosocial factor associated with heart disease worsening has been termed “triggering.” A growing body of research indicates that the sudden experience of intense emotions, such as stress, anger, or sadness, in vulnerable individuals may trigger acute cardiac events within a matter of hours (123). Kark et al (62) found that deaths due to cardiovascular causes spiked amid the first day of missile

strikes on Israeli cities during the Persian Gulf War. Leor et al (75) examined Los Angeles County coroner reports for the week before, the day of, and six days after the 1994 Northridge earthquake. They found that the number of deaths due to acute cardiac causes increased from a daily average of 4.6, during the week before, to 24 on the day of the earthquake. They further reported that 16 of the deceased individuals either exhibited premonitory symptoms or died during the first hour after the quake began. A study by Jianwei et al (61) explored the incidence of cardiac admissions to a hospital in Brooklyn, New York 60 days prior to and 60 days following the terrorist attacks on September 11th, 2001. They found a significant increase in admissions for acute myocardial infarctions and tachyarrhythmia in the days following the attacks. Lampen et al (71) studied the incidence rate of cardiac emergencies in the greater Munich area during the 2006 Fédération Internationale de Football Association (FIFA) World Cup. They observed that on days in which the German team played cardiac emergencies increased by 2.66 times compared to a control period. They also found that the highest rate of events occurred during the initial 2 hours following the start of a match.

Takotsubo cardiomyopathy (TC) is another form of acute cardiovascular syndrome that appears to be triggered by sudden emotional stress (66). It can occur without significant prior coronary disease and presents similarly to acute coronary syndrome. Its name is derived from the Japanese word for an octopus fishing pot (蛸壺), due to the heart's left ventricle taking on a pot-like shape during TC. It occurs primarily in middle-aged and older women after experiencing sudden, extreme emotional distress and is usually reversible with proper treatment.

The biological processes underlying emotional triggering may include a reduction in parasympathetic nervous system activity, sudden changes in heart rate and blood pressure, neuroendocrine activation, inflammatory responses involving cytokines, and increased blood platelet activity (123). Those processes then increase the likelihood of coronary plaque disruption, thrombus formation, cardiac dysrhythmia, and myocardial ischemia (123).

THEORIES OF EMOTION RELEVANT TO HEALTH AND DISEASE

Affective researchers differ in the definitions of what is an emotion and what causes one to experience a given emotion. For example, in summarizing the affect and emotion literature, Moors (90) proposed that there are five principal components to an affective experience:

(a) a cognitive component; (b) a feeling component, referring to emotional experience; (c) a motivational component, consisting of action tendencies or states of action readiness (e.g., tendencies to flee or fight); (d) a somatic component, consisting of central and peripheral physiological responses; and (e) a motor component, consisting of expressive behavior (e.g., fight and flight and facial and vocal expressions). These components correspond to functions such as: (a) stimulus evaluation or appraisal; (b) monitoring (which may serve the further function of control or regulation); (c) preparation and support of action; and (d) action. (pp. 626)

Various theoretical approaches to emotion differ in the extent to which they include and emphasis these components.

Another key difference in the various theories of emotion is the proposed mechanism by which emotional experiences arise. For example, some theorists, such as B.F. Skinner and Paul Ekman, have proposed that emotions, through learning history and evolutionary selection, arise in response to environmental stimuli and prompt us in the direction of adaptive behavior (111). A different school of thought, first developed by William James, is that emotions arise as a result of physiological changes in response to events, which does not require any form of cognitive evaluation (111). In contrast to these two non-evaluative schools of emotional theory, conceptualizations by researchers like Richard Lazarus and Aaron Beck have argued that cognitive appraisals, in some theories conscious and in others unconscious, are the fundamental cause of emotions (111).

Another dimension along which approaches to emotion diverge regards whether different emotions are associated with unique physiological activation or a more general response. One well known example of the latter would be Schachter and Singer's (112) proposal that the physiological arousal associated with emotions is nonspecific, with emotions only differing based on the cognitive appraisal following the arousal. Other researchers have proposed that specific emotions differ in the physiological or behavioral responses they elicit and/or that elicit them, i.e., autonomic specificity of emotions (76). Those who propose that emotions have autonomic specificity argue that there are primary emotions, each of which have an associated unique pattern of physiological activation and behavior. For example, Ekman's (33) theory proposes that there are basic emotions that differ from one another in their associated behaviors (e.g., facial expressions). Based on the concept of autonomic specificity of emotions, it would then follow that some

patterns of physiological activation associated with specific emotions may have more detrimental consequences for already stressed organ systems in the body, such as the heart in a patient with CHF. Therefore, the theory of autonomic specificity of emotions suggests one potential mechanism by which specific emotions may have unique consequences for health outcomes in CHF patients.

ANGER AND CARDIOVASCULAR DISEASE

Anger has long been associated with worsened cardiac health, both in folk wisdom and scientific research. Some of the first major research linking anger and cardiovascular disease came about in the 1970's as a result of growing interest in the Type A personality construct (125). Type A individuals were thought to be more likely to exhibit competitiveness, impatience, aggressiveness, intense work focus, and anger (36). Research conducted over ensuing decades did not bear out a strong or consistent link between the full Type A personality construct and cardiovascular illness, but the hostility and aggression subcomponents of the larger Type A construct were found to predict the development of cardiovascular diseases (125).

The discovery of anger's link to cardiac illnesses has led to the continued modern research interest in anger as a predictor of heart disease. Currently, researchers often use a three-factor model to understand anger-related experiences (125). The three-factors are anger, hostility, and anger expression. Anger is generally used to refer to the actual affective experience of being angry and is divided into a more acute form, state anger, and a more chronic dispositional form, trait anger. Hostility is the cognitive dimension of anger and is often characterized by cynicism and negative attributions regarding the

behaviors of others. Finally, anger expression refers to verbal or physical behavior that is antagonistic in nature.

Numerous studies have explored the link between the three forms of anger experience and cardiovascular illness. For example, Jenner et al (59) examined hospital readmissions amongst a sample of 175 CHF patients and found that trait anger significantly predicted length of stay in the hospital, but not number of readmissions. Newman et al (96) conducted a 10 year prospective study with 1,749 participants to elucidate the relationship between hostility and CAD. They found that the presence of any observed hostility (as measured via a structured interview) at baseline was associated with a doubled risk of developing CAD during the course of the study, when controlling for other cardiovascular and psychosocial risk factors. Newman et al. also used a self-report measure of hostility, but found that it did not significantly correlate with increased risk of developing CAD and it only had a .12 correlation with the observational hostility measure.

When examined across multiple meta-analyses, the three forms of anger experience generally provide a mixed level of risk prediction and are often reduced to non-significance when controlling for other risk factors (125). While some measures of anger have not produced highly consistent and significant results, state anger may still prove to be a useful measure in relation to predicting cardiovascular events.

Anger as a Trigger

There is a growing body of literature that indicates the importance of acute anger in triggering cardiac events. Mittleman et al (88) conducted a study using a case-crossover methodology to examine whether there is a link between acute experiences of

anger and myocardial infarctions. They found that the relative risk of a myocardial infarction was 2.3 during the 2 hours following experiencing an episode of heightened anger. Tofler et al (131) completed a similar case-crossover study and found that patients had a 4.1 relative risk of myocardial infarction in the 2 hours following an episode of intense anger. A meta-analysis conducted by Mostofsky et al (92) found that the risk of cardiovascular events was heightened for 2 hours after experiencing an outburst of anger in a sample of nine case-crossover studies. The same meta-analysis also found that outbursts of anger increase individuals' risk of various cardiovascular events, including: cardiac arrhythmia, ischemic and hemorrhagic stroke, myocardial infarction, and acute coronary syndrome (any condition in which blood supply to the heart is suddenly obstructed; 92). A study of patients with implanted cardioverter-defibrillators (ICDs) found that heightened levels of anger were significantly associated with the 15 minute period prior to the development of a ventricular arrhythmia (72). Episodes of anger were also associated with a heightened risk of experiencing myocardial ischemia in a study of patients with CAD (41).

ANXIETY AND HEART DISEASE

As with anger, strong evidence has accumulated that anxiety contributes to the development and exacerbation of heart disease. Barlow described anxiety as “a future-oriented mood state in which one is ready or prepared to attempt to cope with upcoming negative events” (4). The experience of anxiety is connected with significant physiological activation which acts to ready the body for responding to whatever threat may be eliciting the anxiety. In this regard anger and anxiety have a functional overlap in

acting to prepare for response to a threat and can potentially be seen as opposite sides of the same fight-or-flight coin.

A meta-analysis of 20 studies produced evidence that individuals with more anxiety were at increased risk of developing CAD and dying due to cardiac causes, independent of demographic variables, biological risk factors, and health behaviors (107). The parasympathetic physiological activation produced by anxiety, particularly heightened heart rate, has a clear risk of possibly directly exacerbating already present heart conditions. Frequent and/or sustained physiological activation may burden the cardiovascular system and could be part of why anxiety has been found to be predictive of developing heart disease.

Anxiety as a Risk Factor for CHF

There is also extensive research evidence linking anxiety to negative outcomes in CHF specifically. A meta-analysis of 73 studies that included both CHF patients and measures of anxiety found that up to 55% of the meta-sample of 26,366 patients reported elevated symptoms of anxiety and up to 29% of the patients reported clinically significant anxiety symptoms (30). A retrospective analysis of 236,079 Veteran's Administration patients found that individuals with a diagnosed anxiety disorder had a hazard ratio of 1.19 for developing CHF (42). When pharmacological treatment for anxiety was controlled for, the hazard ratio increased to 1.46 (42). A prospective study of 238 CHF patients found that anxiety scores at baseline were associated with baseline physical functioning and predicted deterioration in physical functioning after a 6 month time period (115). Another study of physical functioning in CHF patients provided evidence that anxiety was associated with reduced self-report physical functioning and that its

impact was moderated by utilization of avoidant coping strategies (32). A study of CHF patients treated with an implantable cardioverter defibrillator (ICD) found that higher anxiety was associated with reduced adherence to important prescribed dietary restrictions, such as reducing salt and fluid intake (80). Similarly, another study found that reduced medication compliance mediated a relationship between higher anxiety and shorter event-free survival in patients with CHF (22). Overall, these studies indicate that anxiety appears to both have direct negative impacts on CHF and indirect health behavior impacts that reduce treatment compliance, which in turn leads to more frequent negative outcomes.

STRESS

The term stress has many different definitions and may encapsulate numerous levels of analysis. There are considered to be three main categories of stress research (18). The first of these categories defines stress as a physiological reaction to demanding situations. This approach derived from the works of Walter Cannon and Hans Selye, and is often concerned with the measurement of hormones and other biomarkers of physiological reactivity (18).

The second category of stress research is based around measuring objective external events that are frequently associated with adaptive demands (18). This research is based on the assumption that numerous and/or major life changes, including positive ones like marriage or a promotion, are inherently stressful. Part of the research in this area exclusively focuses on either just major life events or just minor daily events. Minor life events characterize daily hassles such as being cutoff in traffic or arguing with someone.

The final category of stress research was founded out of the work of Richard Lazarus and defines stress as occurring when organisms perceive that environmental demands will exceed their coping capacity and experience a negative emotional reaction (73). This category of stress is concerned with measuring one's appraised capacity to respond to situational demands and can be referred to as "perceived stress" (18). The Perceived Stress Scale is one measure that was designed to quantify the extent to which an individual appraises events or situations in one's life as stressful or being out of one's control (17). The PSS has been used to measure stress in behavioral, epidemiological, and clinical research encompassing a wide range of samples and populations (3; 11; 16; 17; 47; 74). For example, the PSS was used in one study to provide evidence that individuals reporting higher perceived stress also demonstrated lower proinflammatory cytokine production at the site of a wound (3).

Stress and Cardiovascular Disease

Numerous studies have examined the relationship between cardiovascular disease and stress. Significant findings have been produced by various studies examining the relationship between laboratory mental stressors and cardiac ischemia (disruption in blood supply; 67). Mental stress tasks that have been used include activities such as public speaking (103) and mental arithmetic tasks (12). Stress, among other factors, may also trigger cardiac events (see Psychosocial Risk Factors above). A large multinational case-control study (INTERHEART) found that chronic stress was associated with a doubled risk for experiencing a myocardial infarction (108). The Whitehall II study produced evidence that individuals with stressful work and low control over their jobs had an increased incidence rate of CAD (8). There is also a literature associating

perceived stress with the development of cardiovascular disease. A meta-analysis of six studies found that increased perceived stress had an aggregate risk ratio of 1.27 for with elevated coronary heart disease incidence (105).

Stress and CHF

Psychological stress is known to indirectly affect CHF, by negatively influencing a number of the factors, such as alcohol use and triggering of inflammatory responses, which are predictive of CHF outcomes (124). Limited research has been conducted regarding the degree to which stress directly influences CHF outcomes and hospitalizations. Most research that has been conducted in this area has involved either retrospective designs, which have not been able to firmly establish causation, or short-term laboratory based experiments with high impact events, which lack ecological validity compared to the kinds of long-term stressors that most people face in their lives (86; 140). One such laboratory study of CHF patients did provide evidence that a stress provoking task, such as verbally subtracting digits while being urged to perform better, can lead to blood flow disruptions in the heart comparable to those produced by a potent vasodilator (136). There is also one prospective cohort study which found that individuals who had poor health at baseline and reported high levels of chronic stress had nearly double the risk of developing CHF (97).

Perceived Stress and CHF

The relationship between stress appraisal and CHF is another topic upon which limited research has been conducted. A correlational study of heart failure patients found that those who had a greater sense of perceived control, a core element of stress appraisal, were more likely to exhibit less emotional distress and higher functional status (27). A

study examining stress appraisal and CHF by Endrighi et al (34) was conducted using the BETRHEART study sample. This study found that patients who repeatedly reported high levels of appraised stress on the PSS had a higher likelihood of cardiovascular related hospitalizations and death, when compared to patients with lower stress scores. A Master's Thesis study by this author (25), also using the BETRHEART dataset, explored the unique and common contributions of state anger and appraised stress to cardiovascular related hospitalizations or deaths, self-reported CHF symptom status, and functional status. This study found that perceived stress was more strongly associated with outcomes than state anger. State anger was associated with short-term fluctuations in decreased functional status and mean worsened symptom status in CHF patients, but psychological stress was more strongly associated with hospitalizations and death, functional status, and symptom status than state anger. After controlling for perceived stress, state anger was not associated with any of the outcome measures. This study provided evidence that the effects of state anger may operate through its associations with psychological stress. The results of this study point to an important issue regarding the overlap between emotions and stress and raise questions about the shared and unique characteristics of each of these psychological variables.

OVERLAP BETWEEN STRESS, ANGER, AND ANXIETY

As previously noted, an important question rarely addressed by research is the degree to which stress, anger, and anxiety overlap with each other. Most studies treat stress, anger, and anxiety as wholly separate variables. However, the overlap between these constructs may be important in predicting cardiovascular outcomes. In discussing emotions and their association with cardiovascular disease, a review by Suls and Bunde

(23) noted that it is not known whether the contribution to cardiovascular disease of each of these constructs is independent, or whether it results from the overlap between these variables. Although their discussion was directed at specific emotions, one can argue that psychological stress also has many points of overlap with emotions and is potentially confounded with them in some cardiovascular studies. Kubzansky and Winning (70) further make the point that:

Environmental events are considered stressors and emotions are considered responses to stressors. A negative emotion response occurs if demands are perceived to exceed one's ability to cope. Important to note is that any given stressor can be associated with different emotions. For example, losing one's job may provoke anger in some individuals and depression in others. Thus, emotions can be considered products of stressors as well as mediators of their effects. (pp. 616)

Thus, these authors view emotions as one of several possible responses to stress. In addition, emotions can also play a role in mediating other possible responses to stress, such as physiological and/or behavioral changes. In a similar manner to Kubzansky and Winning (70), the theoretical framework for this study will assume that when individuals experience a potentially threatening event and appraise that they do not have sufficient coping abilities to effectively respond to it, they will then perceive themselves to be stressed. Subsequent to perceiving themselves as stressed, they will experience a negative emotional response that will vary depending on situational and/or organismic factors, such as learning history, genetics, etc.

Previous studies have also, to varying degrees, explored the relationship between stress, anger, and anxiety. As mentioned above, this author (25) found that when state anger and perceived stress were simultaneously analyzed for predicting CHF outcomes, perceived stress came out as the only significant predictor. Smith et al (117) conducted a set of studies on hostility and found that individuals who experience high hostility and anger are more likely to experience more severe and more frequent daily stressors, reduced social support satisfaction, and have fewer social supports. Each of those associated factors could lead to increased perceived stress and increased activity of the hypothalamic-pituitary-adrenocortical axis and sympathetic-adrenal-medullary system, which can promote the development of cardiovascular disease. A study of the psychometric properties of the Weekly Stress Inventory (a measure of stressful minor events someone experienced over the last week) when used with a heart failure population found that minor events were significantly correlated with a measure of Type A personality, a trait associated with anger (91). Girardi et al (46) found that increased interpersonal conflict in the workplace, which may lead to both stress and anger, was related to increased serum levels of pro-inflammatory cytokines (intercellular messaging proteins). A heightened inflammatory response may contribute to the development of atherosclerosis, which can lead to the development of CHF. In addition, an experimental laboratory study provided evidence that situations which lead to feelings of uncertainty and which are perceived by individuals as being unavoidable, will produce anxiety. On the other hand, situations which lead to feeling uncertainty and are perceived as being something that someone else could have prevented happening produce both anxiety and anger (2). A study by Ohira et al (98) examined the relationship between anger, anxiety,

depression, and carotid arterial wall thickness (a subclinical indicator of cardiovascular disease development). Anger was the only independent variable that was significantly associated with thicker carotid walls (indicating the presence of plaque formation). Anger remained significant even when controlling for anxiety and depression. In sum, a body of evidence indicates that there are important interactions between stress, anger, and anxiety. At this time, however, the full extent of this relationship is not clear and further research appears to be warranted. Simultaneous analyses of psychological risk factors may be vital for appropriately differentiating the unique and shared contributions of said risk factors to CHF outcomes.

As mentioned above, there are several physiological mechanisms by which stress, anger, and anxiety may independently or in combination contribute to the development of heart disease: activation of the autonomic nervous system and hypothalamic-pituitary-adrenal axis, serotonergic dysfunction, secretion of proinflammatory cytokines (cell signaling proteins), and blood platelet activation (25). Stress, anger, and anxiety likely also have unique and common contributions to behaviors that lead to worse CHF outcomes, such as physical inactivity, medication non-compliance, and poor dietary control.

RACIAL DIFFERENCES IN CARDIOVASCULAR DISEASE AND EMOTIONAL EXPERIENCE

There is significant evidence of race differences in the risk and progression of cardiovascular diseases and in the psychosocial responses to such conditions. For example, African-Americans have a threefold increased risk of ventricular hypertrophy when compared to Caucasians (141). African-Americans also have a 3 to 7 times higher risk of developing hypertension than Caucasians (110). When treating hypertension in

African-Americans, beta-blockers and angiotensin-converting-enzyme (ACE) inhibitors appear to have a blunted effect compared to when they are used with Caucasian patients (15; 128). This frequently necessitates the adjunctive use of a diuretic, which can in turn further lower the effectiveness of beta-blockers and ACE inhibitors (13; 15; 128). CHF occurs at a rate of approximately 9.1 cases per 1000 individuals in African-Americans and approximately 6 cases per 1000 individuals in Caucasians (113). This difference in CHF incidence may be in part due to risk factors such as hypertension and diabetes, which occur at higher rates in African-Americans than Caucasians (113). African-Americans are also at increased risk for an earlier onset of CHF (28). Caucasian patients are predominantly diagnosed with ischemic CHF, while African-American patients are more likely to develop non-ischemic CHF (113). African-Americans with CHF also experience an increased risk of mortality compared to Caucasian patients (45).

Additionally, there may be important racial differences in the experience of anger, anxiety, and stress. Anger and hostility may present differently in African-Americans when compared to Caucasians, potentially leading to a distinct impact on the course of CHF. There is evidence that exposure to racist stimuli can cause increased anger and elevated diastolic blood pressure in African-American men (37). A study by Finney et al (38) found that African-American men with low self-reported hostility scores had significantly higher blood pressure reactivity to a laboratory stress task than high hostility score African-American men and low and high hostility score European-American men. A study by Williams et al (138) found a significant association between trait anger and intima-medial thickness (IMT) of the carotid artery in African-American men. They did not find the same association in Caucasian men or women of either race.

Regarding anxiety, there has been limited research conducted examining anxiety specifically in African-Americans. However, a large epidemiological study found that African-Americans were more likely to meet criteria for PTSD during adulthood, but Caucasian individuals have a higher incidence of panic disorder, generalized anxiety disorder, social anxiety, and PTSD during childhood. However, when African-Americans met criteria for an anxiety disorder, they reported higher levels of symptomatology, distress, and functional impairment compared to Caucasians (55). When an anxiety disorder is present in African-American individuals, this greater level of distress and functional impairment may increase their risk for developing cardiovascular diseases, including CHF.

For stress, there are a number of studies and hypotheses linking African-American race with an increased experience of stress. Sherman James proposed a hypothesis he termed “John Henryism” to explain the higher rates of stress-related health conditions in African-Americans (58). James posited that individuals of low socioeconomic status, African-Americans in particular, experienced an increased frequency of psychosocial stressors, such as financial hardships and racial discrimination. These daily stressors in turn can be highly taxing on an individual’s coping capacity. This hypothesis states that some individual will respond to these frequent stressors with sustained high effort coping strategies. Consequently, those individuals will be more likely to develop stress-related illnesses as the strain of continued high effort coping accumulates over time. Studies by James and his colleagues also provided empirical support for his hypothesis (58). There is additional evidence that stereotype threat (the fear of confirming stereotypes of a

minority social group) is another unique stressor that African-Americans experience, and it has been linked with increases in mean arterial blood pressure (7).

Relevant to the present study, it is possible to hypothesize that at least some of the health disparities between African-Americans and Caucasians in CHF outcomes may be due to differences in both the frequency and the way they experience stress and negative emotions, such as anger and anxiety. Although a complete review of racial and cultural differences is beyond the scope of this dissertation, since the study sample consists of predominantly African-Americans, these issues are important to consider in interpreting results.

DETERMINANTS OF HOSPITALIZATIONS IN HEART FAILURE

Heart failure is characterized by high rates of hospitalizations. As noted earlier in this chapter, up to 35% of CHF patients are re-hospitalized within 30 days of being released from the hospital (24), and up to 50% are re-hospitalized after 6 months (21). The high rates of recurrent hospitalizations in CHF patients pose an obvious concern to health care providers and to medical care systems. Numerous studies have attempted to explore what factors contribute to or are associated with repeated CHF patient hospitalizations.

Direct symptoms of CHF that can lead to hospitalization include excessive fluid buildup, particularly in the lungs, and insufficient blood flow, due to cardiac muscle weakening (142). Evidence also indicates that failure to comply with medication or diet regimens are important predictors of hospitalizations as well. A meta-analysis of 10 studies examining digoxin medication compliance in patients with CHF and/or atrial fibrillation (another serious heart condition that leads to poor blood flow) found that

43.1% of patients across the studies were not compliant with their medication treatment (65). A prospective study by van der Wal et al (134) examined CHF patient compliance with non-pharmacologic interventions following release from hospitalization, specifically: diet change, fluid restriction, daily weight monitoring, and exercise. They found that being non-compliant with even one of the interventions led to a significantly higher risk of death or CHF related hospitalization (hazard ratio = 1.40).

CHF patients also quite frequently have comorbid conditions, both cardiovascular and non-cardiovascular, which further contribute to repeat hospitalization rates. Comorbid cardiovascular conditions, such as hypertension and arrhythmias, can have a synergistic effect with CHF and cause a continued reshaping and weakening of the heart (142). Consequently, a patient may become hospitalized for an arrhythmia or myocardial infarction that was potentiated by the progression of the patient's CHF. Diabetes mellitus, sleep disordered breathing, and thyroid dysfunction are common examples of non-cardiovascular comorbid conditions often seen in CHF patients. These conditions can exacerbate or be exacerbated by poor cardiac functioning, possibly leading to hospitalizations (142).

It is also important to consider that most individuals who develop CHF—at least ischemic heart failure—are older and have a reduced overall health status (56). Thus, they may have an increased risk of developing diseases such as cancer and experiencing accidents, such as falls, that lead to hospitalizations.

Due to numerous ways that CHF can indirectly lead to hospitalizations, CHF patients may present with many hospitalizations that are not primarily attributed to CHF. A study examining CHF cases in Olmsted County, Minnesota from 1987 through 2006

found that of 1077 CHF patients, 895 had been hospitalized at least once and 43% (n = 459) had experienced 4 or more hospitalizations (29). They further found that the CHF patients as a group had been hospitalized a total of 4,359 times. CHF was considered the primary cause of 713 (16.5%) hospitalizations, 936 (21.6%) hospitalizations were attributed to other cardiovascular conditions, and the majority of hospitalizations (n = 2,679, 61.9%) were identified as not being directly cardiovascular related (29). This suggests the importance of considering all-cause, as well as cardiovascular or heart-failure related hospitalizations, in research assessing health outcomes in heart failure patients.

Post-Hospital Syndrome

The repeated admissions of CHF patients to hospitals may also been related to what has been called post-hospital syndrome, which is a 30 day period of vulnerability to subsequent medical events that occurs following hospitalization (69). It has been proposed that post-hospital syndrome occurs as a result of the various physical and psychosocial stressors that patients experienced during and immediately after hospitalization (69). A few examples of these stressors include reduced sleep time and quality, reductions in physical activity, and insufficient nutrition (69). There is also evidence that stressful hospitalization experiences may lead to acute stress disorder and PTSD in some patients (31). The existence of a post-hospital syndrome is consistent both with the idea that stress and emotions can exacerbate a patient's health status and with the hypotheses proposed in this dissertation.

MULTILEVEL ANALYSES IN HEALTH RESEARCH

Most epidemiologic studies of CHF use a single baseline measure to predict outcomes. Some studies use standard regression models or repeated measures ANOVA, both of which are restricted to examining between-subject effects by the assumptions of their models. Both of those types of traditional statistical approach do not allow for determining the degree to which changes in an independent variable over time are correlated with changes in the dependent variables, a within-subject effect (23).

Additionally, the assumptions of those traditional approaches require that any participants with even a single missing data point be excluded from the entire analysis (95). This poses a significant issue for longitudinal studies conducted over long timespans, particularly in the health sciences where some participants may be too sick at times to have data collected at a given time point. Consequently, these analyses can lose significant power due to excluding data from numerous participants (95).

Recently, multilevel analyses have been growing in popularity because of their ability to address a number of the problems of using traditional analyses with health science data. Mixed models are one example of multilevel analyses. A mixed model receives its name from the fact that it incorporates both fixed and random effects (23). Fixed effects are assumed to have a relatively consistent impact across participants, such as response to a treatment, and will generally be the primary focus of interest for researchers. Random effects, on the other hand, are assumed to vary widely from individual to individual, but are important to model in order to reduce the overall unexplained variance in the data (23). Mixed models produce models of each participant's individual data over the course of the study. Consequently, between-subject effects can be observed by averaging across individuals and within-subject effects can be

observed by looking at deviations from an individual's own average (95). Mixed models have an additional advantage in that their assumptions allow for missing data from participants (95). There are also important limitations to mixed models. Mixed models can only provide correct inferences about missing data if it is missing in a random manner (23). This limitation is also true to an even greater extent in traditional analyses, since mixed models preserve all of the non-missing data from a participant versus the traditional approaches excluding all of the participant's data if a single time point is missing. In order to be valid, mixed models also depend on their underlying assumptions being met. For example, incorrectly specifying the covariance structure of a mixed model can significantly bias its results.

Marginal models, on the other hand, model the averaged response of the population to an IV. Marginal models have many of the same advantages of mixed models, including being able to handle missing data and produce between-subjects and within-subjects level effects estimates. Mixed models and marginal models, when fitted with a maximum likelihood-based method (51), will also yield nearly identical estimates for continuous DVs (57). A unique advantage of marginal models is that they are more robust against misspecification of the underlying covariance structure of the data (51).

When selecting to use either mixed models or marginal models for non-linear data, a case in which the two modeling methods will not produce equivalent results, researchers must consider whether they are more interested in subject-specific outcomes (mixed models) or population level outcomes (marginal models) in order to be able to properly interpret the results.

SUMMARY AND RATIONALE

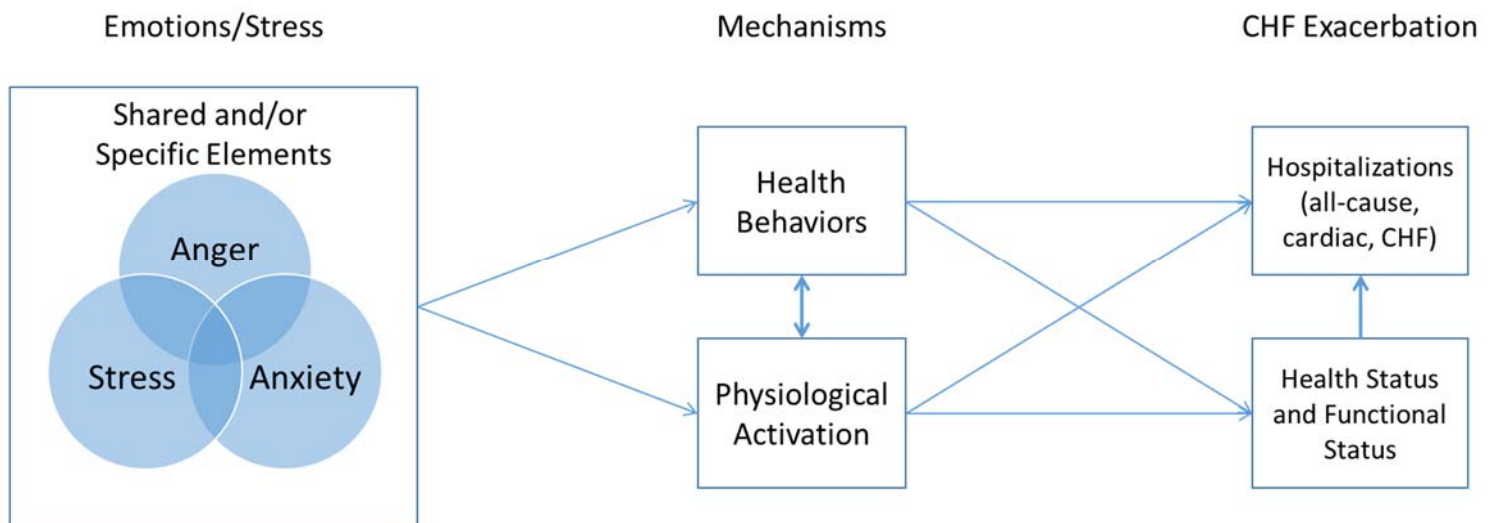
CHF significantly reduces the quality and length of life of millions of individuals and cost patients and health care systems billions of dollars each year. Numerous studies have been conducted to better understand the biological and psychosocial risk factors for developing CHF and CHF worsening. Anger has previously been identified as likely playing a significant part in the progression and exacerbation of CHF, including triggering acute cardiac events. Anxiety is also an emotion that has been associated with the development and worsening of CHF in previous studies. Stress in general has also been identified as probably contributing to the development and course of CHF. However, limited research has been conducted that specifically examines the degree to which stress appraisal may specifically contribute to CHF outcomes. Similarly, there appears to be a lack of research that assesses the potential overlap and unique contributions of anger, anxiety, and stress to CHF, particularly using a mixed model statistical approach.

A previous study (34) produced from the same Behavioral Triggers of Heart Failure (BETRHEART) project as this study found that scores on the Perceived Stress Scale, a measure of stress appraisal, were related to adverse events (deaths and hospitalizations) over a nine month period. A study conducted by this author (25) also using BETRHEART data over the same nine month timeframe found that anger did not predict outcomes when controlling for perceived stress, but perceived stress was still significantly associated with outcomes when controlling for anger. This study sought to extend those results and compare the relative importance of stress appraisal, anger, and anxiety in predicting outcomes for CHF patients over a 39 month timespan.

Conceptual Model

The conceptual model for the study is illustrated below. Anger, anxiety, and stress are presented as having overlapping and unique characteristics which lead to negative effects on patients' level of physiological activation, such as increased heart rate, blood pressure, inflammatory responses, etc. These emotions also have effects on the patients' engagement in health behaviors, such as drinking more alcohol to reduce anxiety or forgetting to take medications because they are distressed about something. There are also effects of emotions on symptom perception and responses to illness (70). Consequently, increases in physiological activation and/or changes in health behaviors can lead to increased risk of hospitalizations and reductions in health and functional status. The reductions in health status and functional status themselves can then also lead to an increased risk of hospitalization, as the patients become more vulnerable to adverse events that could necessitate hospitalization.

Conceptual Model of Study



Specific Aims and Hypotheses

Anger, anxiety, and stress are overlapping psychological concepts that have each been associated with risk of poor cardiovascular disease outcomes. In a longitudinal design involving repeated assessments, the present study investigated the unique and common contributions of these variables to poor outcomes in patients with heart failure. We also compared chronic vs. acute relationships between psychological measures and CHF outcomes. The study aims were as follows:

Aim 1: To determine whether psychosocial measures of anger, anxiety, and stress predict adverse outcomes and reductions in functional status in CHF patients over a 39 month period.

Hypothesis 1a: In a study involving repeated assessments of anger and health status at 6 month intervals, there will be a predictive relationship between anger (measured by an ad-hoc instrument using items from the Weekly Stress Inventory; WSI) and subsequent poorer health status (measured by the Kansas City Cardiomyopathy Questionnaire; KCCQ). There will not be a relationship between anger and subsequent hospitalizations.

Hypothesis 1b: Increased anxiety (measured by the State Trait Anxiety Inventory; STAI), will be associated with increased hospitalizations and poorer health status.

Hypothesis 1c: Increased stress (measured by the Perceived Stress Scale; PSS) will be associated with increased hospitalizations and poorer health status.

Aim 2: To determine the independent contributions of anger, anxiety, and stress to CHF worsening.

Hypothesis 2a: Independent of stress and anxiety, increases in anger will not be significantly related to hospitalizations. Anger will be negatively associated with health status.

Hypothesis 2b: Independent of stress and anger, anxiety will be prospectively related to higher rates of hospitalizations and reduced health status.

Hypothesis 2c: Independent of anxiety and anger, stress will be prospectively related to higher rates of hospitalizations and reduced health status.

Aim 3: To compare the predictive power for hospitalizations of self-reported health status to the predictive power of stress, anger, and anxiety.

Hypothesis 3: Both acute and chronic KCCQ measures of health status will have the strongest association with subsequent hospitalizations, compared to stress, anger, and anxiety.

Aim 4: To compare the chronic vs. acute effects of stress, anger, and anxiety on hospitalizations, symptoms, and health status.

Hypothesis 4: Chronic high stress and anxiety, but not acute increases in stress and anxiety, will be associated with more hospitalizations and poorer health status. Chronic anger vs acute increases in anger will be associated with more symptoms and poorer health status.

CHAPTER 2: Method

PARTICIPANTS

The sample for this study consisted of 147 patients diagnosed with systolic CHF at the University of Maryland Medical Center (UMMC).

Eligibility criteria for participation in the study consisted of having been diagnosed with heart failure and: (1) exhibiting a New York Heart Association Class II-IV functional status for at least three months; (2) displaying a left ventricular ejection fraction less than or equal to 40%; and (3) being 21 years of age or older.

The following exclusion criteria were used for the study: (1) clinically significant mitral valve disease; (2) myocarditis diagnosed in the past six months; (3) thyroid dysfunction as primary etiological factor of HF; (4) current alcohol abuse or alcohol abuse within the past 6 months; (5) implanted left ventricular assist device; (6) prior heart transplantation; (7) active cancer treatment; (8) living in nursing home; and (9) cognitive impairments interfering with consent or questionnaire completion, determined by a passing score (greater than 13) on the Mini-Mental State Examination-Brief Version (MMSE-BV).

All participants were fully informed about the study and they provided written consent to participate. The study was approved by the IRBs of the Uniformed Services University of the Health Sciences and the UMMC.

PROCEDURE

Potential participants were initially identified by treatment providers and referred to the study. Interested individuals then scheduled a baseline visit. During the baseline visit the potential participants were informed about the study and screened for

participation eligibility. If they were determined to be eligible, they then completed a set of baseline psychosocial questionnaires; their functional status, symptoms, and subjective health were assessed; and CHF biomarkers were obtained.

After the baseline visit, participants were contacted once every two weeks over the course of a two and a half month time period for a total of five interim phone interviews. Questionnaires were verbally administered during each interim phone interview and information about cardiovascular related hospitalizations (“adverse events”) since the previous interim phone call was collected. Participants scoring in the top or bottom 30 percent of the PSS distribution, approximately reflecting high (≥ 15) and low (≤ 9) scores were scheduled for an interim clinic assessment an average of 4 ± 3 days following the interim phone assessment. Because the PSS is not a diagnostic tool with validated cutoffs (17), the scores were chosen a priori to ensure sampling of high and low tails of the PSS distribution and adequate numbers of participants at each interim assessment (16). Since participation in the interim clinic visits was based on previous interim phone interview PSS scores, participants differed in the number and timing of interim clinic assessments. During these interim clinic visits: self-report measures of symptoms and CHF health status were obtained, objective functional status assessments were completed, and biomarkers (e.g., BNP, IL-6, ET-1, and various others) were sampled. Three months following the baseline visit all participants repeated the same measures as at baseline, including psychosocial and health questionnaires, functional status assessment, and CHF biomarker sampling.

A follow-up telephone interview was scheduled six months after the last clinic visit (nine months after the baseline visit). Changes in clinical status, including

hospitalizations or death from any cause were recorded and subsequently verified via medical record review. If the participant had died, the spouse or next of kin was interviewed regarding the date and cause of death. Five further follow-up calls of the same nature were conducted every six months, for a total of 36 months of follow-up. The present data are from the full 39 months of the study beginning from the baseline visit, with the exception of the interim phone interviews and interim clinic visits.

MEASURES

Psychosocial Questionnaires

Perceived Stress Scale (PSS)

The 10-item PSS (17) measures the generalized appraisal of stress over the past two weeks. This standardized instrument was developed to measure the extent to which an individual appraises events or situations in one's life as stressful or being out of one's control. The PSS has been used to measure stress in behavioral, epidemiological, and clinical research encompassing a wide range of samples and populations (3; 11; 16; 17; 47; 74). For example, in CAD patients, there is evidence that high stress appraisal measured with the PSS is an independent predictor of poor outcomes, including adverse events (3). Possible scores range from 0 to 40 with higher scores indicating a greater appraisal of psychosocial stress. A meta-analysis of 12 studies that used the PSS across a variety of participants and settings found that the PSS had a mean internal consistency of .83 (minimum = .74 and maximum = .91; 74). Regarding validity, the PSS was found to have a strong negative correlation ($r = -.70$) with the mental component of health status as measured by the Medical Outcomes Study–Short Form 36 in a sample of individuals that had lost a significant other or family member to suicide (87). There is also evidence,

from a sample of college students, that PSS scores correlate highly ($r = .70$) with trait anxiety (106).

State-Trait Anxiety Inventory (STAI)

The STAI (119) is a 40-item questionnaire that assesses trait anxiety (20 items) and state anxiety (20 items). The trait anxiety questions ask how the respondent feels “generally” and the state anxiety questions ask how the respondent feels “right now.” Example trait anxiety items include: “I become tense and upset when I think about my present concerns” and “I feel that difficulties are piling up so that I can't overcome them.” Example state anxiety items include: “I am jittery” and “I feel overexcited and rattled.” These statements are each endorsed by respondents on a 4-point Likert scale that ranges from “not at all” to “very much so” for state anxiety and “almost never” to “almost always” for trait anxiety. A meta-analysis of studies using the STAI with various populations found that across 52 studies the state anxiety scale had a mean internal consistency of .91 (minimum = .65 and maximum = .96) and a mean test-retest consistency of .70 (minimum .34 and maximum .96) across 7 studies. The same meta-analysis found that the trait anxiety scale across 51 studies had a mean internal consistency of .89 (minimum .72 and maximum .96) and a mean test-retest consistency of .88 (minimum .82 and maximum .94) across 7 studies (5). A review of four studies that each compared the STAI to the Beck Anxiety Inventory found a mean convergent validity of .57 (minimum .44 and maximum .68) with the trait anxiety scale and .55 (minimum .47 and maximum .64) with the state anxiety scale (84).

Weekly Stress Inventory-Short Form (WSI-SF), State-Trait Anger Expression Inventory-2 (STAXI-2), and Profile of Mood States-Short Form (POMS-SF)

Since existing instruments specifically designed to measure anger were not given during the long-term follow-up interviews, an ad hoc measure of anger was constructed for the purpose of this study. Three additional instruments were used to construct and validate an ad-hoc measure of anger. These instruments were the WSI-SF, the STAXI-2, and the POMS-SF.

WSI-SF

The WSI-SF (9) is a 25-item questionnaire designed to measure stressful minor events over the last week. Each item asks if a specific event, such as “had someone cut in front of you in line,” happened to the participant during the last week. Participants respond to the items by either indicating that they did not experience that event or by rating how stressful the event was on a 7-point scale that ranges from one (“happened not stressful”) to seven (“extremely stressful”). The WSI-SF produces two summary scores: WSI-SF Events and WSI-SF Impact. The WSI-SF Events score is equal to all of the items that the participant endorsed as having occurred during the last week, which can range from 0 to 25. The WSI-SF Impact score is equal to the sum of how stressful each endorsed item was, which can range from 0 to 175.

The full form WSI was primarily derived from items on three other scales: the Daily Stress Inventory, the Hassles Scale, and the Inventory of Small Life Events (10). Items from those scales were chosen based on covering eight general domains: work/school, transportation, household, personal, social, money, marital/family, and leisure. The convergent validity of the full length WSI was tested by correlating it with the Hassles Scale ($r = .61$) and measures of major life events ($r = .45$ to $.53$; 10).

The WSI-SF was, in turn, developed by using principal component factor analyses on data collected from the full form of the WSI administered to a combined sample of low-income, predominantly African American medical patients and general community members (9). Items that accounted for the most variance and were endorsed at least 10% of the time were retained to create the WSI-SF (9). The WSI-SF had high internal consistency for both WSI-SF Events (.92) and WSI-SF Impact (.91) in a sample of adults visiting general medicine clinics in a hospital (9). In the same sample of patients, WSI-SF Impact score had a correlation of .79 with the full length WSI Impact score and WSI-SF Event score had a correlation of .78 with the full length WSI Event score.

STAXI-2

The STAXI-2 (120) is a 57-item questionnaire that measures State Anger (15 items), Trait Anger (10 items), Anger Expression (16 items), and Anger Control (16 items). The State Anger items ask how the respondent feels “right now” and the Trait Anger, Anger Expression, and Anger Control items ask how the respondent “generally” feels or reacts to things. Respondents endorse statements, such as “I feel angry,” on a 4-point Likert scale that ranges from one (“almost never”) to four (“almost always”) for each item. The internal consistency of the STAXI-2 had a median of .84 (minimum = .73 and maximum = .95) in its normative sample tests, including individuals from the general population and hospitalized psychiatric patients (121). A study using the Dutch version of the STAXI-2 found a mean State Anger scale internal consistency of .94 across samples of college students (.91), psychiatric patients (.96), and the general population (.96; 78). The same study found a mean Trait Anger scale internal consistency of .88 across

samples of college students (.83), psychiatric patients (.92), and the general population (.88).

POMS-SF

The POMS-SF (85) is a 37-item questionnaire that measures the respondent's mood on six subscales: Fatigue-Inertia, Vigor-Activity, Tension-Anxiety, Depression-Dejection, Anger-Hostility, and Confusion-Bewilderment. Each item on the POMS-SF is an adjective and the respondent indicates with a 5-point Likert scale the degree to which that adjective describes how he or she felt during the last week. A study of the psychometric properties of the POMS-SF found that it had high mean internal consistency across chronic samples of bone marrow transplant survivors, bone marrow transplant candidates, renal transplant survivors, benign breast disease patients, breast cancer patients, and healthy adults Cronbach's alphas for (Fatigue-Inertia = .92, Vigor-Activity = .92, Tension-Anxiety = .89, Depression-Dejection = .93, Anger-Hostility = .88, and Confusion-Bewilderment = .81; 20).

Measurement of Anger Experiences: Construction and Validation of the WAI

Selected questions from the Weekly Stress Inventory-Short Form (WSI-SF) were used to create a 10-item ad-hoc measure of anger experiences: the Weekly Anger Inventory (WAI), which was retroactively scored for each participant at each time point from their WSI-SF responses. The items making up the new measure were chosen based on the criteria of having a correlation of .30 or higher with either the State Anger score from the STAXI-2 or the Anger-Hostility scale from the POMS-SF at both baseline and the 3-month time point (see Table 1 on page 44).

Ten items produced sufficient correlations at both time points to be included in the new measure (see Table 2 on page 45). The completed measure, WAI, was then correlated with State Anger from the STAXI-2 and Anger-Hostility from the POMS-SF at both baseline and the 3-month time point to confirm its construct validity. At baseline, it produced a correlation of .44 with State Anger and .60 with Anger-Hostility (see Table 3 on pages 46-47). At the 3-month time point the WAI had a correlation of .62 with State Anger and .66 with Anger-Hostility (see Table 4 on pages 48-49). At both baseline and the 3-month time points, POMS-SF Anger-Hostility produced the highest correlation with the WAI of all measures tested. STAXI-2 State Anger had the second highest correlation with WAI at the 3-month time point. This indicates that the WAI generally has acceptable convergent validity with previously established measures of anger.

Conversely, at both baseline and 3-months, Tables 3 and 4 indicate that the WAI had relatively low correlations with POMS-SF Vigor-Activity and Fatigue-Inertia, which supports having discriminant validity from those measures. The WAI also showed middling to strong correlations with PSS, STAI State Anxiety, POMS-SF Depression-Dejection, Confusion-Bewilderment, and Tension-Anxiety.

There was also a high degree of inter-correlation amongst a number of the established scales, such as PSS and State Anxiety. This result is not unexpected and lends support to Suls & Bunde's assertion that there is a great deal of overlap in what is measured by scales designed to examine supposedly unique psychological constructs. Additionally, the POMS-SF measures may show fairly good correlations with the WAI in part due to them both asking about the same timeframe, the past week. Regarding internal

consistency, the WAI produced a Cronbach's Alpha level of .78 at baseline and .84 at the 3-month time point.

Comment on the WAI

The results at both baseline and 3-months indicate that the WAI has adequate internal consistency, and convergent and discriminant validity. Moreover, a strength of using consistent correlations at both baseline and 3-months to include items in the WAI is that this procedure reduces the risk that chance correlations would influence the determination of items.

A counterintuitive result was the stronger evidence for convergent and discriminant validity at 3-month testing compared to results at baseline. Regardless of what may have caused these higher correlations at 3-months, the fact that a correlation at both time points was needed to be included in the WAI eliminates the problem of regression to the mean in the development of this scale.

Measures of Heart Failure Severity

Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is a 23-item scale used to measure CHF symptoms and health status (49). The KCCQ includes questions about physical limitations, symptoms (frequency, severity, and change over time), self-efficacy, CHF knowledge, social interference, and quality of life. Respondents answer the questions on a five point Likert scale and indicate to what extent the contents of each item have impacted them over the past two weeks.

The KCCQ yields the following subscales: CHF Symptoms, Physical Limitation, Social Limitation, Self-efficacy, and Quality of Life. The KCCQ subscales can also be used to produce two summary scores. A summary score of functional status (KCCQ-Functional

Status) is calculated by combining the scores from the physical limitations and symptoms subscales. A total clinical summary score (KCCQ-Clinical Summary) can also be derived by combining the functional status summary score with the quality of life and social interferences subscales. The KCCQ-Clinical Summary score ranges from 0-100, with higher values indicating less symptom burden and better health status. This study used the summary scales of KCCQ-Functional Status and KCCQ-Clinical Summary to measure patient functional status and overall health status, respectively, because of their associations with NYHA functional status (KCCQ-Functional Status Scale) and with subsequent CHF hospitalizations (KCCQ-Clinical Summary Scale; 49).

The original validation study of the KCCQ demonstrated generally high internal consistency, with the exception of Self-efficacy, (Symptoms = 0.88, Physical Limitation = 0.90, Social Limitation = 0.86, Self-efficacy = 0.62, Quality of Life = 0.78, KCCQ-Functional Status = 0.93, and KCCQ-Clinical Summary = 0.95) in a sample of stable CHF patients (49). A study comparing nine measures of CHF change (including multiple health status instruments, physician-assessed functional class, an exercise test, patient weight, and a biomarker) found that the KCCQ-Clinical Summary scale was the most sensitive to clinical changes in patients of the compared measures (118). There is also evidence that the KCCQ-Clinical Summary scale is a useful measure of risk for CHF related hospitalizations and/or mortality (54).

Hospitalizations

Hospitalizations were assessed by patient self-report and subsequently verified via hospital record review. There were a total of 534 all-cause hospitalizations, which were categorized into CHF (n = 168) and/or cardiovascular (CV)-related causes (which

included HF related hospitalizations; $n = 277$) vs. hospitalizations for non-CV causes (e.g., acute illnesses, non-cardiac surgeries, and injuries; $n = 257$). CHF hospitalizations were classified as hospitalizations with a primary diagnosis of CHF exacerbation, characterized by a primary admitting diagnosis of pump failure or fluid overload. CV-related hospitalizations were characterized by a primary admitting diagnosis of conditions such as arrhythmia, myocardial infarction, angina, myocardial ischemia, and also for cardiac revascularization procedures. Classification of hospitalization categories was determined by the treating physician and the emergency medical team at the time of hospitalization.

Our primary outcome measures of hospitalization were binary counts of CHF hospitalizations, CV-related hospitalizations, and cases of hospitalization for any cause. We set the counts to 1 if a patient was at all hospitalized and 0 if they were not hospitalized in the corresponding time period. We chose to include CV-related hospitalizations, which incorporates CHF hospitalizations plus other CV hospitalizations, as opposed to just hospitalizations medically classified as CHF-related, because cardiac events in a CHF patient are likely to have some level of relationship to his or her heart failure status. For a similar reason we also examined all-cause hospitalizations, regardless of whether they were CV-related. For example, a patient might experience a heart failure caused disruption in blood flow leading to loss of balance and a fall. If the patient were to then hit his or her head and be hospitalized for it, the medical classification of the hospitalization's cause would likely be based on having taken a fall, but would fail to capture the underlying causal contribution of CHF. Another rationale for using all-cause

hospitalizations as an outcome in this study is that trait anger and hostility, at baseline, were related to all-cause hospitalizations in prior BETRHEART analyses (63).

Unlike the study by Endrighi et al. (34), we did not combine deaths and hospitalizations in the binary counts for the present analyses. First, this choice was made partly because we were interested in understanding hospitalizations as recurrent events that have significant healthcare system costs associated with them. Deaths, on the other hand, are by their very nature limited to a one-time occurrence. Second, hospitalizations and deaths could potentially be different in their underlying causal associations. Consequently, including them in the same outcome measure could potentially obscure true relationships with the IVs due to conflicting associations. Third, 19 of the 33 deaths during the study are already captured in the binary counts of the hospitalizations, due to some patients having at least one hospitalization during the time period in which he or she died.

Table 1. Individual WSI Item Correlations with Measures of Anger

WSI Item Correlations					
Baseline WSI Item Number	Baseline State Anger	Baseline POMS Anger-Hostility	3-Month WSI Item Number	3-Month State Anger	3-Month POMS Anger-Hostility
1	.216**	.305**	1	.568**	.663**
2	-0.013	.195*	2	.438**	.470**
3	.232**	.302**	3	.540**	.552**
4	.525**	.453**	4	.399**	.342**
5	0.131	0.141	5	.452**	.285**
6	.268**	.329**	6	.368**	.387**
7	.162*	.328**	7	.271**	0.127
8	0.058	0.129	8	.218*	.306**
9	0.069	.272**	9	.335**	.524**
10	0.003	0.158	10	.350**	.384**
11	0.099	.237**	11	.252**	0.110
12	0.046	.169*	12	.191*	0.124
13	.174*	.251**	13	.554**	.342**
14	0.065	.177*	14	.510**	.308**
15	0.138	.302**	15	.543**	.461**
16	.385**	.442**	16	.358**	.482**
17	.222**	.221**	17	.580**	.447**
18	.378**	.485**	18	.414**	.261**
19	-0.038	0.140	19	.495**	.457**
20	.176*	.301**	20	.309**	.245**
21	0.017	.202*	21	.392**	.362**
22	0.054	.309**	22	.373**	.425**
23	-0.010	0.031	23	.402**	0.103
24	0.140	.261**	24	.395**	.281**
25	.247**	.303**	25	.302**	.581**

Note. Bolded items met criteria to be included in final WAI measure.

*p < .05, ** p < .01

Table 2. Items Constituting the Weekly Anger Inventory

Weekly Anger Inventory Items	WSI Item #
Had pet peeve violated (someone fails to knock, etc.)	1
Was without privacy	3
Was ignored by others	4
Was lied to, fooled or tricked	6
Not enough time for fun (movie, eating out) or recreation	15
Had someone disagree with you	16
Argued with a friend	18
Forgot something	20
Lost or misplaced something (wallet, keys)	22
Had someone cut in front of you in line	25

Table 3. Baseline Correlations of WAI, STAXI-2 State Anger, STAI State Anxiety, PSS, and POMS-SF Subscales

Baseline Correlations											
		WAI	STAXI-2 State Anger	POMS Anger- Hostility	STAI State Anxiety	PSS	POMS Depression -Dejection	POMS Vigor- Activity	POMS Confusion- Bewilderm ent	POMS Tension- Anxiety	POMS Fatigue -Inertia
WAI	<i>r</i>	1	.443**	.601**	.334**	.493**	.517**	-0.076	.571**	.583**	.431**
	<i>p</i>		0.000	0.000	0.000	0.000	0.000	0.362	0.000	0.000	0.000
	N	147	147	145	146	146	145	145	145	145	145
STAXI-2 State Anger	<i>r</i>	.443**	1	.611**	.481**	.327**	.487**	-0.069	.452**	.430**	.352**
	<i>p</i>	0.000		0.000	0.000	0.000	0.000	0.411	0.000	0.000	0.000
	N	147	147	145	146	146	145	145	145	145	145
POMS Anger- Hostility	<i>r</i>	.601**	.611**	1	.469**	.606**	.752**	-.171*	.698**	.670**	.585**
	<i>p</i>	0.000	0.000		0.000	0.000	0.000	0.040	0.000	0.000	0.000
	N	145	145	145	144	144	145	145	145	145	145
STAI State Anxiety	<i>r</i>	.334**	.481**	.469**	1	.536**	.476**	-.420**	.517**	.462**	.271**
	<i>p</i>	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.000	0.001
	N	146	146	144	146	145	144	144	144	144	144
PSS	<i>r</i>	.493**	.327**	.606**	.536**	1	.625**	-.451**	.574**	.565**	.494**
	<i>p</i>	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.000
	N	146	146	144	145	146	144	144	144	144	144

Table 3 Continued.

		WAI	STAXI-2 State Anger	POMS Anger- Hostilit y	STAI State Anxiet y	PSS	POMS Depression -Dejection	POMS Vigor- Activity	POMS Confusion- Bewilderm ent	POMS Tension- Anxiety	POMS Fatigue -Inertia
POMS Depression- Dejection	<i>r</i>	.517**	.487**	.752**	.476**	.625**	1	-.363**	.740**	.687**	.639**
	<i>p</i>	0.000	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.000
	N	145	145	145	144	144	145	145	145	145	145
POMS Vigor- Activity	<i>r</i>	-0.076	-0.069	-.171*	-.420**	-.451**	-.363**	1	-.257**	-.233**	-.305**
	<i>p</i>	0.362	0.411	0.040	0.000	0.000	0.000		0.002	0.005	0.000
	N	145	145	145	144	144	145	145	145	145	145
POMS Confusion- Bewildermen t	<i>r</i>	.571**	.452**	.698**	.517**	.574**	.740**	-.257**	1	.721**	.584**
	<i>p</i>	0.000	0.000	0.000	0.000	0.000	0.000	0.002		0.000	0.000
	N	145	145	145	144	144	145	145	145	145	145
POMS Tension- Anxiety	<i>r</i>	.583**	.430**	.670**	.462**	.565**	.687**	-.233**	.721**	1	.585**
	<i>p</i>	0.000	0.000	0.000	0.000	0.000	0.000	0.005	0.000		0.000
	N	145	145	145	144	144	145	145	145	145	145
POMS Fatigue- Inertia	<i>r</i>	.431**	.352**	.585**	.271**	.494**	.639**	-.305**	.584**	.585**	1
	<i>p</i>	0.000	0.000	0.000	0.001	0.000	0.000	0.000	0.000	0.000	
	N	145	145	145	144	144	145	145	145	145	145

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

* . Correlation is significant at the 0.05 level (2-tailed).

Table 4. 3-Month Time Point Correlations of WAI, STAXI-2 State Anger, STAI State Anxiety, PSS, and POMS-SF Subscales

3-Month Correlations											
		WAI	STAXI-2 State Anger	POMS Anger- Hostilit y	STAI State Anxiet y	PSS	POMS Depression -Dejection	POMS Vigor- Activity	POMS Confusion- Bewilderm ent	POMS Tension- Anxiety	POMS Fatigue -Inertia
WAI	<i>r</i>	1	.619**	.656**	.516**	.581**	.466**	-0.080	.480**	.597**	.358**
	<i>p</i>		0.000	0.000	0.000	0.000	0.000	0.377	0.000	0.000	0.000
	N	126	126	125	126	126	125	125	125	125	124
STAXI-2 State Anger	<i>r</i>	.619**	1	.636**	.563**	.470**	.460**	-0.134	.331**	.485**	.300**
	<i>p</i>	0.000		0.000	0.000	0.000	0.000	0.136	0.000	0.000	0.001
	N	126	126	125	126	126	125	125	125	125	124
POMS Anger- Hostility	<i>r</i>	.656**	.636**	1	.596**	.662**	.800**	-0.137	.620**	.806**	.512**
	<i>p</i>	0.000	0.000		0.000	0.000	0.000	0.126	0.000	0.000	0.000
	N	125	125	125	125	125	125	125	125	125	124
STAI State Anxiety	<i>r</i>	.516**	.563**	.596**	1	.772**	.659**	-.510**	.567**	.561**	.405**
	<i>p</i>	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.000	0.000
	N	126	126	125	126	126	125	125	125	125	124
PSS	<i>r</i>	.581**	.470**	.662**	.772**	1	.713**	-.422**	.572**	.664**	.446**
	<i>p</i>	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.000
	N	126	126	125	126	126	125	125	125	125	124

Table 4 Continued.

		WAI	STAXI-2 State Anger	POMS Anger- Hostilit y	STAI State Anxiet y	PSS	POMS Depression -Dejection	POMS Vigor- Activity	POMS Confusion- Bewilderm ent	POMS Tension- Anxiety	POMS Fatigue -Inertia
POMS Depression- Dejection	<i>r</i>	.466**	.460**	.800**	.659**	.713**	1	-.324**	.753**	.748**	.669**
	<i>p</i>	0.000	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.000
	N	125	125	125	125	125	125	125	125	125	124
POMS Vigor- Activity	<i>r</i>	-0.080	-0.134	-0.137	-.510**	-.422*	-.324**	1	-.209*	-0.070	-.352**
	<i>p</i>	0.377	0.136	0.126	0.000	0.000	0.000		0.019	0.436	0.000
	N	125	125	125	125	125	125	125	125	125	124
POMS Confusion- Bewildermen t	<i>r</i>	.480**	.331**	.620**	.567**	.572**	.753**	-.209*	1	.717**	.575**
	<i>p</i>	0.000	0.000	0.000	0.000	0.000	0.000	0.019		0.000	0.000
	N	125	125	125	125	125	125	125	125	125	124
POMS Tension- Anxiety	<i>r</i>	.597**	.485**	.806**	.561**	.664**	.748**	-0.070	.717**	1	.456**
	<i>p</i>	0.000	0.000	0.000	0.000	0.000	0.000	0.436	0.000		0.000
	N	125	125	125	125	125	125	125	125	125	124
POMS Fatigue- Inertia	<i>r</i>	.358**	.300**	.512**	.405**	.446**	.669**	-.352**	.575**	.456**	1
	<i>p</i>	0.000	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	
	N	124	124	124	124	124	124	124	124	124	124

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

***.** Correlation is significant at the 0.05 level (2-tailed).

STATISTICAL ANALYSES

Marginal models (MMs) with compound symmetrical covariance modeling, which can produce equivalent results to linear mixed models, were used for analyses with KCCQ scores as the DV. MMs takes into account the dependence between participant observations. They also allow for missing values, differing time lengths between observations, and varying numbers of observations for each participant. Due to the positively skewed nature of hospitalization rates, we used generalized marginal models (GMMs) with logit transformation of the dichotomized dependent variable, binomial distribution for the error term (both corresponding to logistic regression), and the method of generalized estimating equations with an exchangeable correlation matrix and robust error variance estimation to account for within-subject correlation for analyses that included hospitalizations as the DV. We chose to use GMMs versus generalized linear mixed models because we were interested in the population level associations with hospitalizations, which is more informative about healthcare system level impacts and implications, and because they are robust against being biased by misspecification of the covariance structure (51). Time was entered as a categorical variable in all models (see Figures 1 and 2 on page 54 for distributions of DV scores across time points). The exposure variables for the first set of analyses were scores on the PSS, STAI, and WAI measured at 8 time points (baseline, 3 month, 9 month, 15 month, 21 month, 27 month, 33 month, and 39 month follow-ups). The outcome variables were binary counts of all-cause hospitalizations, binary counts of cardiovascular hospitalizations, binary counts of CHF hospitalizations, functional status (as reported on the KCCQ-Functional Status scale), and health status (as reported on the KCCQ-Clinical Summary scale).

As the exposure variables, the second set of analyses used PSS, STAI, WAI, KCCQ-Functional Status, and KCCQ-Clinical Summary scores measured at 8 time points (baseline, 3 month, 9 month, 15 month, 21 month, 27 month, 33 month, and 39 month follow-ups). The outcome variables were binary counts of all-cause, cardiac, and CHF hospitalizations.

To address Aim 4 we utilized comparisons of different models of the data. For the MMs, a likelihood ratio chi square test with one degree of freedom was used to test the hypothesis of equivalence between the within- and between-subjects effects by comparing two models. The "full" model included separate parameters for the between-subjects (mean) independent variable and the within-subject (deviation) independent variable. The "reduced" model included a single parameter for the independent variable that was not decomposed into mean and deviation variables. If the model fit for the "full" model was significantly better than for the "reduced" model then we concluded that the within- and between-subjects effects differed significantly. For the GMMs, a Wald chi square test with one degree of freedom was used to test the hypothesis of equivalence between the within- and between-subjects effects by comparing the parameter on the subject-level (mean) independent variable with the parameter on the within-subject (deviation) independent variable. This test was carried out using the "test" postestimation command in STATA version 14.

Parameter estimates of associations between exposure and outcomes are reported as B (SE). Analyses were conducted both unadjusted and adjusted for medical covariates. Data are presented as means and standard deviations, or N and percentages, as appropriate. Unless otherwise specified, alpha level for analyses were set at $p < .05$.

Power Analyses

Power analyses were computed using G*Power 3.1.9.2. Power estimates for 2-tailed tests were set at alpha level of .05. All between-subject level analyses in this study with KCCQ as the DV, when using a sample size of 147, power of .80, 1 predictor, and 7 covariates, are estimated to be able to detect an R^2 effect size of .054 or greater. All between-subject level analyses in this study with hospitalizations as the DV, when using a sample size of 147, power of .80, 1 predictor, and 9 covariates, are estimated to be able to detect a change in relative risk of 1.519 for every one standard deviation increase in predictor variable. This power calculation is conservative because it does not account for the increase in precision achieved with multiple observations per subject; actual power will be higher.

For power estimates of the within-subjects effects an effective sample size of 339 was calculated based on Killip et al's formula (with $m = 4.63$, $k = 147$, and $\rho = .5$; 64). All within-subject level analyses in this study with KCCQ as the DV, when using a sample size of 339, power of .80, 1 predictor, and 7 covariates, are estimated to be able to detect an R^2 effect size of .023 or greater. All within-subject level analyses in this study with hospitalizations as the DV, when using a sample size of 339 power of .80, 1 predictor, and 9 covariates, are estimated to be able to detect a change in relative risk of 1.326 for every one standard deviation increase in predictor variable.

Covariates

Age, race, gender, and income (a proxy for socioeconomic status) were included a priori as covariates in adjusted analyses because of their documented relationships to perceived stress (1). The other medical covariates used in the adjusted analyses were

determined via testing which of the potential covariates contribute the most to predicting outcomes. The initial pool of potential covariates consisted of BMI, NYHA class, ejection fraction, creatinine, hypertensive status, presence of type I and/or type II diabetes, and implantable defibrillator status, all collected at baseline. Each of the potential covariates was individually entered as a predictor into models with binary count all-cause hospitalizations, binary count cardiac hospitalizations, binary count HF hospitalizations, KCCQ-Functional Status score, or KCCQ-Clinical Summary score as the DVs, respectively. Potential covariates that produced a p value < 0.1 for all three of the hospitalization measures were retained for conducting adjusted hospitalization analyses and potential covariates that produced a p value < 0.1 for both of the KCCQ measures were retained for use as covariates in adjusted KCCQ analyses. The final covariates for adjusted hospitalization analyses were: ejection fraction, NYHA class, hypertension status, diabetes status, implantable defibrillator status, age, race, gender, and income. The final covariates for adjusted KCCQ analyses were: BMI, NYHA, hypertension status, age, race, gender, and income.

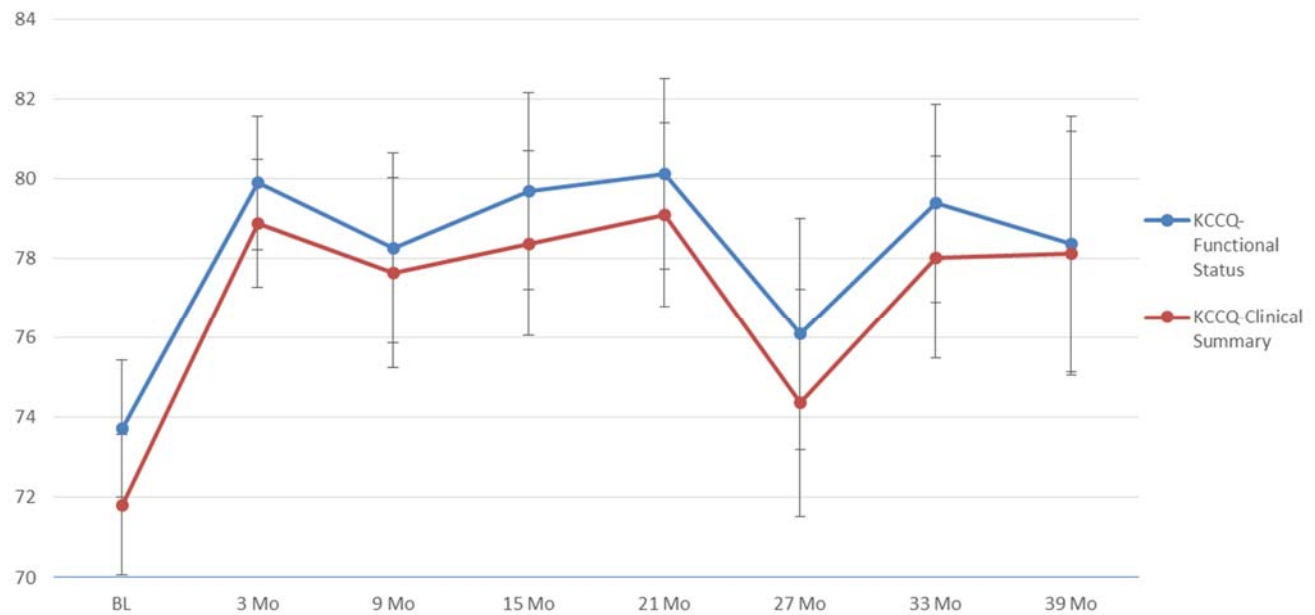


Figure 1. Time series graph of average KCCQ summary scores during study.

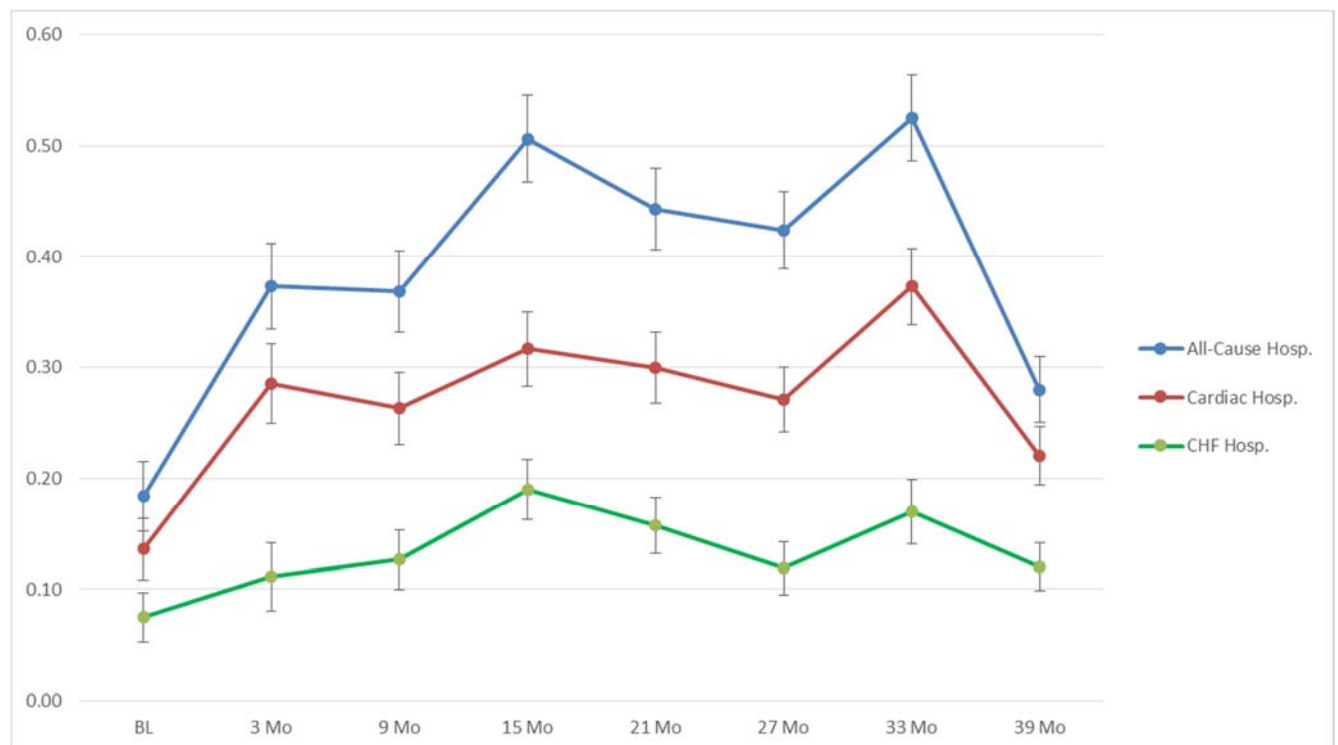


Figure 2. Time series graph of proportion of patients hospitalized subsequent to each time point during study.

Chapter 3: Results

SAMPLE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Summary demographic and medical characteristics of the participants are presented in Table 5 on page 74. Participants were predominantly male, African-American, and age 50 or later. Most of the participants had hypertension and roughly half had non-ischemic CHF and/or an implanted defibrillator. Diabetes was also common in the participants at a rate slightly over 40%. The descriptive statistics for the study psychological and KCCQ measures are summarized in Table 6 on page 75. The score ranges for the psychological measures exhibited a floor effect and KCCQ measures exhibit a ceiling effect, this may indicate that the participants as a whole were not overly psychologically distressed or ill due to their CHF and/or were engaging in underreporting of distress and CHF symptomology.

HOSPITALIZATION EVENTS

Across all time points and participants, there were 534 all-cause (mean = 3.56, SD = 9.27), 277 cardiac (mean = 1.85, SD = 3.16), and 168 CHF (mean = 1.12, SD = 2.35) hospitalizations. All three types of hospitalizations had a median of one and a mode of zero. The distribution of each type of hospitalizations across patients was non-normal (see Figure 3 on page 87 for distribution of all cause hospitalizations), including one individual that had 103 hospitalizations. Consequently, we utilized binary (yes/no) counts of hospitalizations between time points for analyses to prevent the results of the analyses being biased by the non-normal distribution of raw counts.

Numbers of participants remaining in the sample during each of the follow-ups are presented in Figure 4 on page 88, as are number of patients who were hospitalized

(yes/no) between each of the follow-ups. These data indicated that the longer the follow-up period, the fewer patients remained in the sample. However, the number of patients who experienced at least one hospitalization between assessments remained relatively stable even as the sample size decreased.

CORRELATIONS BETWEEN PSYCHOSOCIAL VARIABLES

The correlations between the psychosocial variables at baseline are summarized in Table 7 on page 76 and the correlations at 3-months are summarized in Table 8 on page 77. All five measures demonstrated significant intercorrelations, with the magnitude of correlations ranging from -.23 to .93. Although the PSS, WAI, STAI correlations were in the moderate range, correlations were lower between the WAI and KCCQ measures. The measures appear to be relatively stable in their intercorrelations between baseline and 3 month time points.

EXPOSURE AND OUTCOME VARIABLES USED IN ANALYSES

As noted in the Methods section, the analytic plan for most of the study hypotheses involved mixed model analyses with the psychosocial measures being the exposure variables with KCCQ and hospitalizations (yes/no) as the outcome variables. The first set of analyses examined the effects of psychosocial variables. Following this, a second set of analyses examined the independent effects of each psychosocial variable controlling for the others. As noted in the Methods, medical covariates used in adjusted hospitalization analyses were: ejection fraction, NYHA class, hypertension status, diabetes status, implantable defibrillator status, age, race, gender, and income. The medical covariates for adjusted KCCQ analyses were: BMI, NYHA, hypertension status, age, race, gender, and income.

The presented analyses of associations between psychosocial measures and outcomes using all available time points. The analyses consist of: a Mean IV score computed by aggregating over all assessments for each subject (i.e., a subject-level variable), and a Deviation IV score (an assessment-level variable), computed as the difference between the IV score at each assessment and the patient's own Mean IV score. Note that patients without IV data at a given time point will not have a Deviation IV score for that time point. An effect for Mean IV score indicates a between-subject association, and for Deviation IV score a within-subject association (53).

The distribution of Mean IV and Deviation IV scores are presented for perceived stress, state anxiety, and anger in Figure 5 and Figure 6 on pages 89 and 90, respectively. These data indicate that Mean IV scores for the PSS were slightly positively skewed, with the modal number of subjects having a score of approximately nine with a fairly even distribution of scores higher than or lower than nine. The STAI and WAI both exhibited a stronger floor effect with modal scores of zero and visibly positively skewed score distributions. Results in Figure 6 on page 90 indicate that the deviation scores for PSS, STAI, and WAI were generally normally distributed around a mean of zero, as should be expected for deviation scores.

ANALYSES FOR AIMS AND HYPOTHESES

Aim 1

The first aim of this study was to determine whether psychosocial measures of anger, anxiety, and stress predict adverse outcomes and reductions in functional status in CHF patients over a 39 month period. The exposure variables for Aim 1 were scores on the PSS, STAI, or WAI measured at 8 time points (baseline, 3 month, 9 month, 15 month,

21 month, 27 month, 33 month, and 39 month follow-ups). The outcome variables were binary counts of all-cause hospitalizations, binary counts of cardiovascular hospitalizations, binary counts of CHF hospitalizations, functional status (as reported on the KCCQ-Functional Status scale), and health status (as reported on the KCCQ-Clinical Summary scale).

Hypothesis 1a

This hypothesis was that there would be a predictive relationship between anger and reduced health assessed via the KCCQ, but not between anger and hospitalizations. Using MM analyses, patients with higher, compared to lower, mean anger scores had poorer KCCQ-Functional Status (unadjusted $B = -0.91$, $SE = 0.17$, $p < 0.001$; adjusted $B = -0.86$, $SE = 0.16$, $p < 0.001$; see Table 9 on pages 78-79) and KCCQ-Clinical Summary scores (unadjusted $B = -0.94$, $SE = 0.16$, $p < 0.001$; adjusted $B = -0.87$, $SE = 0.16$, $p < 0.001$; see Table 9, and Figure 7 on page 91). There was also a robust within-subject association for both KCCQ-Functional Status (unadjusted $B = -0.36$, $SE = 0.09$, $p < 0.001$; adjusted $B = -0.36$, $SE = 0.09$, $p < 0.001$; see Table 9) and KCCQ-Clinical Summary (unadjusted $B = -0.41$, $SE = 0.08$, $p < 0.001$; adjusted $B = -0.41$, $SE = 0.08$, $p < 0.001$; see Table 9), indicating that when a patient experienced higher, compared to lower, than his/her average anger level the same patient experienced worsened CHF symptoms and overall functioning.

Using GMM analyses, patients with higher, compared to those with lower, mean anger scores across assessments did not differ in the odds of a hospitalization before the next assessment for all-cause (unadjusted $p = 0.329$; adjusted $p = 0.344$; see Table 9), cardiac (unadjusted $p = 0.70$; adjusted $p = 0.872$; see Table 9), and CHF hospitalizations

(unadjusted $p = 0.398$; adjusted $p = 0.470$; see Table 9). Also, there was no within-subjects association between anger and all-cause (unadjusted $p = 0.989$; adjusted $p = 0.981$; see Table 9), cardiac (unadjusted $p = 0.146$; adjusted $p = 0.129$; see Table 9), and CHF hospitalizations (unadjusted $p = 0.103$; adjusted $p = 0.091$; see Table 9).

Hypothesis 1b

This hypothesis was that state anxiety would be predictive of both health status and hospitalizations. Using MM analyses, patients with higher, compared to lower, mean STAI scores had poorer KCCQ-Functional Status (unadjusted $B = -1.05$, $SE = 0.16$, $p < 0.001$; adjusted $B = -0.90$, $SE = 0.16$, $p < 0.001$; Table 10 on pages 80-81) and KCCQ-Clinical Summary scores (unadjusted $B = -1.18$, $SE = 0.15$, $p < 0.001$; adjusted $B = -1.05$, $SE = 0.16$, $p < 0.001$; Table 10, and Figure 7 on page 91). There was also a robust within-subject association for both KCCQ-Functional Status (unadjusted $B = -0.34$, $SE = 0.07$, $p < 0.001$; adjusted $B = -0.34$, $SE = 0.07$, $p < 0.001$; Table 10) and KCCQ-Clinical Summary (unadjusted $B = -0.47$, $SE = 0.07$, $p < 0.001$; adjusted $B = -0.46$, $SE = 0.07$, $p < 0.001$; Table 10), indicating that when a patient experienced higher, compared to lower, than his/her average state anxiety level the same patient experienced worsened CHF symptoms and overall functioning.

Using GMM analyses, the odds of hospitalization for any cause before the next assessment were greater in patients with higher, compared to those with lower, mean STAI scores across assessments (unadjusted: $B = 0.058$, $SE = 0.02$, $p < 0.001$, $OR = 1.06$, $95\% CI = 1.03, 1.09$; adjusted: $B = 0.061$, $SE = 0.02$, $p < 0.001$, $OR = 1.06$, $95\% CI = 1.03, 1.10$; see Table 10). There was not a significant within-subjects association between state anxiety and all-cause hospitalizations (unadjusted $p = 0.308$; adjusted $p = 0.394$).

Similarly, the odds of a cardiac-related hospitalization before the next assessment were greater in patients with higher mean state anxiety scores across assessments (unadjusted: $B = 0.045$, $SE = 0.02$, $p = 0.006$, $OR = 1.05$, 95% $CI = 1.01, 1.08$; adjusted: $B = 0.05$, $SE = 0.02$, $p = 0.003$, $OR = 1.05$, 95% $CI = 1.02, 1.09$; see Table 10). There was not a significant within-subjects association between state anxiety and cardiac hospitalizations (unadjusted $p = 0.370$; adjusted $p = 0.381$).

In addition, the odds of a CHF-related hospitalization before the next assessment were also greater in patients with higher mean state anxiety scores across assessments (unadjusted: $B = 0.046$, $SE = 0.02$, $p = 0.015$, $OR = 1.05$, 95% $CI = 1.01, 1.09$; adjusted: $B = 0.052$, $SE = 0.02$, $p = 0.010$, $OR = 1.05$, 95% $CI = 1.01, 1.09$; see Table 10). There was not a significant within-subjects association between state anxiety and CHF hospitalizations (unadjusted $p = 0.794$; adjusted $p = 0.843$).

Hypothesis 1c

This hypothesis was that perceived stress would be predictive of both health status and hospitalizations. Using MM analyses, patients with higher, compared to lower, mean PSS scores had poorer KCCQ-Functional Status (unadjusted $B = -1.43$, $SE = 0.18$, $p < 0.001$; adjusted $B = -1.41$, $SE = 0.19$, $p < 0.001$; see Table 11 on pages 82-83) and KCCQ-Clinical Summary scores (unadjusted $B = -1.60$, $SE = 0.17$, $p < 0.001$; adjusted $B = -1.59$, $SE = 0.18$, $p < 0.001$; see Table 11, and Figure 7 on page 91). There was also a robust within-subject association for both KCCQ-Functional Status (unadjusted $B = -0.60$, $SE = 0.09$, $p < 0.001$; adjusted $B = -0.61$, $SE = 0.09$, $p < 0.001$; see Table 11) and KCCQ-Clinical Summary (unadjusted $B = -0.72$, $SE = 0.09$, $p < 0.001$; adjusted $B = -0.73$, $SE = 0.09$, $p < 0.001$; see Table 11), indicating that when a patient experienced

higher, compared to lower, than his/her average stress level the same patient experienced worsened CHF symptoms and overall functioning.

Using GMM analyses, the odds of a hospitalization due to any cause before the next assessment were greater in patients with higher, compared to those with lower, mean PSS scores across assessments (unadjusted: $B = 0.061$, $SE = 0.02$, $p = 0.003$, $OR = 1.06$, 95% $CI = 1.02, 1.11$; adjusted: $B = 0.060$, $SE = 0.02$, $p = 0.004$, $OR = 1.06$, 95% $CI = 1.02, 1.11$; see Table 11). There was also a within-subjects association between stress and all-cause hospitalizations (unadjusted: $B = 0.033$, $SE = 0.01$, $p = 0.012$, $OR = 1.03$, 95% $CI = 1.01, 1.06$; adjusted: $B = 0.031$, $SE = 0.01$, $p = 0.022$, $OR = 1.03$, 95% $CI = 1.00, 1.06$; see Table 11).

The odds of a hospitalization due to cardiac causes before the next assessment were greater in patients with higher mean PSS scores across assessments (unadjusted: $B = 0.048$, $SE = 0.02$, $p = 0.027$, $OR = 1.05$, 95% $CI = 1.01, 1.09$; adjusted: $B = 0.045$, $SE = 0.02$, $p = 0.032$, $OR = 1.05$, 95% $CI = 1.00, 1.09$; see Table 11). In contrast, there was no within-subjects association between stress and cardiac hospitalizations (unadjusted $p = 0.14$; adjusted $p = 0.15$). This indicates that at any assessment when a patient reported higher stress level compared to his/her average there was no change in the likelihood of experiencing an imminent hospitalization.

There were no significant associations at the between-subject (unadjusted $p = 0.09$; adjusted $p = 0.127$) or within-subject (unadjusted $p = 0.672$; adjusted $p = 0.731$) levels between perceived stress and CHF hospitalizations.

Aim 2

The second aim of this study was to determine the independent contributions of anger, anxiety, and stress to CHF worsening. Analyses for Aim 2 were similar to those for Aim 1, with the exception that all of the psychosocial variables were included simultaneously in the model in order to discern the contribution of each variable independent of the other psychosocial variables.

Hypothesis 2a

This hypothesis was that independent of stress and anxiety, anger would be negatively associated with health status and that anger would not be related to hospitalizations.

In order to determine the independent contributions of anger, multivariable MM and GMM analyses were conducted that controlled for perceived stress and anxiety, along with medical and demographic covariates. When controlling for the other IVs and covariates, between-subject level (chronic) WAI scores were significantly associated with reduced CHF hospitalizations ($B = -0.06$, $SE = 0.03$, $p = 0.024$; see Table 9) and within-subject level (acute) WAI scores were associated with worse KCCQ-Functional Status ($B = -0.20$, $SE = 0.09$, $p = 0.023$; see Table 9) and KCCQ-Clinical Summary ($B = -0.21$, $SE = 0.08$, $p = 0.012$; see Table 9) scores.

Hypothesis 2b

This hypothesis was that independent of stress and anger, anxiety will be prospectively related to higher rates of hospitalizations and reduced health status.

In order to determine the independent contributions of anxiety, multivariable MM and GMM analyses were conducted that controlled for perceived stress and anger, along

with medical and demographic covariates. When controlling for the other IVs and covariates, between-subject level (chronic) STAI scores were significantly associated with increased CHF ($B = 0.06$, $SE = 0.03$, $p = 0.047$; see Table 10) and all-cause hospitalizations ($B = 0.06$, $SE = 0.03$, $p = 0.019$; see Table 10) and within-subject level (acute) STAI scores were associated with worse KCCQ-Clinical Summary scores ($B = -0.25$, $SE = 0.07$, $p = 0.001$; see Table 10).

Hypothesis 2c

This hypothesis was that independent of anxiety and anger, stress will be prospectively related to higher rates of hospitalizations and reduced health status.

In order to determine the independent contributions of stress, multivariable MM and GMM analyses were conducted that controlled for anxiety and anger, along with medical and demographic covariates. When controlling for the other IVs and covariates, between-subject level (chronic) PSS scores were significantly associated with worse KCCQ-Functional Status ($B = -1.13$, $SE = 0.32$, $p = 0.001$; see Table 11) and KCCQ-Clinical Summary ($B = -1.29$, $SE = 0.31$, $p < 0.001$; see Table 11) scores. At the within-subject level (acute) PSS was associated with increased all-cause hospitalizations ($B = 0.03$, $SE = 0.02$, $p = 0.04$; see Table 11) and worse KCCQ-Functional Status ($B = -0.43$, $SE = 0.11$, $p < 0.001$; see Table 11) and KCCQ-Clinical Summary scores ($B = -0.49$, $SE = 0.10$, $p < 0.001$; see Table 11).

Aim 3

The third aim of this study was to compare the predictive power for hospitalizations of self-reported health status to the predictive power of anger, anxiety, and stress. For the analyses of Aim 3, the exposure variables were PSS, STAI, WAI,

KCCQ-Functional Status, and KCCQ-Clinical Summary scores measured at 8 time points (baseline, 3 month, 9 month, 15 month, 21 month, 27 month, 33 month, and 39 month follow-ups). The outcome variables were binary counts of all-cause, cardiac, and CHF hospitalizations.

Hypothesis 3

This hypothesis was that both acute and chronic KCCQ measures of health status will have the strongest association with subsequent hospitalizations, compared to anger, anxiety, and stress. Using GMM analyses, KCCQ-Functional Status was significantly associated with the occurrence of hospitalization at both the between-subjects and within-subjects level for all three types of hospitalizations (CHF, cardiac, and all-cause; see Table 12 on pages 84-85). KCCQ-Clinical Summary was associated with all three types of hospitalizations at the between-subjects level and with cardiac and all-cause hospitalizations at the within-subjects level (see Table 12). In multivariable GMM analyses, which controlled for stress, anxiety, and anger (along with medical and demographic covariates), KCCQ-Functional Status and KCCQ-Clinical Summary were both associated with all three types of hospitalization at both the between-subjects and within-subjects levels (see Table 12).

Conversely, in the same multivariable GMM analyses, between-subjects level STAI scores were associated with increased all-cause hospitalizations (controlling for KCCQ-Functional Status: $B = 0.06$, $SE = 0.02$, $p = 0.011$; controlling for KCCQ-Clinical Summary: $B = 0.06$, $SE = 0.02$, $p = 0.017$) and between-subjects level WAI scores were associated with decreased CHF hospitalizations (controlling for KCCQ-Functional

Status: $B = -0.08$, $SE = 0.03$, $p = 0.016$; controlling for KCCQ-Clinical Summary: $B = -0.08$, $SE = 0.03$, $p = 0.014$).

Aim 4

The fourth aim of this study was to compare the chronic vs. acute effects of anger, anxiety, and stress on hospitalizations, symptoms, and health status.

Hypothesis 4

This hypothesis was that chronic high stress and anxiety, but not acute increases in stress and anxiety, will be associated with more hospitalizations and poorer health status and that chronic anger vs acute increases in anger will be associated with more symptoms and poorer health status. This hypothesis was explored via examining the results from Aim 1 analyses and using likelihood ratio chi square tests and Wald chi square tests.

Covariate adjusted mean (chronic) stress was predictive of cardiac hospitalizations, all-cause hospitalizations, KCCQ-Functional Status, and KCCQ-Clinical Summary (see Table 11). Covariate adjusted deviation (acute) stress was also predictive of all-cause hospitalizations, KCCQ-Functional Status, and KCCQ-Clinical Summary, but not cardiac hospitalizations (see Table 11). Likelihood ratio chi square tests indicated a significant difference between within-subject PSS and between-subject PSS for the KCCQ analyses (KCCQ-Functional $\chi^2 = 14.76$, $p < .001$ and KCCQ-Clinical $\chi^2 = 19.09$, $p < .001$). Wald chi square tests found no significant difference between within-subject PSS and between-subject PSS for the hospitalization analyses (all-cause $p = .251$, cardiac $p = .369$, and CHF $p = .218$).

Covariate adjusted mean anxiety was predictive of all three types of hospitalizations (CHF, cardiac, and all-cause) and both KCCQ measures (see Table 10). Covariate adjusted deviation anxiety was only predictive of the two KCCQ measures (see Table 10). Likelihood ratio chi square tests indicated a significant difference between within-subject STAI and between-subject STAI for the KCCQ analyses (KCCQ-Functional $\chi^2 = 14.56, p < .001$ and KCCQ-Clinical $\chi^2 = 16.77, p < .001$). Wald chi square tests found significant differences between within-subject PSS and between-subject PSS for all-cause and CHF hospitalization analyses (all-cause $p = .019$ and CHF $p = .027$), but not for cardiac ($p = .102$).

Covariate adjusted mean and deviation anger were both only predictive of the two KCCQ measures (see Table 9). Likelihood ratio chi square tests indicated a significant difference between within-subject WAI and between-subject WAI for the KCCQ analyses (KCCQ-Functional $\chi^2 = 6.87, p = .009$ and KCCQ-Clinical $\chi^2 = 6.49, p = .011$). Wald chi square tests found no significant difference between within-subject WAI and between-subject WAI for the hospitalization analyses (all-cause $p = .397$, cardiac $p = .64$, and CHF $p = .172$).

In summary, for PSS and STAI there were more significant effects for adjusted means than for adjusted deviations. For WAI, mean and deviation results were both significant for KCCQ. There were significant differences between within-subject and between-subject level effects in all of the analyses with a KCCQ measure as a DV. There was also a significant difference just for STAI and the analyses of all-cause and CHF hospitalizations. Across anger, anxiety, and stress, all of the estimated B values for the between-subjects (chronic) effects were greater than the estimated B values for the

within-subject (acute) effects. Additionally, the SDs for each of the IVs at the chronic level were greater than the SDs for the same IVs at the acute level (see Table 6 on page 75). Consequently, a one point increase in an individual's mean anger, anxiety, or stress would predict a worse outcome than a one point deviation in the individual's anger, anxiety, or stress.

ADDITIONAL ANALYSES

Aim 1 Results Controlling for Depression

To determine whether depression may have contributed to results of Aim 1 analyses, baseline Beck Depression Inventory (BDI) score was added as a covariate in addition to the medical covariates in analyses of the relationship of WAI, STAI, and PSS to KCCQ and hospitalizations, respectively. Note that BDI scores were only available from the baseline and 3-month time points, so the baseline BDI score was used. For the WAI, mean and deviation scores were still significantly associated with scores on both of the KCCQ summary measures when controlling for BDI. As in prior analyses, neither mean or deviation WAI scores were associated with hospitalizations. For the STAI, mean and deviation scores were still significantly associated with scores on both of the KCCQ summary measures and mean STAI scores were still significantly associated with all three types of hospitalization when controlling for BDI. For the PSS, mean and deviation scores were still significantly associated with scores on both of the KCCQ summary measures and with all-cause hospitalizations when controlling for BDI. Additionally, mean PSS was still predictive of cardiac hospitalizations when controlling for BDI. In summary, controlling for patients' baseline depression did not significantly impact the results of analyses for Aim 1.

Prospective Association of Study Variables with Hospitalizations

Anxiety and Stress

To determine whether the associations of higher mean state anxiety (Mean STAI) and higher mean perceived stress (Mean PSS), respectively, with hospitalizations were prospective and not a result of recent prior hospitalization, analyses were conducted using only STAI and PSS scores measured prior to a patient having any hospitalization in the study. Among patients with at least one hospitalization, we averaged all their STAI and PSS scores before their first hospitalization in the study ('Event Patients—Before First Event'). These scores were then compared, respectively, with Mean STAI and Mean PSS scores of those who had no hospitalizations in the study (No Event Patients). STAI and PSS scores of Event Patients—Before First Event were not significantly higher than scores of No Event Patients (STAI $p = 0.218$ and PSS $p = 0.65$).

KCCQ and Hospitalizations

To further clarify whether there were prospective differences between hospitalized and never hospitalized patients, analyses were conducted using only KCCQ scores measured prior to a patient having any hospitalization in the study. Among patients with at least one hospitalization, we averaged all their KCCQ scores before their first hospitalization in the study. These scores were then compared KCCQ scores of those who had no hospitalizations in the study. KCCQ scores of Event Patients—Before First Event were not significantly higher than scores of No Event Patients (KCCQ-Functional Status $p = 0.989$ and KCCQ-Clinical Summary $p = 0.71$).

Post-Hospital Effects of Study Variables

Anxiety and Stress

To determine whether experiencing a hospitalization increased anxiety or stress (post-hospitalization stress effect), we conducted an analysis using only those patients who experienced at least one hospitalization during the study. STAI and PSS scores measured at assessments occurring immediately after one (or more) hospitalizations ('After Event') were compared, respectively, with STAI and PSS scores at assessments not preceded by a hospitalization ('Control Assessments'). STAI and PSS scores After Event were not significantly higher compared with Control Assessments (STAI $p = 0.636$ and PSS $p = 0.787$). This indicates that anxiety and stress were not significantly higher following a hospitalization (when controlling for time and other covariates). As another way of looking for a post-hospitalization effect, we took all of the STAI and PSS scores from patients after their first hospitalization ('Event Patients—After First Event') and compared them to the respective scores of the No Event Patients. Again, there was no significant difference in scores (STAI $p = 0.55$ and PSS $p = 0.665$).

KCCQ and Hospitalizations

To determine whether experiencing a hospitalization impacted symptoms and functional status, we conducted an analysis using only those patients who experienced at least one hospitalization during the study. KCCQ scores measured at assessments occurring immediately after one (or more) hospitalizations were compared, respectively, with KCCQ scores at assessments not preceded by a hospitalization. KCCQ scores After Event were significantly higher (better) compared with Control Assessments (Functional Status: $B = 5.95$, $SE = 1.69$, $p < 0.001$ and Clinical Summary: $B = 4.64$, $SE = 1.65$, $p =$

0.005). This indicates that symptoms were lower and functional status higher following a hospitalization (when controlling for time and other covariates).

As with STAI and PSS, we next compared the KCCQ scores of Event Patients—After First Event with No Event Patients and found no significant difference in scores (Functional Status $p = 0.228$ and Clinical Summary $p = 0.455$).

Explanation of Additional Figures to Display Study Results

To better understand the study findings, an attempt was made to graphically present these results. In interpreting these figures it should be remembered, as with most MMs and GMMs, it is difficult to graphically display the multi-leveled relationships and effects that are explored with these analyses. Consequently, imprecise approximations often must be used, even if they are only able to capture the general thrust of the results.

Figures 8, 9, and 10 on pages 92-94 take the data from the prospective association analyses and graphs the means for No Event Patients, Event Patients-Before First Event, and Event Patients-After First Event at each time point. In Figures 8 and 9, the No Event Patients, Event Patients-Before First Event, and Event Patients-After First Event groups appear to be roughly equivalent in scores. Figure 8 does show a growing difference in scores between the two event patient groups, but this might be in part due to the previously mentioned skew in numbers of observations for the Event Patients-Before First Event as the time points move to the right. Figure 10, on the other hand, shows a particularly interesting pattern of increase in stress scores for the Event Patients-After First Event group. Unlike the WAI, this pattern starts much earlier in the time series and carries on throughout, making it less likely to be due to skewing of the observation numbers.

Because of this pattern of rising scores following the first hospitalization, it is difficult to completely rule-out some form of post-hospital effect, even if the additional post-hospital effect analyses were non-significant. It is possible that there is something that analysis missed by looking at all of the event patients' scores and hospitalizations, versus the graph's simplification to just looking at patients before and after their first hospitalizations.

Figures 11, 12, and 13 on pages 95-96 attempt to graphically portray the within-subjects associations of the IVs with KCCQ scores and hospitalizations. These figures were produced by taking all of the deviation scores with a positive value and considering them "greater than usual" and all of the negative deviation values as "less than usual." The KCCQ-Clinical scores and all-cause hospitalization rates associated with each IV score in the "greater than usual" and "less than usual" groups, respectively, were then averaged to produce the bar values. The KCCQ bars capture the significant associations of all the IVs with KCCQ scores at the within-subject level, with greater than usual anger (Figure 11), anxiety (Figure 12), or stress (Figure 13) being associated with worse KCCQ scores. The hospitalization bars, on the other hand, are not fully able to reflect the obtained significant within-subjects association of PSS with all-cause hospitalizations. It is possible that the somewhat small effect size of that association requires the more nuanced modeling of all of a patient's individual time points provided by the full GMM analyses in order to be fully apparent.

Figures 14, 15, and 16 on page 96-97 pool all observations to display the relationship between quintiles of scores in anger (Fig. 14), anxiety (Fig. 15), and stress (Figure 16) with subsequent all-cause hospitalizations. Note that anxiety (which produced

significant between-subjects effects in the main analyses) and stress (which produced significant within-subjects and between-subjects effects in the main analyses) both exhibit a clear stepwise progression of greater percentages of hospitalizations in the time following anxiety or stress scores in the higher quintiles. Additionally, anger (which did not have an association with hospitalizations in the main analyses) demonstrates no clear dose-response pattern, other than scores in the highest quintile having a somewhat higher than average rate of subsequent hospitalizations. In summary, from these figures it is possible to infer that higher anxiety and stress were generally associated with an increased risk of hospitalization in this study.

RESULTS TABLES

Table 5. Baseline Socio-demographic and Clinical Characteristics (N = 147)

Variable	Mean $\pm$ SD or %
Age (yrs)	57.40 $\pm$ 11.46
Male Sex (%)	76.9
Race	
African American (%)	70.1
Non-African American (%)	29.9
BMI (kg/m ²)	30.81 $\pm$ 7.58
Ejection Fraction (%)	23.13 $\pm$ 7.48
Heart Failure Type	
ischemic (%)	45.4
non-ischemic (%)	54.6
Hypertension	
yes (%)	79.6
no (%)	20.4
Type I and/or Type II Diabetes	
yes (%)	41.1
no (%)	58.9
Implantable Defibrillator	
yes (%)	50.3
no (%)	49.7
Employment Status	
full time (%)	14.3
part time (%)	7.5
disabled (%)	52.3
unemployed (%)	4.8
retired (%)	21.1

Note. BMI = body mass index; BP = blood pressure; NYHA = New York Heart Association.

Table 6. Summary Statistics of Baseline Independent Variables

Measure	Mean	SD	Minimum	Maximum
Baseline PSS	13.22	8.26	0.00	32.00
Baseline STAI	30.28	10.26	20.00	65.00
Baseline WAI	10.61	10.43	0.00	47.00
Baseline KCCQ-Functional	73.73	20.76	19.00	100.00
Baseline KCCQ-Clinical	71.82	21.05	19.00	100.00
Mean PSS	11.54	7.24	0.00	32.25
Mean STAI	30.14	8.64	20.00	55.50
Mean WAI	8.08	8.50	0.00	46.50
Mean KCCQ-Functional	75.25	18.80	19.79	100.00
Mean KCCQ-Clinical	74.02	18.71	23.18	100.00
Deviation PSS	0.00	5.17	-17.00	29.63
Deviation STAI	0.00	6.58	-25.00	39.71
Deviation WAI	0.00	5.78	-27.00	28.60
Deviation KCCQ-Functional	0.00	11.72	-52.21	41.88
Deviation KCCQ-Clinical	0.00	11.36	-56.58	41.31

Note. PSS = Perceived Stress Scale; STAI = State Trait Anxiety Inventory-State Anxiety score; WAI = Weekly Anger Inventory score; KCCQ-Functional = Kansas City Cardiomyopathy Questionnaire-Functional Status score; KCCQ-Clinical = Kansas City Cardiomyopathy Questionnaire-Clinical Summary score. Possible range of scores for PSS are 0 – 40, for STAI are 20 – 80, for WAI are 0 – 70, and for both forms of KCCQ are 0 – 100. Higher KCCQ scores indicate less CHF symptom burden and better health status.

Table 7. Correlations between Subject Means at Baseline

		WAI	STAI	PSS	BDI	KCCQ-Functional	KCCQ-Clinical
WAI	<i>r</i>	-	.329**	.491**	.430**	-.232**	-.294**
	<i>p</i>	-	0.000	0.000	0.000	0.005	0.000
	N	-	146	147	145	146	146
STAI	<i>r</i>	.329**	-	.537**	.559**	-.310**	-.389**
	<i>p</i>	0.000	-	0.000	0.000	0.000	0.000
	N	146	-	146	144	145	145
PSS	<i>r</i>	.491**	.537**	-	.717**	-.443**	-.537**
	<i>p</i>	0.000	0.000	-	0.000	0.000	0.000
	N	147	146	-	145	146	146
BDI	<i>r</i>	.430**	.559**	.717**	-	-.504**	-.607**
	<i>p</i>	0.000	0.000	0.000	-	0.000	0.000
	N	145	144	145	-	144	144
KCCQ-Functional	<i>r</i>	-.232**	-.310**	-.443**	-.504**	-	.932**
	<i>p</i>	0.005	0.000	0.000	0.000	-	0.000
	N	146	145	146	144	-	146
KCCQ-Clinical	<i>r</i>	-.294**	-.389**	-.537**	-.607**	.932**	-
	<i>p</i>	0.000	0.000	0.000	0.000	0.000	-
	N	146	145	146	144	146	-

Note. PSS = WAI = Weekly Anger Inventory score; STAI = State Trait Anxiety Inventory-State Anxiety score; Perceived Stress Scale; BDI = Beck Depression Inventory; KCCQ-Functional = Kansas City Cardiomyopathy Questionnaire-Functional Status score; KCCQ-Clinical = Kansas City Cardiomyopathy Questionnaire-Clinical Summary score.

** $p < .01$

Table 8. Correlations between Subject Means at 3-Months

		WAI	STAI	PSS	BDI	KCCQ-Functional	KCCQ-Clinical
WAI	<i>r</i>	-	.514**	.581**	.405**	-.460**	-.411**
	<i>p</i>	-	0.000	0.000	0.000	0.000	0.000
	N	-	126	126	126	126	126
STAI	<i>r</i>	.514**	-	.770**	.565**	-.374**	-.421**
	<i>p</i>	0.000	-	0.000	0.000	0.000	0.000
	N	126	-	-	126	126	126
PSS	<i>r</i>	.581**	.770**	-	.684**	-.490**	-.536**
	<i>p</i>	0.000	0.000	-	0.000	0.000	0.000
	N	126	126	126	126	126	126
BDI	<i>r</i>	.405**	.565**	.684**	-	-.537**	-.624**
	<i>p</i>	0.000	0.000	0.000	-	0.000	0.000
	N	126	126	126	-	126	126
KCCQ-Functional	<i>r</i>	-.460**	-.374**	-.490**	-.537**	-	.914**
	<i>p</i>	0.000	0.000	0.000	0.000	-	0.000
	N	126	126	126	126	-	126
KCCQ-Clinical	<i>r</i>	-.411**	-.421**	-.536**	-.624**	.914**	-
	<i>p</i>	0.000	0.000	0.000	0.000	0.000	-
	N	126	126	126	126	126	-

Note. PSS = Weekly Anger Inventory score; STAI = State Trait Anxiety Inventory-State Anxiety score; Perceived Stress Scale; BDI = Beck Depression Inventory; KCCQ-Functional = Kansas City Cardiomyopathy Questionnaire-Functional Status score; KCCQ-Clinical = Kansas City Cardiomyopathy Questionnaire-Clinical Summary score.

** $p < .01$

Table 9. Associations between WAI Score and Outcomes Variables

Covariates	Exposure ^a	Outcomes ^b				
		CHF Hosp.	Cardiac Hosp.	All-Cause Hosp.	KCCQ-Functional	KCCQ-Clinical
Unadjusted	Mean WAI ^c	-0.02 (0.03)	0.01 (0.02)	0.02 (0.02)	-0.91*** (0.17)	-0.94*** (0.16)
Cov. Adjusted ^d	Mean WAI	-0.02 (0.03)	0.00 (0.02)	0.02 (0.02)	-0.86*** (0.16)	-0.87*** (0.16)
Adjusted All ^c	Mean WAI	-0.06* (0.03)	-0.03 (0.02)	-0.02 (0.02)	-0.33 (0.19)	-0.22 (0.18)
Unadjusted	Deviation WAI ^c	0.02 (0.01)	0.02 (0.01)	0.00 (0.01)	-0.36*** (0.09)	-0.41*** (0.08)
Cov. Adjusted ^d	Deviation WAI	0.02 (0.01)	0.02 (0.01)	0.00 (0.01)	-0.36*** (0.09)	-0.41*** (0.08)
Adjusted All ^c	Deviation WAI	0.03 (0.01)	0.01 (0.01)	-0.01 (0.01)	-0.20* (0.09)	-0.21* (0.08)

Note. WAI = Weekly Anger Inventory score, CHF Hosp. = heart failure-related hospitalizations, Cardiac Hosp. = cardiac-related hospitalizations, All-Cause Hosp. = hospitalizations due to any cause, KCCQ-Functional = Kansas City Cardiomyopathy Questionnaire-Functional Status summary score, KCCQ-Clinical = Kansas City Cardiomyopathy Questionnaire-Clinical Summary

score, Cov. Adjusted = analyses adjusted for covariates, Adjusted All = analyses adjusted for covariates, PSS, and STAI State Anxiety.

^aExposure refers to the Mean WAI score and Deviation WAI score for their respective analyses. (See text for details).

^bOutcomes are hospitalizations occurring after each assessment (baseline, 3 month, 9 month, 15 month, 21 month, 27 month, 33 month, and 39 month follow-ups) and KCCQ summary scores at each assessment (baseline, 3 month, 9 month, 15 month, 21 month, 27 month, 33 month, and 39 month follow-ups; see text for details). Values are parameter estimates B (SE) from marginal models (KCCQ scores) or generalized marginal models (hospitalizations).

^cMean WAI scores and Deviation WAI scores are entered concurrently (see text). All models include time as a within-subject variable.

^dAdjusted analyses for KCCQ measures include the following covariates: BMI, NYHA class, hypertensive status, age, gender, income, and race (parameter estimates for time or covariates not shown). Adjusted analyses for hospitalizations include the following covariates: ejection fraction, NYHA class, hypertensive status, presence of type I or type II diabetes, implantable defibrillator status, age, gender, income, and race (parameter estimates for time or covariates not shown).

^eAnalyses including above covariates, PSS, and STAI State Anxiety.

* $p < .05$, ** $p < .01$, *** $p < .001$.

Table 10. Associations between STAI Score and Outcomes Variables

Covariates	Exposure ^a	Outcomes ^b				
		CHF Hosp.	Cardiac Hosp.	All-Cause Hosp.	KCCQ-Functional	KCCQ-Clinical
Unadjusted	Mean STAI ^c	0.05* (0.02)	0.04** (0.02)	0.06*** (0.02)	-1.05*** (0.16)	-1.18*** (0.15)
Cov. Adjusted ^d	Mean STAI	0.05* (0.02)	0.05** (0.02)	0.06*** (0.02)	-0.90*** (0.16)	-1.05*** (0.16)
Adjusted All ^c	Mean STAI	0.06* (0.03)	0.06 (0.03)	0.06* (0.03)	-0.03 (0.25)	-0.14 (0.23)
Unadjusted	Deviation STAI ^c	0.00 (0.01)	0.01 (0.01)	0.01 (0.01)	-0.34*** (0.07)	-0.47*** (0.07)
Cov. Adjusted ^d	Deviation STAI	0.00 (0.01)	0.01 (0.01)	0.01 (0.01)	-0.34*** (0.07)	-0.46*** (0.07)
Adjusted All ^c	Deviation STAI	-0.01 (0.02)	0.00 (0.01)	0.00 (0.01)	-0.15 (0.08)	-0.25** (0.08)

Note. STAI = State Trait Anxiety Inventory-State Anxiety score, CHF Hosp. = heart failure-related hospitalizations, Cardiac Hosp. = cardiac-related hospitalizations, All-Cause Hosp. = hospitalizations due to any cause, KCCQ-Functional = Kansas City Cardiomyopathy Questionnaire-Functional Status summary score, KCCQ-Clinical = Kansas City Cardiomyopathy Questionnaire-

Clinical Summary score, Cov. Adjusted = analyses adjusted for covariates, Adjusted All = analyses adjusted for covariates, PSS, and WAI.

^aExposure refers to the Mean STAI score and Deviation STAI score for their respective analyses. (See text for details).

^bOutcomes are hospitalizations occurring after each assessment (baseline, 3 month, 9 month, 15 month, 21 month, 27 month, 33 month, and 39 month follow-ups) and KCCQ summary scores at each assessment (baseline, 3 month, 9 month, 15 month, 21 month, 27 month, 33 month, and 39 month follow-ups; see text for details). Values are parameter estimates B (SE) from marginal models (KCCQ scores) or generalized marginal models (hospitalizations).

^cMean STAI scores and Deviation STAI scores are entered concurrently (see text). All models include time as a within-subject variable.

^dAdjusted analyses for KCCQ measures include the following covariates: BMI, NYHA class, hypertensive status, age, gender, income, and race (parameter estimates for time or covariates not shown). Adjusted analyses for hospitalizations include the following covariates: ejection fraction, NYHA class, hypertensive status, presence of type I or type II diabetes, implantable defibrillator status, age, gender, income, and race (parameter estimates for time or covariates not shown).

^eAnalyses including above covariates, PSS, and WAI.

* $p < .05$, ** $p < .01$, *** $p < .001$.

Table 11. Associations between PSS Score and Outcomes Variables

Covariates	Exposure ^a	Outcomes ^b				
		CHF Hosp.	Cardiac Hosp.	All-Cause Hosp.	KCCQ-Functional	KCCQ-Clinical
Unadjusted	Mean PSS ^c	0.04 (0.03)	0.05* (0.02)	0.06** (0.02)	-1.43*** (0.18)	-1.60*** (0.17)
Cov. Adjusted ^d	Mean PSS	0.04 (0.03)	0.04* (0.02)	0.06** (0.02)	-1.41*** (0.19)	-1.59*** (0.18)
Adjusted All ^e	Mean PSS	0.03 (0.04)	0.01 (0.04)	0.01 (0.03)	-1.13** (0.33)	-1.29*** (0.31)
Unadjusted	Deviation PSS ^c	0.01 (0.02)	0.02 (0.02)	0.03* (0.01)	-0.60*** (0.09)	-0.72*** (0.09)
Cov. Adjusted ^d	Deviation PSS	0.01 (0.02)	0.03 (0.02)	0.03* (0.01)	-0.61*** (0.09)	-0.73*** (0.09)
Adjusted All ^e	Deviation PSS	0.00 (0.02)	0.02 (0.02)	0.03* (0.02)	-0.43*** (0.11)	-0.49*** (0.10)

Note. PSS = Perceived Stress Scale score, CHF Hosp. = heart failure-related hospitalizations, Cardiac Hosp. = cardiac-related hospitalizations, All-Cause Hosp. = hospitalizations due to any cause, KCCQ-Functional = Kansas City Cardiomyopathy Questionnaire-Functional Status summary score, KCCQ-Clinical = Kansas City Cardiomyopathy Questionnaire-Clinical Summary

score, Cov. Adjusted = analyses adjusted for covariates, Adjusted All = analyses adjusted for covariates, WAI, and STAI State Anxiety.

^aExposure refers to the Mean PSS score and Deviation PSS score for their respective analyses. (See text for details).

^bOutcomes are hospitalizations occurring after each assessment (baseline, 3 month, 9 month, 15 month, 21 month, 27 month, 33 month, and 39 month follow-ups) and KCCQ summary scores at each assessment (baseline, 3 month, 9 month, 15 month, 21 month, 27 month, 33 month, and 39 month follow-ups; see text for details). Values are parameter estimates B (SE) from marginal models (KCCQ scores) or generalized marginal models (hospitalizations).

^cMean PSS scores and Deviation PSS scores are entered concurrently (see text). All models include time as a within-subject variable.

^dAdjusted analyses for KCCQ measures include the following covariates: BMI, NYHA class, hypertensive status, age, gender, income, and race (parameter estimates for time or covariates not shown). Adjusted analyses for hospitalizations include the following covariates: ejection fraction, NYHA class, hypertensive status, presence of type I or type II diabetes, implantable defibrillator status, age, gender, income, and race (parameter estimates for time or covariates not shown).

^eAnalyses including above covariates, WAI, and STAI State Anxiety.

* $p < .05$, ** $p < .01$, *** $p < .001$.

Table 12. Associations between KCCQ Scores and Hospitalizations

Covariates	Exposure ^a	Outcomes ^b					
		KCCQ-Functional Status			KCCQ-Clinical Summary		
		CHF Hosp.	Cardiac Hosp.	All-Cause Hosp.	CHF Hosp.	Cardiac Hosp.	All-Cause Hosp.
Unadjusted	Mean KCCQ ^c	-0.03** (0.01)	-0.03*** (0.01)	-0.03*** (0.01)	-0.03** (0.01)	-0.03*** (0.01)	-0.03*** (0.01)
Cov. Adjusted ^d	Mean KCCQ	-0.03** (0.01)	-0.03*** (0.01)	-0.03*** (0.01)	-0.03** (0.01)	-0.03** (0.01)	-0.03*** (0.01)
Adjusted All ^e	Mean KCCQ	-0.03** (0.01)	-0.03** (0.01)	-0.03** (0.01)	-0.03** (0.01)	-0.03** (0.01)	-0.02* (0.01)
Unadjusted	Deviation KCCQ ^c	-0.02* (0.01)	-0.03** (0.01)	-0.03** (0.01)	-0.02 (0.01)	-0.02** (0.01)	-0.02** (0.01)
Cov. Adjusted ^d	Deviation KCCQ	-0.03* (0.01)	-0.03** (0.01)	-0.02** (0.01)	-0.02 (0.01)	-0.03** (0.01)	-0.02* (0.01)
Adjusted All ^e	Deviation KCCQ	-0.03* (0.01)	-0.03** (0.01)	-0.03** (0.01)	-0.03* (0.01)	-0.03** (0.01)	-0.02** (0.01)

Note. CHF Hosp. = heart failure-related hospitalizations, Cardiac Hosp. = cardiac-related hospitalizations, All-Cause Hosp. = hospitalizations due to any cause, Cov. Adjusted = analyses adjusted for covariates, Adjusted All = analyses adjusted for covariates, PSS, STAI State Anxiety, and WAI.

^aExposure refers to the Mean KCCQ score and Deviation KCCQ score for their respective analyses. (See text for details).

^bOutcomes are hospitalizations occurring after each assessment (baseline, 3 month, 9 month, 15 month, 21 month, 27 month, 33 month, and 39 month follow-ups; see text for details). Values are parameter estimates B (SE) from marginal models (KCCQ scores) or generalized marginal models (hospitalizations).

^cMean KCCQ scores and Deviation KCCQ scores are entered concurrently (see text). All models include time as a within-subject variable.

^dAdjusted analyses for hospitalizations include the following covariates: ejection fraction, NYHA class, hypertensive status, presence of type I or type II diabetes, implantable defibrillator status, age, gender, income, and race (parameter estimates for time or covariates not shown).

^eAnalyses including above covariates, PSS, STAI State Anxiety, and WAI.

* $p < .05$, ** $p < .01$, *** $p < .001$.

RESULTS FIGURES

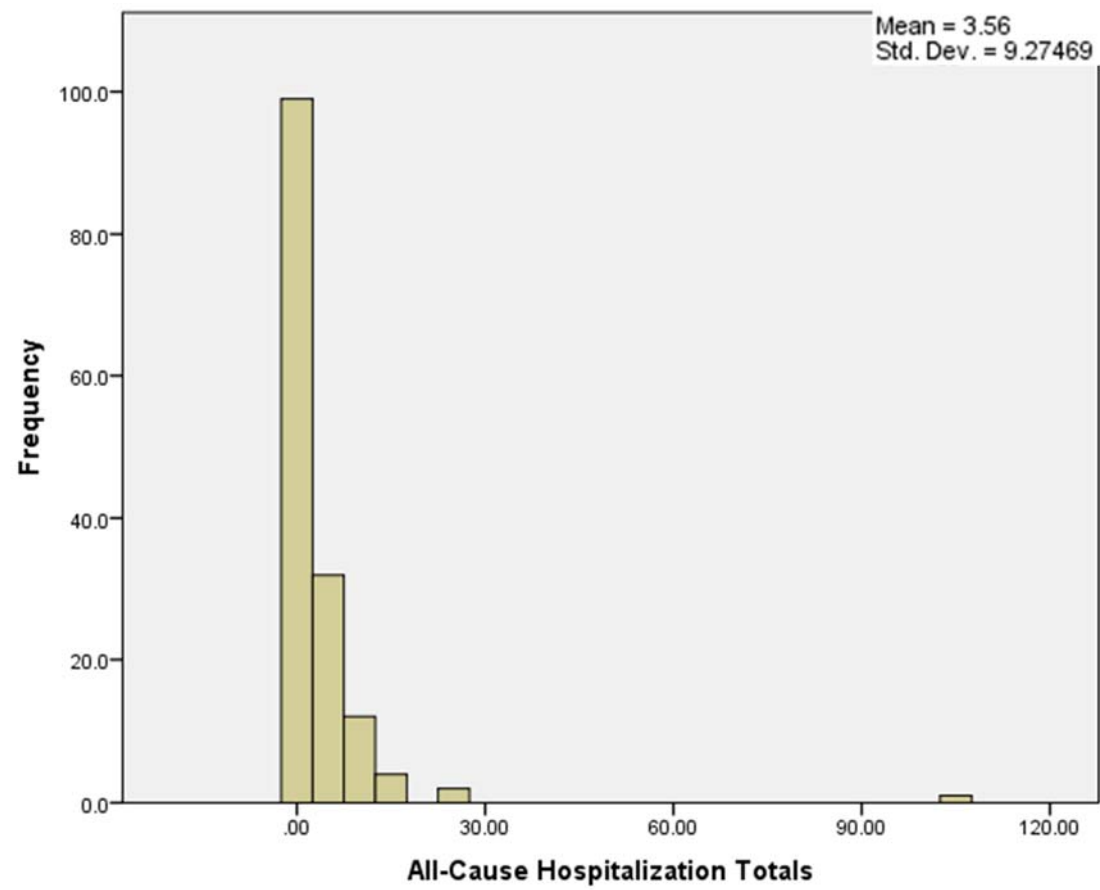


Figure 3. Distribution of full study period all-cause hospitalization totals.

Assessment Points in Study

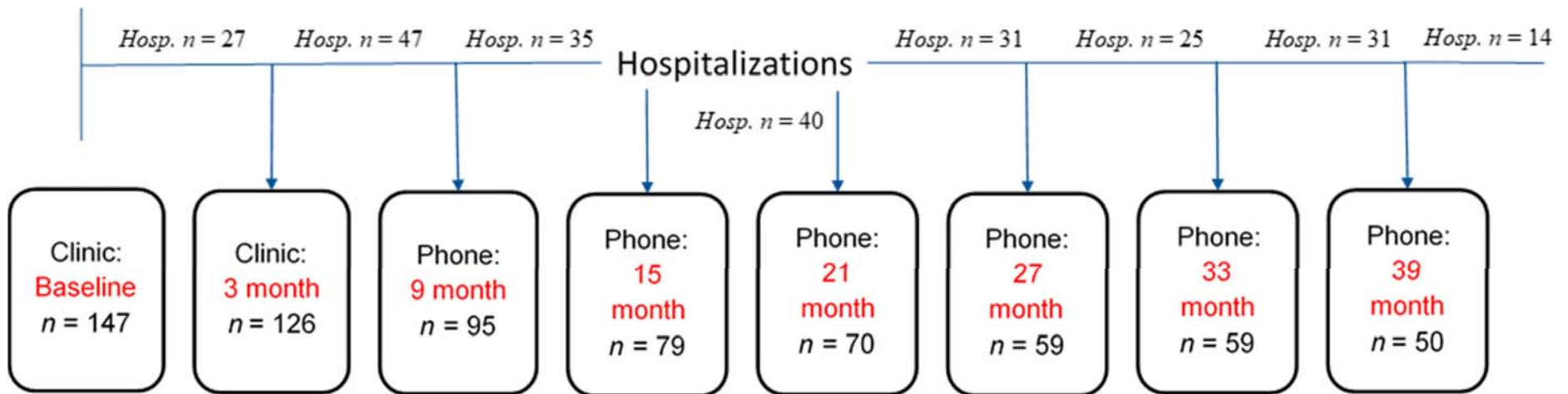


Figure 4. Time course of study including methods of data collection, number of patients who provided data at each time point, and number of patients who had at least one hospitalization between time points.
n = number of patients that provided data at the time point
Hosp. n = number of participants that experienced at least one hospitalization after the preceding time point

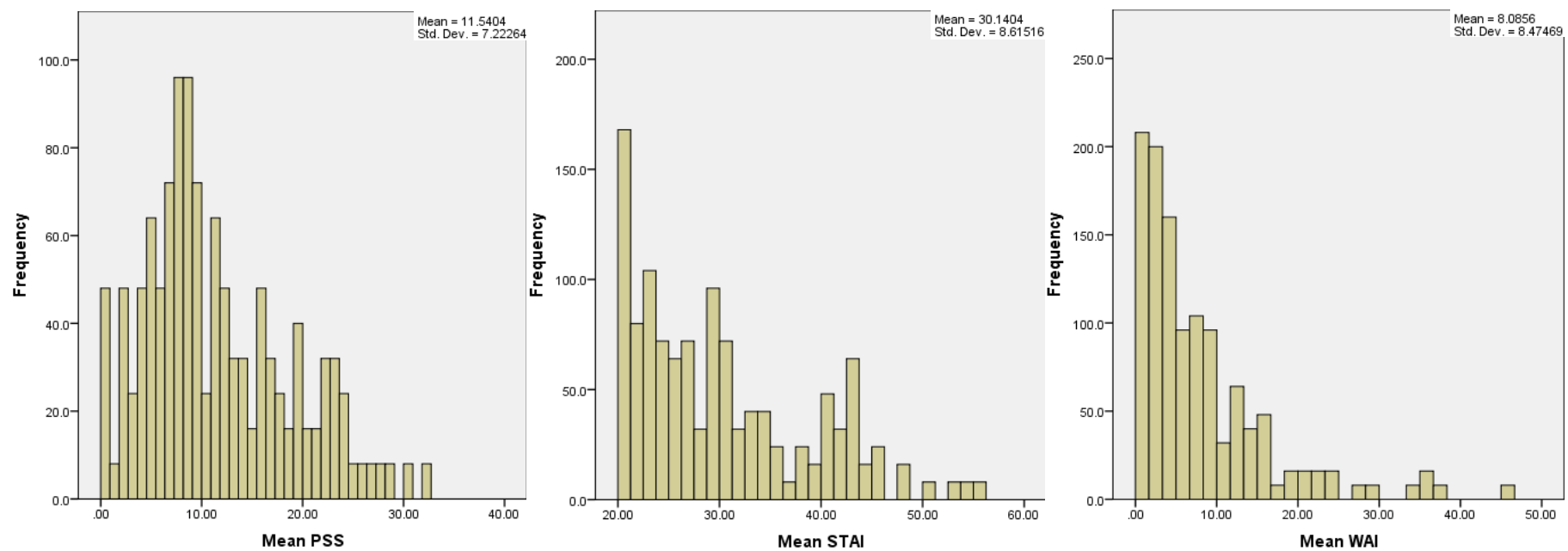


Figure 5. Mean PSS, STAI, and WAI scores aggregated across participants and time points.

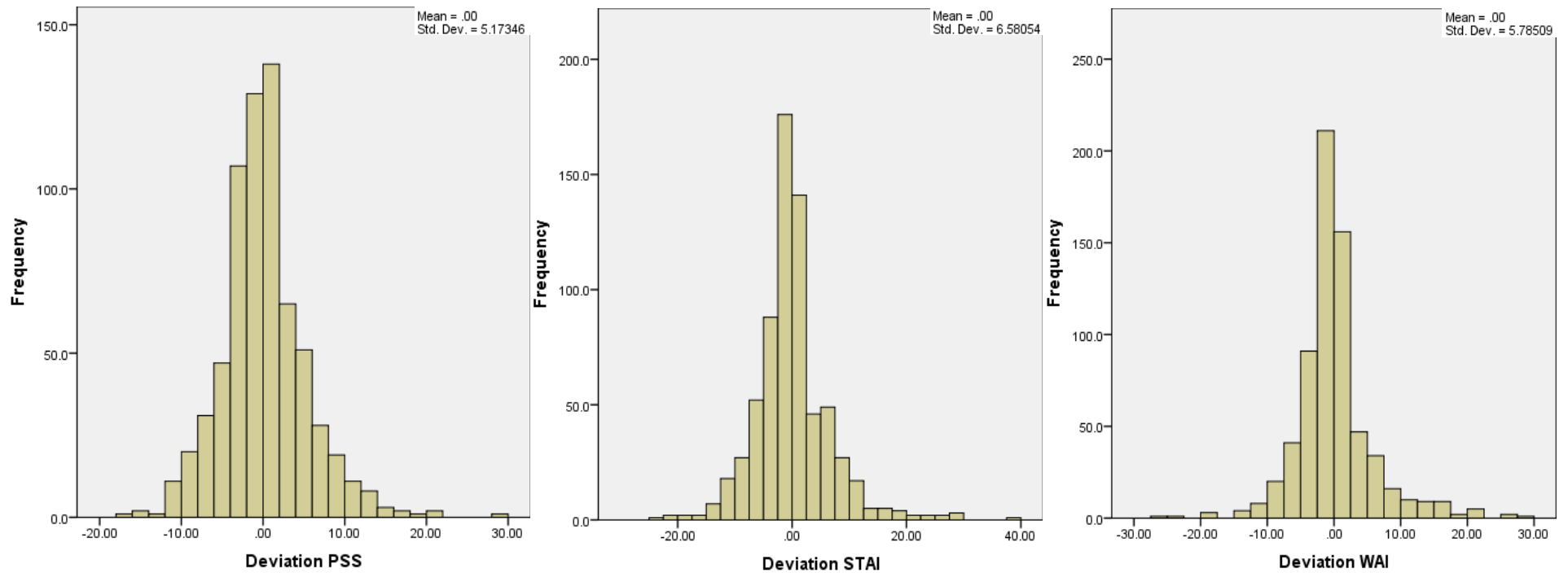


Figure 6. Deviation of PSS, STAI, and WAI scores at each time point from each participant's total mean across time point.

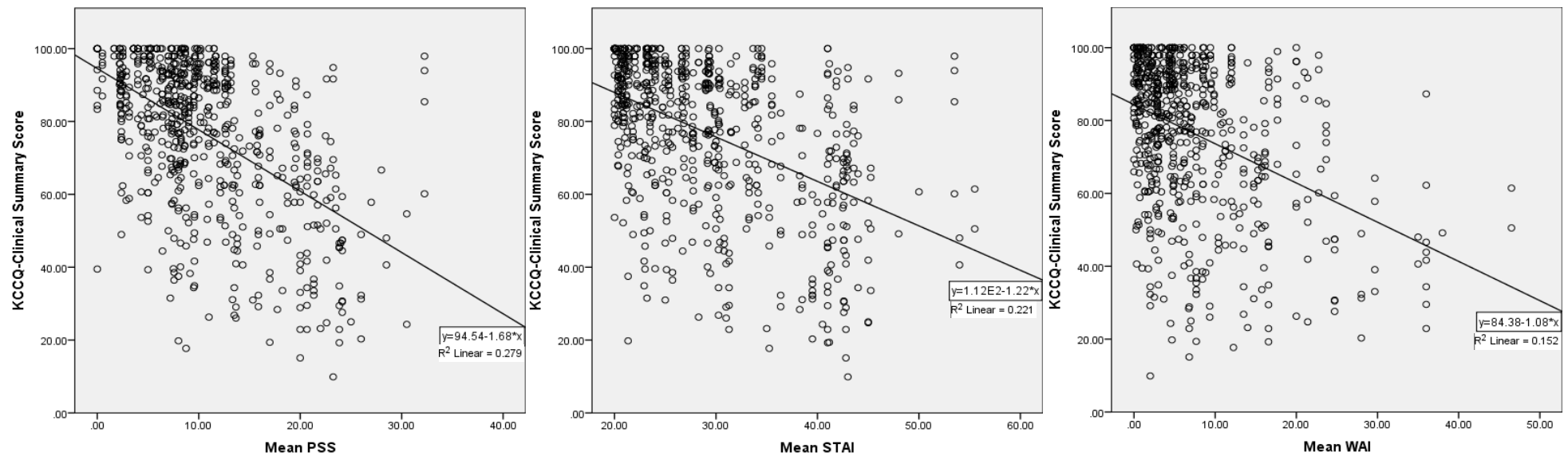


Figure 7. Correlations between KCCQ-Clinical Summary score and unadjusted mean PSS, STAI, or WAI score across all time points.

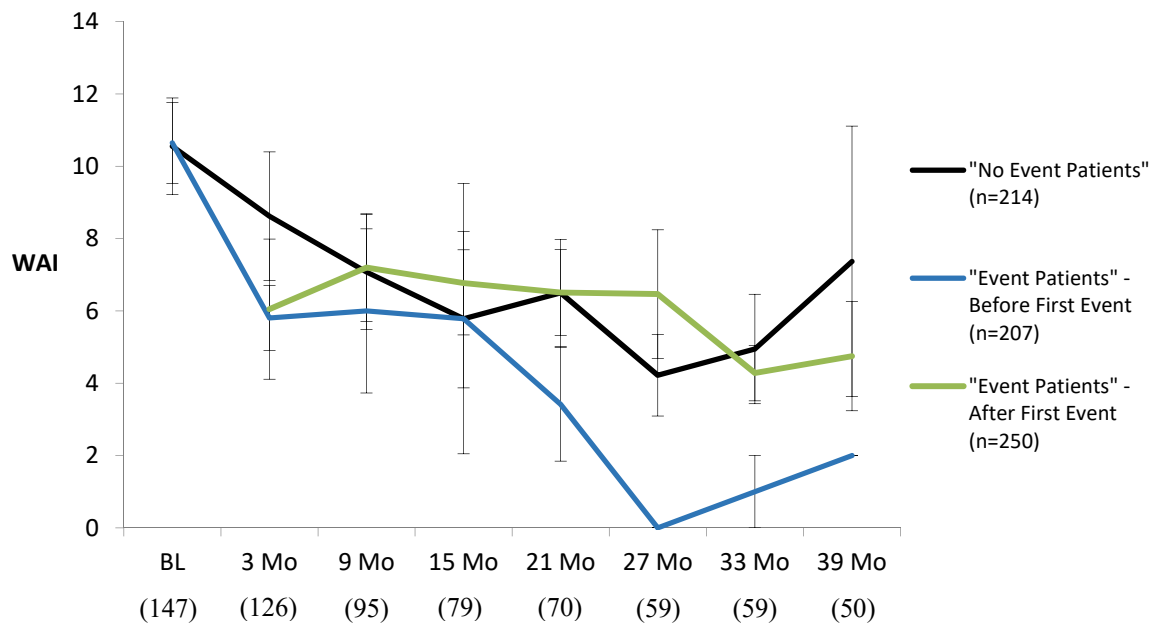


Figure 8. Time series means of WAI scores for groups of patients divided based on presence or absence of any hospitalization during the study and time of first hospitalization.

The numbers of observations included in each group are roughly equivalent, but it is important to recognize that the distribution of observations is skewed in the case of the two groups for event patients. Initially, most event patient observations were in the “before the first event” grouping. However, by the end of the study span all of the event patients had converted to the “after first event” group. Note: Numbers in parentheses equal numbers of subjects assessed at each time point.

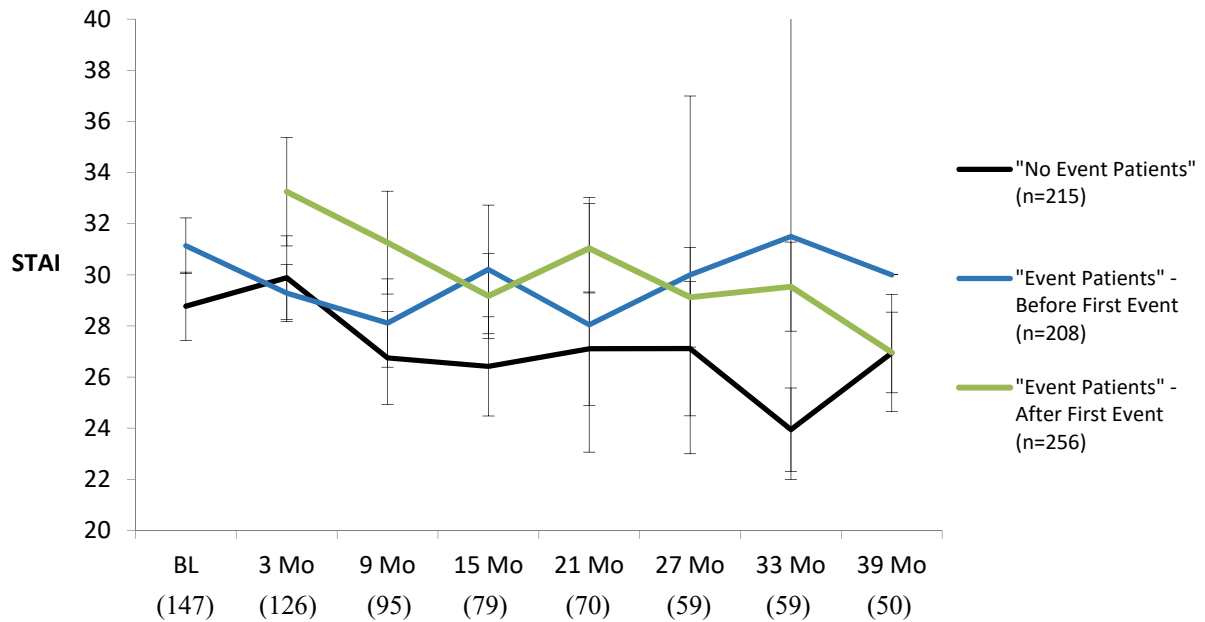


Figure 9. Time series means of STAI scores for groups of patients divided based on presence or absence of any hospitalization during the study and time of first hospitalization.

The numbers of observations included in each group are roughly equivalent, but it is important to recognize that the distribution of observations is skewed in the case of the two groups for event patients. Initially, most event patient observations were in the “before the first event” grouping. However, by the end of the study span all of the event patients had converted to the “after first event” group. Note: Numbers in parentheses equal numbers of subjects assessed at each time point.

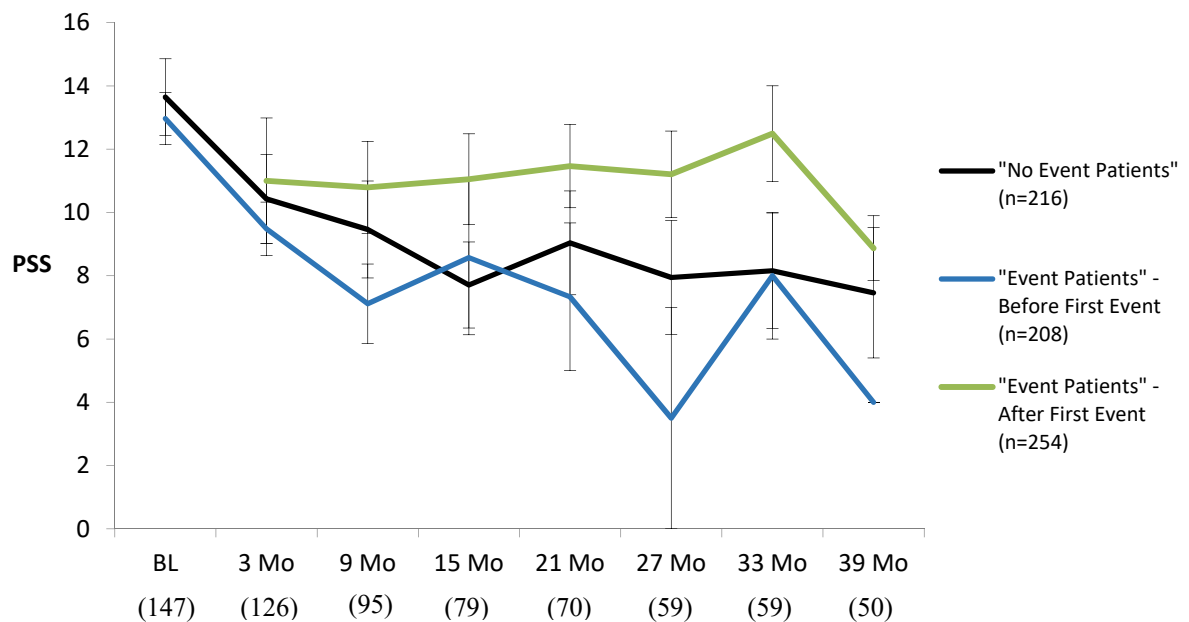


Figure 10. Time series means of PSS scores for groups of patients divided based on presence or absence of any hospitalization during the study and time of first hospitalization.

The numbers of observations included in each group are roughly equivalent, but it is important to recognize that the distribution of observations is skewed in the case of the two groups for event patients. Initially, most event patient observations were in the “before the first event” grouping. However, by the end of the study span all of the event patients had converted to the “after first event” group. Note: Numbers in parentheses equal numbers of subjects assessed at each time point.

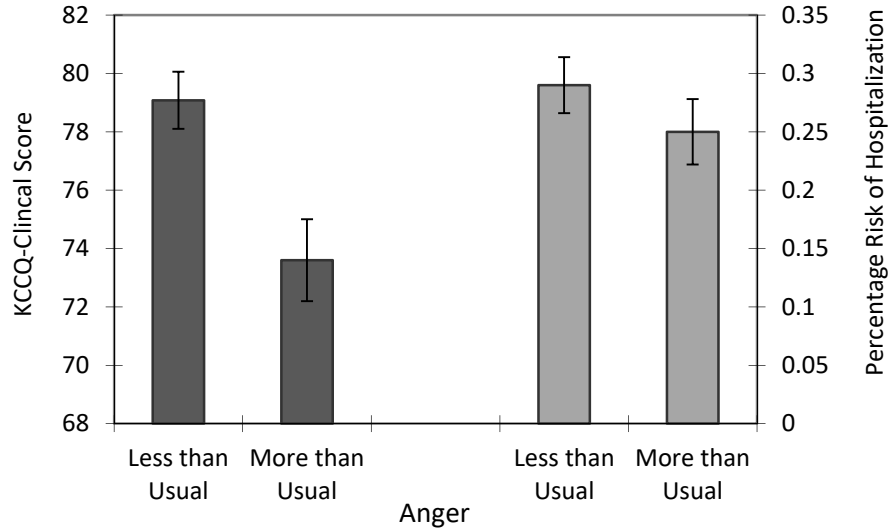


Figure 11. Within-subject level associations comparing “more than usual” vs. “less than usual” levels of anger in relationship to KCCQ-Clinical scores and risk of subsequent hospitalization.

Note: Higher KCCQ scores represent better health status.

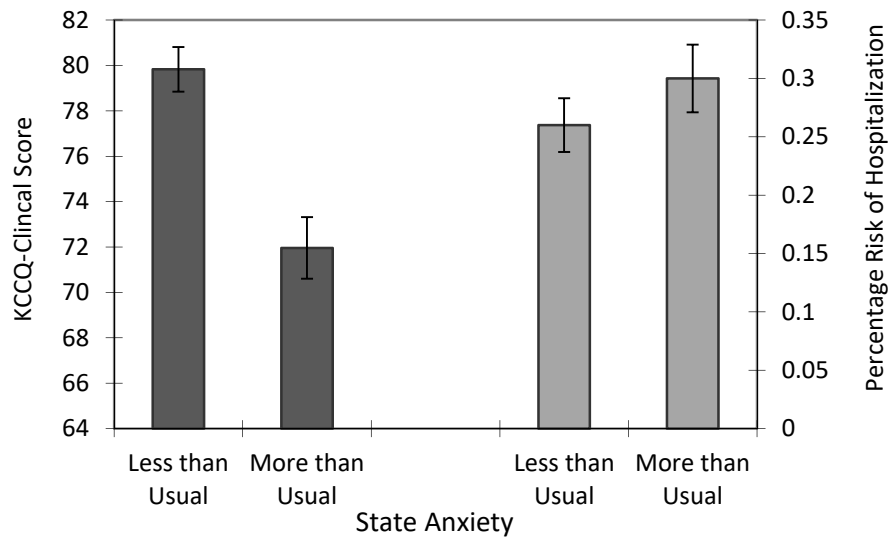


Figure 12. Within-subject level associations between deviations from usual in anxiety and KCCQ-Clinical scores/risk of subsequent hospitalization.

Note: Higher KCCQ scores represent better health status.

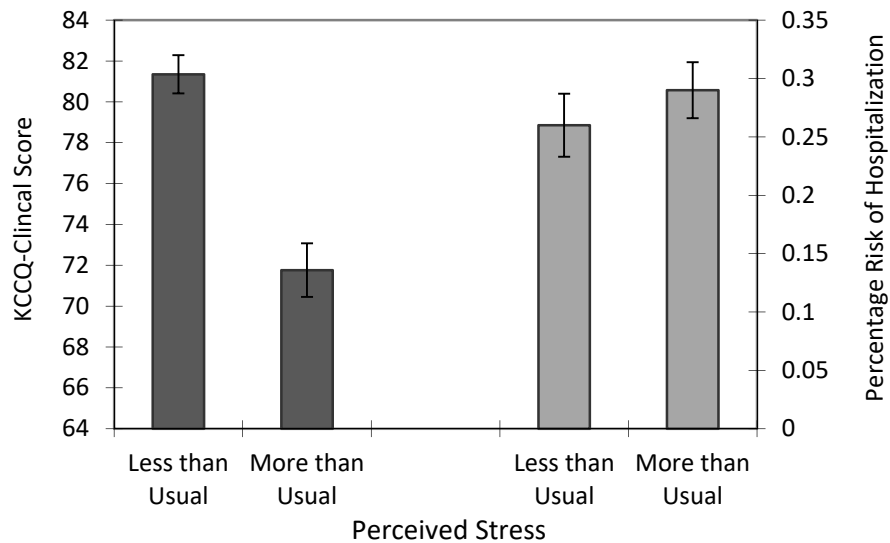


Figure 13. Within-subject level associations between deviations from usual in stress and KCCQ-Clinical scores/risk of subsequent hospitalization.
Note: Higher KCCQ scores represent better health status.

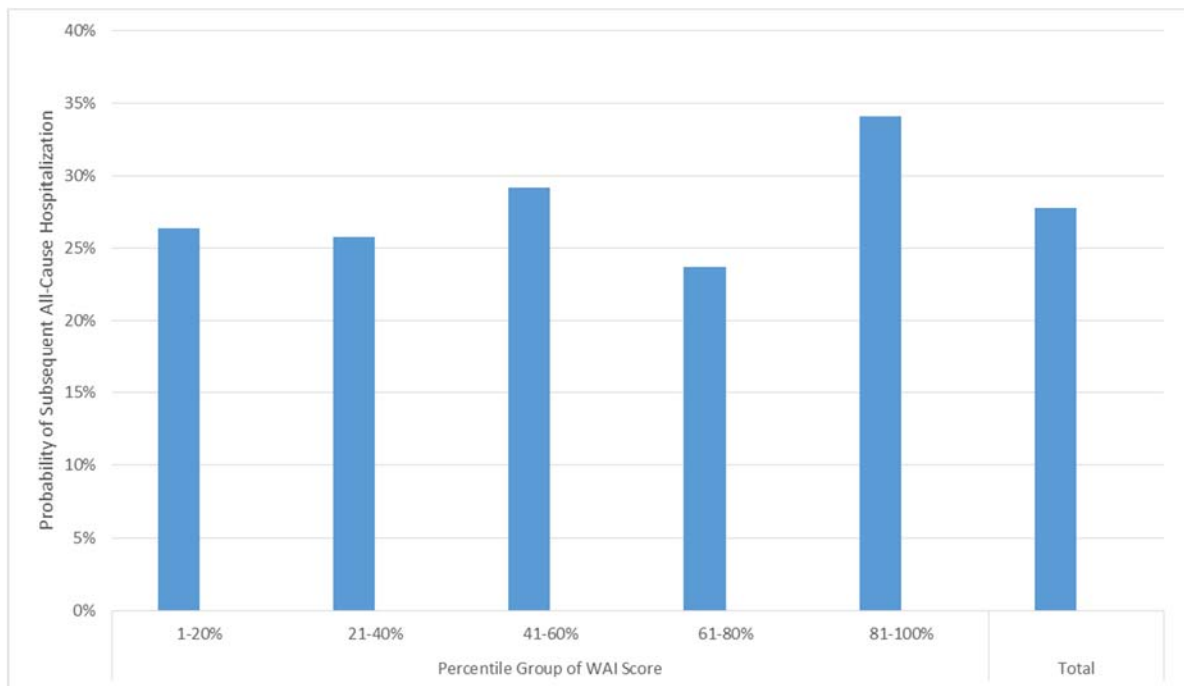


Figure 14. Relationship between anger scores, taken from all patients and all time points then ranked in quintiles, and percentage of individuals that had a hospitalization following a given anger score.

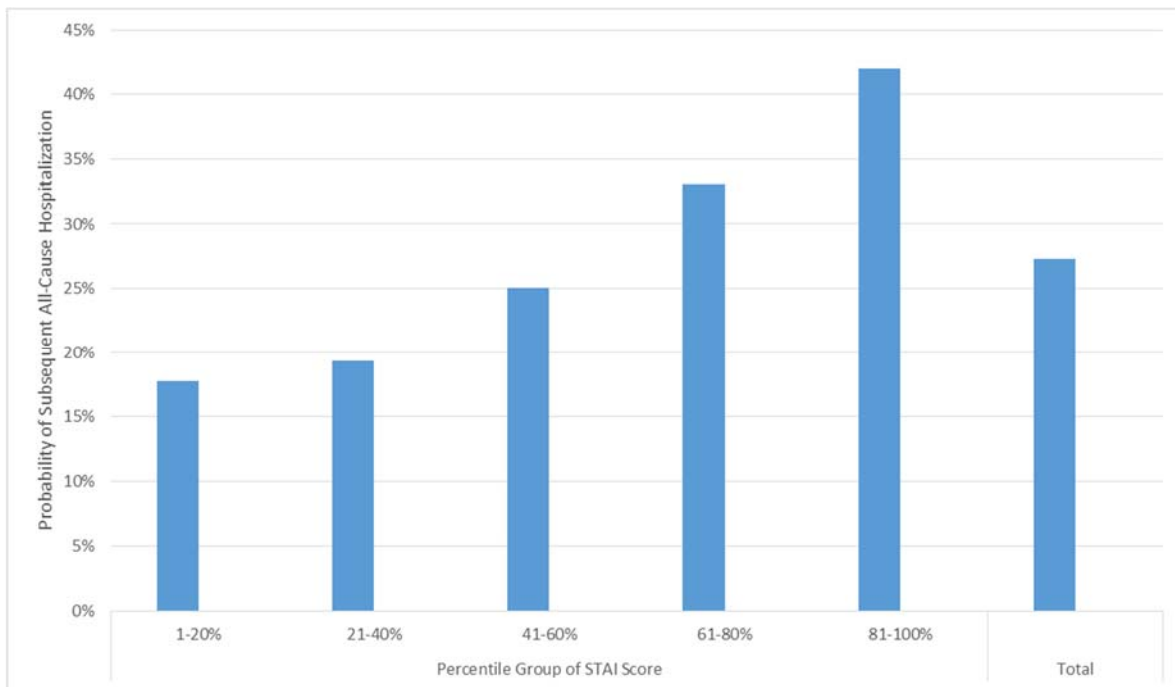


Figure 15. Relationship between anxiety scores, taken from all patients and all time points then ranked in quintiles, and percentage of individuals that had a hospitalization following a given anxiety score.

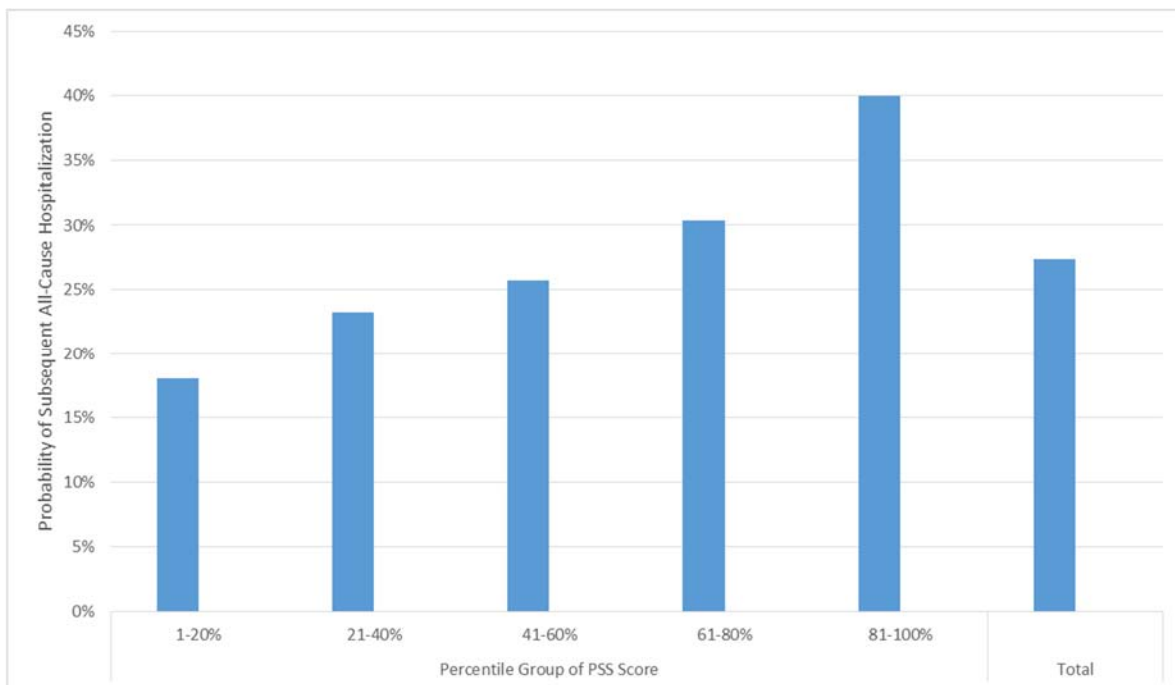


Figure 16. Relationship between stress scores, taken from all patients and all time points then ranked in quintiles, and percentage of individuals that had a hospitalization following a given stress score.

Chapter 4: Discussion

SUMMARY OF RESULTS

This study used marginal model analyses applied in a novel way to test the relationships between stress, anxiety and anger and heart failure worsening. HF worsening was quantified by hospitalizations and by KCCQ scores. Results of the study indicated that stress and anxiety—but not anger—were generally predictive of hospitalizations and KCCQ scores, but whether these effects were within-subject (acute) or between-subjects (chronic) varied depending on the specific analysis and dependent variable. The following Discussion section will first consider each of the study aims and then consider more general issues relevant to all the study aims.

Aim 1 Results

The first aim of the study was to assess whether acute or chronic anger, stress, and anxiety predict worsening of CHF symptoms, reduction of functional status, and increase in hospitalizations. The results of analyses of the KCCQ and hospitalizations addressing this aim are summarized in Table 13.

Based on findings from an earlier study (25), we expected and found a predictive relationship between anger and poorer health assessed via KCCQ, but not between anger and hospitalizations. Anxiety was similarly predictive of KCCQ scores, but was additionally predictive of hospitalizations. Perceived stress was also predictive of KCCQ scores and hospitalizations. For most of these analyses, hospitalizations findings were most robust for all-cause hospitalizations, as opposed to cardiac or HF hospitalizations. All of the above relationships were independent of medical covariates.

Table 13. Summary of Aim 1 Results

	Anger	Anxiety	Stress
KCCQ-Functional Between-Subjects	✓	✓	✓
KCCQ-Functional Within-Subjects	✓	✓	✓
KCCQ-Clinical Between-Subjects	✓	✓	✓
KCCQ-Clinical Within-Subjects	✓	✓	✓
All-Cause Hosp. Between-Subjects		✓	✓
All-Cause Hosp. Within-Subjects			✓
Cardiac Hosp. Between-Subjects		✓	✓
Cardiac Hosp. Within-Subjects			
CHF Hosp. Between-Subjects		✓	
CHF Hosp. Within-Subjects			

Note. ✓ = statistical tests that yielded a p value < 0.05 .

Anger

The above anger results are in-line with our expectations based on a prior study using similar analyses on the Project BETRHEART data, though over a shorter timespan (25). A prior study found the same results using the using a more standard measure of anger (the State-Trait Anger Expression Inventory-2), so these similar results may also lend further support to the validity of the WAI as an ad-hoc measure of anger in this study.

Conversely, these results differed from a prior BETRHEART analysis (63) which found a relationship between baseline hostility and hospitalizations. There are multiple factors that may explain this difference in results. First, the present analyses examined

anger will the prior study found results for hostility. Anger and hostility have important conceptual differences from each other (116). Keith et al. (63) also found that there was a low correlation between baseline state anger and baseline hostility in the BETRHEART sample. Second, the prior study only used a baseline measure of hostility, as compared to the multiple assessment design of the present analyses. Third, the prior study used structural equation modeling, which models different assumptions about the data compared to the present analyses. Fourth, the prior study used winsorized counts of hospitalizations from the entire study period, while the present analyses used binary counts of hospitalizations between assessment points. It is not clear how much each of these individual differences may have contributed to the differing outcomes, but their summed effect likely explains the difference in hospitalizations outcomes in the two sets of analyses.

The association between self-report health status and anger found in our results aligns with the prior literature. However, our hospitalization results do not match the findings of prior studies indicating that anger is associated with increased likelihood of adverse cardiac events (88). This may be due to the fact that the existing body of literature regarding anger and coronary heart disease events has focused on retrospective studies of anger outbursts immediately prior to cardiac events, which sometimes includes just the hours before the events. In addition, our study outcomes were CHF-related, whereas other studies focus on “hard” events such as myocardial infarction or sudden cardiac death. Our study asked subjects to rate potentially angering events for the past seven days, as captured by the WAI. The study also has the advantage of examining the effects of these angering events over a much longer timespan. That is, we examined

events in the 6 months following anger assessment repeatedly for up to 39 months of follow-up. Consequently, our results provide a better picture of the long-term effects of acute and chronic anger on patient health status and hospitalizations.

In many (but not all) prior studies in this area (e.g., 72; 88; 131) anger was reported retrospectively, that is after patients had already experienced a cardiac event. This post-event retrospective reporting of anger after cardiac events may have biased the results of those studies. Following a hospitalization, the accuracy of patient self-report about anger experiences may be biased by several factors. These biasing factors may include the commonly accepted link between anger and cardiovascular events by the general public, leading to them retrospectively reporting anger prior to cardiac events. A strength of the present study is that anger was assessed prospectively, before hospitalizations occurred. This may partly explain the difference in results between this study and others in the wider literature. Since the present study assessed hospitalizations over a longer time frame, the timespan between assessments in this study may also have caused it to miss any highly acute (i.e., hours) triggering effects of anger. Also, there is the issue of this study assessing hospitalizations and the prior anger studies just looking at cardiac events. Since hospitalizations are often recurrent, they represent a far more significant source of cost for the medical system. Also, an event may have to be more severe in order to warrant a hospitalization. Consequently, a difference in the nature and/or severity of the events in prior studies and the hospitalizations in these analyses may be another explanation for the difference in the present results compared to other literature.

For all the results regarding anger in this study, the possibility exists that the ad-hoc WAI anger scale may not be sufficient to detect relationships between anger and dependent variables should they be present.

Anxiety

To our knowledge, this is the first study that has examined relationships between anxiety and hospitalizations and health status using a multiple assessment design. Even with this study design difference, the anxiety results from this study are consistent with past research indicating that anxiety is associated with cardiovascular worsening.

Regarding mechanisms of the effects of anxiety on CHF outcomes, based on the conceptual model for the present analyses (see page 29), it is possible that anxiety contributes to greater sympathetic nervous system arousal (i.e., blood pressure and catecholamine responses, which are associated with poorer CHF outcomes, 102; 133).

Anxiety may also be associated with detrimental changes in health behaviors (e.g., poorer medication compliance, alcohol consumption, etc.) which may lead to negative outcomes for CHF patients. Another possibility is that anxiety heightens patients' illness perception leading to greater self-reported symptoms, somatization, and/or a higher likelihood of seeking greater medical assistance, including hospitalization (129). One limitation of the present study using the state measure on the STAI to measure anxiety is that it asks subjects to report anxiety at this moment, as opposed to capturing a wider window of time prior to the assessment point, as was done by the PSS and WAI. This difference may have influenced the outcome of within-subjects level results for anxiety.

Stress

Finally, the perceived stress results replicated and extended the findings from a prior study that used Project BETRHEART (25), and only included psychological assessments for up to 3 months. That prior study found similar within-subjects and between-subjects level associations between stress and KCCQ scores and a between-subject level association with hospitalizations/deaths, but not a within-subjects effect. The present study did find a within-subject level association between stress and all-cause hospitalizations. It is difficult to explain the within-subjects level effect in the present analyses, which was not found in the prior analyses using this sample. However, it may be that the longer 39 month follow-up in this study is what enabled capturing this effect. The fact that the longer follow-up would generally include the healthier subjects may have been a factor. Also, the prior study used hospitalizations and deaths, while the present study only used hospitalizations. Overall, a within-subject level response would not be unexpected given the large body of literature regarding acute stress trigger adverse physical effects.

Aim 2 Results

The second aim of this study was to determine the independent contributions of anger, anxiety, and stress to CHF worsening. The results of analyses addressing this aim are summarized in Table 14.

Table 14. Summary of Aim 2 Results

	Anger	Anxiety	Stress
KCCQ-Functional Between-Subjects			✓
KCCQ-Functional Within-Subjects	✓		✓
KCCQ-Clinical Between-Subjects			✓
KCCQ-Clinical Within-Subjects	✓	✓	✓
All-Cause Hosp. Between-Subjects		✓	
All-Cause Hosp. Within-Subjects			✓
Cardiac Hosp. Between-Subjects			
Cardiac Hosp. Within-Subjects			
CHF Hosp. Between-Subjects	✓	✓	
CHF Hosp. Within-Subjects			

Note. ✓ = statistical tests that yielded a p value < 0.05 .

Based on findings from an earlier study (23), we expected that between-subjects level (chronic) anger would be associated with health status independently of stress and anxiety, and that anger would not predict increased hospitalizations. This hypothesis was supported for hospitalizations. Only within-subject (acute) anger was independently associated with health status, and within-subjects level anger was unexpectedly associated with decreased CHF hospitalization rate. The only significant independent relationship between anxiety and health status occurred between acute (within-subjects level) anxiety and the KCCQ-Clinical Summary scale. Chronic (i.e., between-subjects level) anxiety was independently associated with both CHF and all-cause hospitalizations. Stress was independently associated with both forms of KCCQ health

status at the between-subjects and within-subjects levels. Stress was also independently associated with all-cause hospitalizations at the within-subjects level.

Anger

The anger results from the present analyses were unexpected based on prior analyses using Project BETRHEART data and a similar analytic design (25). The present analyses indicated that there was a significant association between WAI scores and KCCQ at the within-subjects level. In contrast, using shorter follow-up periods, the prior analyses indicated that state anger was not associated with KCCQ scores at the between-subjects or within-subjects level when controlling for PSS. The prior analyses also did not find any significant associations between state anger and hospitalizations/deaths. These divergent findings may be attributable to differences in timing of assessments and participant attrition, since the prior analyses only examined the first three months of assessment time points. Thus, relationships between the timing of measurements and the CHF outcomes assessed may be important to consider when looking at other prior studies and when designing new studies of CHF. A similar explanation may be relevant to the findings for anxiety and stress discussed below. The prior analyses also used the State Anger scale from the STAXI-2, as opposed to the current study's use of the WAI, and did not include anxiety as a covariate in its model. Nevertheless, in light of the broader anger and CHF literature, the significant within-subjects level association between WAI and both KCCQ health status measures, independent of stress and anxiety measures, in the present analyses supports the notion of increases in anger having a unique impact on a patient's health.

Regarding hospitalizations, the prior analyses also did not find any significant associations between state anger and hospitalizations/deaths, while the present analyses produced a significant negative association between WAI scores and CHF hospitalizations. The suppressor variable phenomenon may be able to explain the significant negative correlation between mean WAI and CHF hospitalizations. At a basic level, suppressor variables are IVs that have little correlation with the DV, but a high correlation with another IV in a multivariate model (81). Due to the high correlation with the other IV, a suppressor variable is able to account for some of the unexplained variance that does not contribute to predicting the DV. Consequently, a suppressor variable will yield a significant association with a sign that is the inverse of the variable for which it acts as a suppressor. In this regard, a suppressor explanation may be used to elucidate the WAI's relationship to CHF hospitalizations as follows. In Table 6 we can see that between-subjects level STAI was positively associated with CHF hospitalizations, and its predictive value slightly increased with the inclusion of anger and stress in the multivariate model. Additionally, in Tables 3 and 4 WAI and STAI had moderate to high correlations at both baseline and 3 months. Therefore, the strengthening of the STAI findings and the previously non-significant WAI association with CHF hospitalizations becoming a significant inverse relationship, along with the correlation between STAI and WAI, make it plausible that the WAI acted as a suppressor variable for the STAI in the between-subjects level CHF hospitalization results.

Anxiety

The results from the present study support wider research findings that anxiety is associated with CHF outcomes. In our analyses, its association with health status did

weaken when controlling for anger and stress, but anxiety still had a significant between-subjects level association with all-cause and CHF hospitalizations. These findings appear to indicate that anxiety makes a unique contribution to CHF hospitalizations. Possibly through specific changes in patient health behaviors, increases in physiological activation, and/or heightened illness perceptions (see discussion of Aim 1 anxiety results and our conceptual model, 102; 129; 133). Our results also align with other prior studies of anxiety and CHF which have found that anxiety is associated with declines in physical functioning (115) and reduced event-free survival time (22).

The above changes in results for anxiety and anger from Aim 1 to Aim 2 analyses, in which the only difference was including the other IVs in the model, appear to provide good support for Suls & Bunde's (126) stance that more cardiovascular disease studies should be conducted that control for multiple emotions in order to determine which emotions truly contribute the most to cardiovascular health decline and should be the primary target of interventions. Consistent with theories that propose autonomic specificity of emotions, it is possible that specific types of physiological activation associated with anger, anxiety, and stress have greater or lesser impacts on patient health.

Stress

As with the Aim 1 analyses, the results for perceived stress from the present analyses were similar to a prior study (25) for KCCQ, but different for hospitalizations. The prior analyses found a between-subjects level association between stress and hospitalization/death when controlling for state anger. The present study, on the other hand, found a within-subjects level association between stress and all-cause hospitalizations. As was mentioned before for the Aim 1 results, it is possible that part of

the difference in results is due to the difference in assessment timespans of the studies and participant attrition.

The significant within-subjects level effect for stress appears to align with prior research on stressful events trigger negative health outcomes (e.g., 62; 71; 75). Given the present results, it is possible that triggering effects are independent of an individual's tendencies towards anxious or angry reactions to the event and are uniquely dependent on how much the individual perceive herself or himself to be able to effectively respond to the event. This, in turn, might lead to increased physiological activation and/or health behavior changes that result in health decline (see the conceptual model on page 29). Additionally, it is possible that patients who perceive or appraise themselves as being unable to cope with psychosocial stressors then feel overwhelmed by health problems and seek medical support, such as at the hospital.

Aim 3 Results

The third aim of this study was to compare the predictive power for hospitalizations of self-reported health status (KCCQ) to the predictive power of anger, anxiety, and stress. Both summary measures from the KCCQ produced significant associations at the acute and chronic level with all three types of hospitalizations, with the exception of within-subjects level (acute) KCCQ-Clinical Summary and CHF hospitalizations. When controlling for anger, anxiety, and stress, both KCCQ measures were significantly associated with all three types of hospitalization, without exception. Even though we found that KCCQ scores are correlated with anxiety, anger, and stress, they are not completely determined by levels of anxiety or stress. This makes sense given that there are questions on the KCCQ regarding functional status, such as your capability

of walking one block or dress yourself, which one would not expect to be associated with emotional state and that would be predictive of a greater likelihood of hospitalizations. A possible mechanism for the relationship between KCCQ scores and hospitalizations is that patient who perceive themselves as being in poor health may then be more likely to seek a higher level of medical care. The present study analyses do indicate that KCCQ health perceptions are associated with hospitalization rates independent of emotions and stress. However, they raise the question of whether the inverse is true, i.e. whether emotions and stress have an impact on hospitalizations that is independent of health perceptions. This is a potential question that could be addressed in future research.

The results of the present study support the significant clinical usefulness of the KCCQ for monitoring the health status of CHF patients. The KCCQ-Clinical Summary score can range from 0 to 100 (higher scores are better). The present analyses found that a single point decrease in score, at either the chronic or acute level, was associated with up to a 3% increased risk of hospitalization, even when controlling for anger, anxiety, and stress. Consequently, both monitoring acute changes in a patient's scores and chronic response patterns may potentially have clinical use for identifying patients with an increased risk of hospitalization who may require further preventive intervention.

Aim 4 Results

The fourth aim of this study was to compare the chronic (between-subjects) vs. acute (within-subjects) effects of anger, anxiety, and stress on hospitalizations, symptoms, and health status. Chronic measures of anxiety and stress were significantly associated with more dependent variables than acute anxiety and stress. There was also a significant difference between the within-subjects and between-subjects level effects for

the associations between each of the IVs and each of the KCCQ DVs and for the STAI's associations with all-cause and CHF hospitalizations. Additionally, for anger, anxiety, and stress, changes in chronic scores had a greater association with dependent variable scores than an equivalent change in acute scores and the chronic scores had greater SDs than the acute scores. For example, a one SD increase in chronic stress, when controlling for just medical covariates, would be associated with an approximately 43% increased risk of all-cause hospitalization, while a one SD increase in acute stress would be associated with an approximately 20% increased risk of all-cause hospitalization. Regarding a possible mechanism for this finding, it may be that chronically increased physiological activation and/or the changes in health behaviors that occur due to sustained anger, anxiety, and/or stress have greater consequences for a patient's health than time-limited responses to spikes in anger, anxiety, and stress.

The results of the present study can be interpreted as supporting the value of studying both the chronic and acute effects of emotions on CHF. Many of the past studies in this area have only looked at acute trigger or taken baseline measures and seen if they were associated with later outcomes. Given the results of the present analyses, there appears to be value in using multiple assessment study designs that allow for separating within-subjects and between-subjects level effects. Additionally, interventions that target a patient's overall tendency towards experiencing anger, anxiety, or stress may have more of an impact than interventions that address only the most acute and severe emotional responses. With a patient who has anger issues, for example, it might be that teaching relaxation techniques, such as diaphragmatic breathing, will be more beneficial than just focusing on strategies for stopping a verbal outburst of anger.

Results of Additional Analyses

One limitation of this study, with regards to simultaneously assessing multiple emotions that may have consequences for CHF, is that it did not include measures of depression at all of the assessment points. However, we were able to use a measure of depression that was given at baseline as a covariate in supplemental analyses and determine that including it in the models did not impact the results of the present analyses. That result possibly suggests that, in the present analyses at least, depression is not a latent factor that could account for the independent associations we found between the DVs and anger, anxiety, and stress. A potential future direction would be designing a similar multiple assessment point study with measures of anger, anxiety, stress, and depression at all time points to have greater evidence to support or refute this possibility.

We also conducted a second set supplemental analyses to determine if there was a prospective difference in the patients who were hospitalized at any point in the study and those that were never hospitalized, i.e. from the very start, were the patients that were destined to be hospitalized at a future point in the study in some way different from the never hospitalized patients. These analyses found no difference in STAI, PSS, or KCCQ scores between the hospitalized patients before their first hospitalizations and the patients that were never hospitalized. This lack of difference between groups runs counter to the finding by Endrighi et al. (34) examining the first few months of BETRHEART data. A possible explanation of this difference in findings is that the prior analyses used a much shorter time span, so there may have been significant prospective differences in the patients that would succumb to an event in such a short time. Whereas, the longer time span in the present analyses may have washed out those effects if patients that had hospitalizations much later were not particularly different from never hospitalized

patients. A possible future direction could be conducting more fine-tuned analyses to determine if these patients with first hospitalizations early in the study were in some important way different from patients that had first hospitalizations later or were never hospitalized.

Post-Hospitalization Effects

Our third set of additional analyses were intended to test for post-hospital effects, such as the post-hospital syndrome postulated by Krumholz (69). Measuring psychological state at either 3 or 6 month intervals, we did not find any changes in state anxiety or perceived stress at the next assessment following a hospitalization. However, we did find that patients reported an improved health status at the assessment following a hospitalization.

Given the time period between assessments, the null result for a post-hospital effect on anxiety and stress does not necessarily provide any evidence against Krumholz's proposed post-hospital syndrome. He clearly specified that the critical period of increased stress is expected to occur in the 30 days following a hospitalization. Because of the 6 month time span between most assessments in this study, many times a hospitalization may have occurred much more than 30 days before the assessment of a patients stress and anxiety. This result does, however, speak to the fact that if there is a post-hospital syndrome its impact is restricted to an acute period following the hospitalization and does not last for multiple months after it. It should be noted that the prior BETRHEART analyses, which used a shorter time span, did find a significant post-hospital effect for PSS (34).

Regarding the improvement in KCCQ scores following hospitalization, this result appears to support the positive effect of medical interventions on a patient's health status. Unfortunately, it is not clear which parts of the hospitalization experience may have contributed to these improvements, such as direct reduction of symptoms via medical intervention, renewed motivation in the patients to make health behavior changes, or receiving additional education, during or after the hospitalization, about how to care for oneself.

General Discussion of Results

Limitations and Strengths

Certain limitations and strengths of this study should be factored into interpretations of its results. The 6 month timeframe between phone assessments may have been too long a period to fully capture participants' experiences of anger, anxiety, and stress during the study. Additionally, the measures of anger, anxiety, and stress each captured a different span of time; the past week, right now, and the past two weeks, respectively. It is possible that these differences in time assessed by the measures could have contributed bias to the results of the analyses, particularly those that included all of the IVs as covariates. It should also be noted that KCCQ scores were obtained at the same time as anger, anxiety, and stress measures, which prevents us from showing a temporal sequence of IV scores predicting KCCQ scores at a later time, as we are able to do with hospitalizations.

This study also obtained a sample of participants that were somewhat different from the overall population of patients with CHF. Our participants were primarily African-American and of lower SES. They were also of a somewhat younger average age

and had a higher prevalence of non-ischemic heart failure than most other CHF study samples. It is notable that there is evidence to suggest that the prognosis of patients with non-ischemic CHF is often better than for patients with ischemic CHF (39).

Consequently, it is possible that a similar study conducted using a sample with a greater proportion of patients with ischemic CHF may produce even stronger associations with hospitalization outcomes. A strength of using this populations is that it adds to the breadth of our knowledge about CHF in individuals of diverse backgrounds, who may not always be fully represented in studies. Conversely, the results from our sample may not generalize to all populations. Additionally, while many of the psychosocial measures used in this study have not been formally validated in African-American populations, they have previously been used in studies that were specific to African-American samples (100; 114; 139). Finally, due to the significant length of our study and the severity of the medical condition being examined, we lost a high percentage (~66%) of patients to follow-up over the course of the study, including 33 (22%) confirmed participant deaths. This in part underscores the importance of understanding CHF in order to improve treatments, but it also may mean that only the healthiest patients were left by the end of the study. If individuals were lost from the study for non-random reasons, such as differences in health, the assumptions of the statistical tests we used may have been violated, which could have biased the outcomes of the results. Consequently, the results of the present analyses may tell us more about outcomes for healthier individuals than they do for the most severe cases of CHF. A strength of this study length is that it allowed us to better examine the long-term health consequences of chronic anger, stress, and anxiety and variations in patients' experience of anger, stress, and anxiety.

Research Implications

Overall, the results of these analyses support the arguments made by Suls & Bunde's (126). Our validation of the WAI, in which it also correlated with anxiety and stress measures and the well validated measures of anger, anxiety, and stress all strongly correlated with each other, supports Suls & Bunde's claim that many of the measures of emotions used in health research may overlap with each other. The results of the present analyses also supports Suls & Bunde's statement that more cardiovascular health studies should examine multiple emotions simultaneously to determine if they have independent or shared effects. In order to address whether there are also advantages to looking at single emotions versus negative affect as a whole, we conducted supplemental analyses in which we standardized and combined the WAI, STAI, and PSS to make a single negative affect proxy measure. Using the same analytic approach from Aim 1, we found that the negative affect proxy measure was associated with between-subjects level all-cause hospitalizations ($B = 0.428$, $SE = 0.16$, $p = 0.008$), along with between-subjects (KCCQ-Functional: $B = -11.451$, $SE = 1.41$, $p < 0.001$; KCCQ-Clinical: $B = -12.559$, $SE = 1.33$, $p < 0.001$) and within-subjects KCCQ (KCCQ-Functional: $B = -5.962$, $SE = 0.87$, $p < 0.001$; KCCQ-Clinical: $B = -7.314$, $SE = 0.81$, $p < 0.001$). It is important to note that this combined measure failed to capture the significant within-subjects association with all-cause hospitalizations and between-subjects level associations with cardiac and CHF-hospitalizations that the PSS and STAI yielded when tested by themselves. Therefore, it appears that looking at total negative affect may potentially not be as useful as separating out the individual negative emotions for understanding hospitalizations in CHF patients.

Regarding the conceptual model for this study, the present analyses appear to support the overall framework of unique and shared contributions of emotions and stress

being associated with health status and hospitalizations. The present analyses were not able to specifically address the intermediary health behaviors and physiological activation components of the conceptual model. Therefore, future studies could be designed to test the relationships of the full conceptual model.

The differences found in our results between within-subjects and between-subjects level effects also indicate the potential value of more CHF studies in the future using multiple assessment point designs and analyses, such as marginal models and mixed models, which are able to take advantage of the additional data points to separate these effect levels. As further evidence for the value of multiple assessments, we re-conducted the analyses from Aim 1 using only baseline measures of WAI, STAI, and PSS. We found that only baseline STAI was associated with all-cause hospitalizations ($B = 0.027$, $SE = 0.01$, $p = 0.02$). Baseline WAI (KCCQ-Functional: $B = -0.384$, $SE = 0.14$, $p = 0.008$; KCCQ-Clinical: $B = -0.424$, $SE = 0.14$, $p = 0.003$), STAI (KCCQ-Functional: $B = -0.484$, $SE = 0.14$, $p = 0.001$; KCCQ-Clinical: $B = -0.600$, $SE = 0.14$, $p < 0.001$), and PSS (KCCQ-Functional: $B = -0.833$, $SE = 0.17$, $p < 0.001$; KCCQ-Clinical: $B = -1.018$, $SE = 0.16$, $p < 0.001$) were all associated with the KCCQ. The analyses using only baseline data failed to capture the significant associations for PSS with all-cause and cardiac hospitalizations and STAI with cardiac and CHF hospitalizations that were produced when using multiple assessment data points. Consequently, using a greater number of assessment points may also improve our understanding of how negative emotions contribute to hospitalizations in CHF patients.

The present analyses used population averaged coefficients to better understand the population-wide effects of emotions on health status and hospitalizations, since these

have important healthcare system implications. Future studies could alternatively use subject specific coefficient models, such as linear mixed models, to better understand the impact of emotions at a more individual level.

Military Relevance

The present study was conducted with patients at UMMC, but also included a substantial number of individuals from the Baltimore VA. Additionally, the present study may have a number of implications for TRICARE, the healthcare program of the U.S. Department of Defense Military Health System, which includes coverage of hospitalizations for CHF in its benefits. TRICARE has 2.24 million beneficiaries who are 65 years old or older (127). Based on CHF estimate statistics for the general U.S. population of individuals who are 65 years old or older (52), TRICARE may cover at least 22,400 patients with CHF, and this does not consider people under 65 years of age. Just the 147 patients in our study experienced a total of 534 hospitalizations over the 39 month study period. Based on Wexler et al's estimate of each CHF hospitalization costing roughly \$7,174 on average, the hospitalizations observed in this study may have had a total cost of approximately \$3.8 million. Projecting that appraisal, and correcting for time, onto care for the 65 year old and older TRICARE beneficiaries yields an estimated cost of \$193 million per year. Obviously these are relatively loose approximations with a number of assumptions, but they provide some sense of the significant fiscal ramifications of CHF hospitalizations for TRICARE. Therefore, the present analyses, and others like it, may be vitally important for guiding the empirical development of targeted psychosocial interventions intended to reduce the rate of hospitalizations in CHF patients.

Clinical Implications

There are a number of potential clinical implications for treating CHF patients raised by the results of these analyses. To summarize some of the points already mentioned in the discussion; anger, anxiety, stress each appear to have independent associations with reduced health status; anxiety and stress are independently associated with increased hospitalizations; chronic anger, anxiety, and stress, as opposed to acute, appear to generally have greater associations with outcomes; and both forms of KCCQ summary scores were associated with hospitalizations. If there are causal relationships between these IVs and DVs, then it would suggest that clinical interventions specifically targeting patients' chronic stress and anxiety would reduce hospitalizations and their associated cost for medical systems. A variety of strategies have been used in an attempt to reduce rehospitalizations in CHF patients, such as greater patient education during hospitalization, post-discharge phone contact, exercise programs, etc. (135). The present analyses' results suggest that mental health interventions, whether through specialty mental health care, integrated behavioral healthcare, pharmacotherapy, etc., may be a highly beneficial component of an integrated treatment approach for patients with CHF (43; 132). An additional advantage of providing mental health interventions to these patients is that such interventions may also improve patient quality of life, which has been documented as being highly important to CHF patients (77). Helping patients reduce their anxiety and stress may then lead to them feeling more able to effectively take part in managing their own care and engage in health enhancing behaviors, such as exercise.

SUMMARY AND CONCLUSION

CHF is a chronic disease that produces high rates of recurrent hospitalizations, reduces quality of life, and leads to high mortality rates. It produces a heavy burden both on the individual patients and on healthcare systems. Significant research has been conducted on the biological and psychological risk factors for cardiovascular disease. However, there have been few prospective studies in patients with CHF examining the relationships of anger, state anxiety, and perceived stress to long-term outcomes. We found that anger was independently associated with health status, but not hospitalizations; state anxiety was associated with hospitalizations, in addition to health status; and perceived stress was also associated with hospitalizations and health status. When PSS and STAI were adjusted for in analyses of WAI, anger retained just a within-subjects level association with health status. When WAI and PSS were adjusted for in analyses of STAI, it retained a within-subjects level association with one KCCQ measure and between-subjects level associations with two types of hospitalization. When WAI and STAI were adjusted for in analyses of PSS, it remained associated with both KCCQ measures at the within-subjects and between-subjects levels and with all-cause hospitalizations at the within-subjects level. It appears that all of these psychosocial roads lead to CHF worsening, but each may get there at a different rate.

REFERENCES

1. American Psychological Association. 2015. Stress in America: Paying with our health, American Psychological Association, Washington, DC
2. Anderson KG, Deschênes SS, Dugas MJ. 2016. Experimental manipulation of avoidable feelings of uncertainty: Effects on anger and anxiety. *Journal of Anxiety Disorders* 41:50-8
3. Arnold SV, Smolderen KG, Buchanan DM, Li Y, Spertus JA. 2012. Perceived stress in myocardial infarction: Long-term mortality and health status outcomes. *Journal of the American College of Cardiology* 60:1756-63
4. Barlow DH. 2000. Unraveling the mysteries of anxiety and its disorders from the perspective of emotion theory. *The American Psychologist* 55:1247-63
5. Barnes LLB, Harp D, Jung WS. 2002. Reliability generalization of scores on the Spielberger State-Trait Anxiety Inventory. *Educational and Psychological Measurement* 62:603-18
6. Bennett SJ, Perkins SM, Lane KA, Deer M, Brater DC, Murray MD. 2001. Social support and health-related quality of life in chronic heart failure patients. *Quality of Life Research* 10:671-82
7. Blascovich J, Spencer SJ, Quinn D, Steele CM. 2001. African Americans and high blood pressure: The role of stereotype threat. *The Journal of the Association for Psychological Science* 12:225-9
8. Bosma H, Peter R, Siegrist J, Marmot M. 1998. Two alternative job stress models and the risk of coronary heart disease. *American Journal of Public Health* 88:68-74
9. Brantley PJ, Bodenlos JS, Cowles M, Whitehead D, Ancona M, Jones GN. 2007. Development and validation of the Weekly Stress Inventory-Short Form. *Journal of Psychopathology and Behavioral Assessment* 29:54-9
10. Brantley PJ, Jones GN, Boudreaux E, Catz S. 1997. Weekly stress inventory. In *Evaluating Stress: A book of Resources*, ed. CP Zalaquett, RJ Wood:405-20. Lanham, MD: Scarecrow Press. Number of 405-20 pp.
11. Brotman DJ, Golden SH, Wittstein IS. 2007. The cardiovascular toll of stress. *The Lancet* 370:1089-100
12. Burg MM, Vashist A, Soufer R. 2005. Mental stress ischemia: Present status and future goals. *Journal of Nuclear Cardiology* 12:523-9
13. Cheng TO. 2006. Beta blockers versus diuretics for congestive heart failure in African-American patients. *The American Journal of Cardiology* 98:568
14. Chung ML, Lennie TA, Dekker RL, Wu J-R, Moser DK. 2011. Depressive symptoms and poor social support have a synergistic effect on event-free survival in patients with heart failure. *Heart & Lung - The Journal of Acute and Critical Care* 40:492-501
15. Clark LT. 1991. Improving compliance and increasing control of hypertension: Needs of special hypertensive populations. *American Heart Journal* 121:664-9
16. Cohen S, Janicki-Deverts D. 2012. Who's stressed? Distributions of psychological stress in the United States in probability samples from 1983, 2006, and 2009. *Journal of Applied Social Psychology* 42:1320-34

17. Cohen S, Kamarck T, Mermelstein R. 1983. A global measure of perceived stress. *Journal of Health and Social Behavior*:385-96
18. Cohen S, Kessler RC, Gordon LU. 1995. Strategies for measuring stress in studies of psychiatric and physical disorders. In *Measuring Stress: A Guide for Health and Social Scientists*, ed. S Cohen, RC Kessler, LU Gordon. New York, NY: Oxford University Press.
19. Cowie MR, Wood DA, Coats AJ, Thompson SG, Suresh V, et al. 2000. Survival of patients with a new diagnosis of heart failure: A population based study. *Heart* 83:505-10
20. Curran SL, Curran SL, Andrykowski MA, Studts JL. 1995. Short Form of the Profile of Mood States (POMS-SF): Psychometric information. *Psychological Assessment* 7:80-3
21. Curtis LH, Greiner MA, Hammill BG, Kramer JM, Whellan DJ, et al. 2008. Early and long-term outcomes of heart failure in elderly persons, 2001-2005. *Archives of Internal Medicine* 168:2481-8
22. De Jong MJ, Chung ML, Wu J-R, Riegel B, Rayens MK, Moser DK. 2011. Linkages between anxiety and outcomes in heart failure. *Heart & Lung: The Journal of Acute and Critical Care* 40:393-404
23. Detry MA, Ma Y. 2016. Analyzing repeated measurements using mixed models. *JAMA* 315:407-8
24. Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, et al. 2013. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. *The Journal of the American Medical Association* 309:355-63
25. Dimond AJ. 2016. *State anger and short-term heart failure outcomes: Comparison with perceived stress*. Uniformed Services University of the Health Sciences, Bethesda, MD
26. Djousse L, Driver JA, Gaziano JM. 2009. Relation between modifiable lifestyle factors and lifetime risk of heart failure. *The Journal of the American Medical Association* 302:394-400
27. Dracup K, Westlake C, Erickson VS, Moser DK, Caldwell ML, Hamilton MA. 2003. Perceived control reduces emotional stress in patients with heart failure. *Journal of Heart and Lung Transplantation* 22:90-3
28. Dries DL, Exner DV, Gersh BJ, Cooper HA, Carson PE, Domanski MJ. 1999. Racial differences in the outcome of left ventricular dysfunction. *New England Journal of Medicine* 340:609-16
29. Dunlay SM, Redfield MM, Weston SA, Therneau TM, Long KH, et al. 2009. Hospitalizations after heart failure diagnosis: A community perspective. *Journal of the American College of Cardiology* 54:1695-702
30. Easton K, Coventry P, Lovell K, Carter L-A. 2016. Prevalence and measurement of anxiety in samples of patients with heart failure. *The Journal of Cardiovascular Nursing* 31:367-79
31. Edmondson D, Richardson S, Falzon L, Davidson KW, Mills MA, Neria Y. 2012. Posttraumatic stress disorder prevalence and risk of recurrence in acute coronary syndrome patients: A meta-analytic review. *PLoS ONE* 7:e38915

32. Eisenberg SA, Shen B-J, Schwarz ER, Mallon S. 2012. Avoidant coping moderates the association between anxiety and patient-rated physical functioning in heart failure patients. *Journal of Behavioral Medicine* 35:253+
33. Ekman P. 1992. An argument for basic emotions. *Cognition and Emotion* 6:169-200
34. Endrighi R, Waters AJ, Gottlieb SS, Harris KM, Wawrzyniak AJ, et al. 2016. Psychological stress and short-term hospitalisations or death in patients with heart failure. *Heart*
35. Everson-Rose SA, Lewis TT. 2005. Psychosocial factors and cardiovascular diseases. *Annu. Rev. Public Health* 26:469-500
36. Eysenck H, Fuler D. 1983. The components of type A behaviour and its genetic determinants. *Personality and Individual Differences* 4:499-505
37. Fang CY, Myers HF. 2001. The effects of racial stressors and hostility on cardiovascular reactivity in African American and Caucasian men. *Health Psychology* 20:64-70
38. Finney ML, Stoney CM, Engebretson TO. 2002. Hostility and anger expression in African American and European American men is associated with cardiovascular and lipid reactivity. *Psychophysiology* 39:340-9
39. Follath F. 2001. Ischemic versus non-ischemic heart failure: Should the etiology be determined? *Heart Failure Monitor* 1:122
40. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, et al. 2008. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes. *Archives of Internal Medicine* 168:847-54
41. Gabbay FH, Krantz DS, Kop WJ, Hedges SM, Klein J, et al. 1996. Triggers of myocardial ischemia during daily life in patients with coronary artery disease: Physical and mental activities, anger and smoking. *Journal of the American College of Cardiology* 27:585-92
42. Garfield LD, Garfield LD, Scherrer JF, Hauptman PJ, Freedland KE. 2014. Association of anxiety disorders and depression with incident heart failure. *Psychosomatic Medicine* 76:128-36
43. Gary RA, Dunbar SB, Higgins MK, Musselman DL, Smith AL. 2010. Combined exercise and cognitive behavioral therapy improves outcomes in patients with heart failure. *Journal of Psychosomatic Research* 69:119-31
44. Giamouzis G, Kalogeropoulos A, Georgiopoulou V, Laskar S, Smith AL, et al. 2011. Hospitalization epidemic in patients with heart failure: risk factors, risk prediction, knowledge gaps, and future directions. *Journal of Cardiac Failure* 17:54-75
45. Gillum RF. 1996. The epidemiology of cardiovascular disease in black Americans. *New England Journal of Medicine* 335:1597-9
46. Girardi D, Falco A, De Carlo A, Benevene P, Comar M, et al. 2015. The mediating role of interpersonal conflict at work in the relationship between negative affectivity and biomarkers of stress. *Journal of Behavioral Medicine*:1-10
47. Glaser R, Kiecolt-Glaser JK, Marucha PT, MacCallum RC, Laskowski BF, Malarkey WB. 1999. Stress-related changes in proinflammatory cytokine production in wounds. *Archives of General Psychiatry* 56:450-6

48. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, et al. 2013. Executive summary: Heart disease and stroke statistics--2013 update: A report from the American Heart Association. *Circulation* 127:143-52
49. Green CP, Porter CB, Bresnahan DR, Spertus JA. 2000. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: A new health status measure for heart failure. *Journal of the American College of Cardiology* 35:1245-55
50. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, et al. 1985. The 6-minute walk: A new measure of exercise capacity in patients with chronic heart failure. *Canadian Medical Association Journal* 132:919-23
51. Heagerty PJ, Zeger SL. 2000. Marginalized multilevel models and likelihood inference. *Statistical Science* 15:1-19
52. Healthcare E. 2018. *Heart Failure Statistics*.
<https://www.emoryhealthcare.org/heart-vascular/wellness/heart-failure-statistics.html>
53. Hedeker D, Mermelstein RJ, Berbaum ML, Campbell RT. 2009. Modeling mood variation associated with smoking: An application of a heterogeneous mixed - effects model for analysis of ecological momentary assessment (EMA) data. *Addiction* 104:297-307
54. Heidenreich PA, Spertus JA, Jones PG, Weintraub WS, Rumsfeld JS, et al. 2006. Health Status Identifies Heart Failure Outpatients at Risk for Hospitalization or Death. *Journal of the American College of Cardiology* 47:752-6
55. Himle JA, Baser RE, Taylor RJ, Campbell RD, Jackson JS. 2009. Anxiety disorders among African Americans, blacks of Caribbean descent, and non-Hispanic whites in the United States. *Journal of Anxiety Disorders* 23:578-90
56. Ho KKL, Pinsky JL, Kannel WB, Levy D. 1993. The epidemiology of heart failure: The Framingham Study. *Journal of the American College of Cardiology* 22:A6-A13
57. Hubbard AE, Ahern J, Fleischer NL, Van der Laan M, Lippman SA, et al. 2010. To GEE or not to GEE: Comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. *Epidemiology* 21:467-74
58. James SA. 1994. John Henryism and the health of African-Americans. *Culture, Medicine and Psychiatry* 18:163-82
59. Jenner RC, Strodl ES, Schweitzer RD. 2009. Anger and depression predict hospital use among chronic heart failure patients. *Australian Health Review* 33:541-8
60. Jiang W, Alexander J, Christopher E, Kuchibhatla M, Gauden LH, et al. 2001. Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. *Archives of Internal Medicine* 161:1849-56
61. Jianwei F, J. LD, M. JM, Vandana K, R. RCV. 2006. Cardiac sequelae in Brooklyn after the September 11 terrorist attacks. *Clinical Cardiology* 29:13-7
62. Kark JD, Goldman S, Epstein L. 1995. Iraqi missile attacks on israel: The association of mortality with a life-threatening stressor. *JAMA* 273:1208-10
63. Keith F, Krantz DS, Chen R, Harris KM, Ware CM, et al. 2017. Anger, hostility, and hospitalizations in patients with heart failure. *Health Psychology*

64. Killip S, Mahfoud Z, Pearce K. 2004. What is an intraclass correlation coefficient? Crucial concepts for primary care researchers. *Annals of Family Medicine* 2:204-8
65. Kongkaew C, Sakunrag I, Jianmongkol P. 2012. Non-compliance with digoxin in patients with heart failure and/or atrial fibrillation: A systematic review and meta-analysis of observational studies. *Archives of Cardiovascular Diseases* 105:507-16
66. Kono T, Sabbah HN. 2014. Takotsubo cardiomyopathy. *Heart Failure Reviews* 19:585-93
67. Krantz DS, Burg MM. 2014. Current perspective on mental stress-induced myocardial ischemia. *Psychosomatic Medicine* 76:168-70
68. Krantz DS, Whittaker KS, Sheps DS. 2012. Psychosocial risk factors for coronary heart disease: Pathophysiological mechanisms. In *Heart and Mind: The Practice of Cardiac Psychology*, ed. R Allan, JA Fisher:91-114. Washington D.C.: American Psychological Association. Number of 91-114 pp.
69. Krumholz HM. 2013. Post-hospital syndrome: An acquired, transient condition of generalized risk. *The New England Journal of Medicine* 368
70. Kubzansky LD, Winning A. 2016. Emotions and health. In *Handbook of Emotions*, ed. LF Barret, M Lewis, JM Haviland-Jones:613-28. New York: The Guilford Press. Number of 613-28 pp.
71. Lampen WU, Leistner D, Greven S, Pohl T, Sper S, et al. 2008. Cardiovascular events during World Cup soccer. *New England Journal of Medicine* 358:475-83
72. Lampert R, Joska T, Burg MM, Batsford WP, McPherson CA, Jain D. 2002. Emotional and physical precipitants of ventricular arrhythmia. *Circulation* 106:1800-5
73. Lazarus RS. 1993. From psychological stress to the emotions: A history of changing outlooks. *Annual Review of Psychology* 44:1-21
74. Lee E-H. 2012. Review of the psychometric evidence of the Perceived Stress Scale. *Asian Nursing Research* 6:121-7
75. Leor J, Poole WK, Kloner RA. 1996. Sudden Cardiac Death Triggered by an Earthquake. *New England Journal of Medicine* 334:413-9
76. Levenson RW. 2003. Autonomic specificity and emotion. In *Handbook of Affective Sciences*:212-24. New York, NY, US: Oxford University Press. Number of 212-24 pp.
77. Lewis EF, Johnson PA, Johnson W, Collins C, Griffin L, Stevenson LW. 2001. Preferences for quality of life or survival expressed by patients with heart failure. *The Journal of Heart and Lung Transplantation* 20:1016
78. Lievaart M, Franken IHA, Hovens JE. 2016. Anger assessment in clinical and nonclinical populations: Further validation of the State-Trait Anger Expression Inventory - 2. *Journal of Clinical Psychology* 72:263-78
79. Luttik ML, Jaarsma T, Moser D, Sanderman R, van Veldhuisen DJ. 2005. The importance and impact of social support on outcomes in patients with heart failure: An overview of the literature. *The Journal of Cardiovascular Nursing* 20:162-9
80. Luyster FS, Hughes JW, Gunstad J. 2009. Depression and anxiety symptoms are associated with reduced dietary adherence in heart failure patients treated with an

- implantable cardioverter defibrillator. *The Journal of Cardiovascular Nursing* 24:10-7
81. Maassen GH, Bakker AB. 2001. Suppressor variables in path models: Definitions and interpretations. *Sociological Methods & Research* 30:241-70
82. Mayo Clinic. 2015. *Heart Failure: Risk Factors*.
<http://www.mayoclinic.org/diseases-conditions/heart-failure/basics/risk-factors/con-20029801>
83. Mayo Clinic. 2015. *Heart Failure: Treatments and Drugs*.
<http://www.mayoclinic.org/diseases-conditions/heart-failure/basics/risk-factors/con-20029801>
84. McDowell I. 2006. *Measuring Health: A Guide to Rating Scales and Questionnaires*. Oxford, UK: Oxford University Press
85. McNair DM, Lorr M, Droppleman LF. 1971. *Manual for the Profile of Mood States*. San Diego, CA: Educational and Industrial Testing Service
86. Middlekauff HR, Nguyen AH, Negrao CE, Nitzsche EU, Hoh CK, et al. 1997. Impact of acute mental stress on sympathetic nerve activity and regional blood flow advanced heart failure: Implications for 'triggering' adverse cardiac events. *Circulation* 96:1835-42
87. Mitchell AM, Crane PA, Kim Y. 2008. Perceived stress in survivors of suicide: Psychometric properties of the Perceived Stress Scale. *Research in Nursing & Health* 31:576-85
88. Mittleman MA, Maclure M, Sherwood JB, Mulry RP, Tofler GH, et al. 1995. Triggering of acute myocardial infarction onset by episodes of anger. *Circulation* 92:1720
89. Mondoa C. 2005. Chronic heart failure. *Practice Nurse* 30:50
90. Moors A. 2010. Theories of emotion causation: A review. In *Cognition and Emotion: Reviews of Current Research and Theories*:1-37. New York, NY, US: Psychology Press. Number of 1-37 pp.
91. Mosley TH, Payne TJ, Plaud JJ, Johnson CA, Wittrock DA, et al. 1996. Psychometric properties of the weekly stress inventory (WSI): Extension to a patient sample with coronary heart disease. *Journal of Behavioral Medicine* 19:273-87
92. Mostofsky E, Penner EA, Mittleman MA. 2014. Outbursts of anger as a trigger of acute cardiovascular events: a systematic review and meta-analysis. *European Heart Journal* 35:1404-10
93. Moudgil R, Haddad H. 2013. Depression in heart failure. *Current Opinion in Cardiology* 28:249-58
94. Müller-Tasch T, Peters-Klimm F, Schellberg D, Holzapfel N, Barth A, et al. 2007. Depression is a major determinant of quality of life in patients with chronic systolic heart failure in general practice. *Journal of Cardiac Failure* 13:818-24
95. Muth C, Bales KL, Hinde K, Maninger N, Mendoza SP, Ferrer E. 2016. Alternative models for small samples in psychological research. *Educational and Psychological Measurement* 76:64-87
96. Newman JD, Davidson KW, Shaffer JA, Schwartz JE, Chaplin W, et al. 2011. Observed Hostility and the Risk of Incident Ischemic Heart Disease: A

- Prospective Population Study From the 1995 Canadian Nova Scotia Health Survey. *Journal of the American College of Cardiology* 58:1222-8
97. Ogilvie RP, Ogilvie RP, Everson-Rose SA, Longstreth WT, Rodriguez CJ. 2016. Psychosocial factors and risk of incident heart failure: The Multi-Ethnic Study of Atherosclerosis. *Circulation* 9:e002243
 98. Ohira T, Tetsuya O, Ana VDR, Joseph FP, Shunichi H. 2012. Associations of anger, anxiety, and depressive symptoms with carotid arterial wall thickness: The Multi-Ethnic Study of Atherosclerosis. *Psychosomatic Medicine* 74:517
 99. Perlman LV, Ferguson S, Bergum KAY, Isenberg EL, Hammarsten JF. 1971. Precipitation of congestive heart failure: Social and emotional factors. *Annals of Internal Medicine* 75:1-7
 100. Peters RM. 2004. Racism and hypertension among African Americans. *Western Journal of Nursing Research* 26:612-31
 101. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJV, et al. 2006. Predictors of mortality and morbidity in patients with chronic heart failure. *European Heart Journal* 27:65-75
 102. Prichard BN, Owens CW, Smith CC, Walden RJ. 1991. Heart and catecholamines. *Acta cardiologica* 46:309-22
 103. Ramachandruni S, Fillingim RB, McGorray SP, Schmalfuss CM, Cooper GR, et al. 2006. Mental stress provokes ischemia in coronary artery disease subjects without exercise- or adenosine-induced ischemia. *Journal of the American College of Cardiology* 47:987-91
 104. Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. 2003. Burden of systolic and diastolic ventricular dysfunction in the community: Appreciating the scope of the heart failure epidemic. *The Journal of the American Medical Association* 289:194-202
 105. Richardson S, Shaffer JA, Falzon L, Krupka D, Davidson KW, Edmondson D. 2012. Meta-analysis of perceived stress and its association with incident coronary heart disease. *The American Journal of Cardiology* 110:1711-6
 106. Roberti JW, Harrington LN, Storch EA. 2006. Further psychometric support for the 10-item version of the perceived stress scale. *Journal of College Counseling* 9:135+
 107. Roest AM, Martens EJ, de Jonge P, Denollet J. 2010. Anxiety and risk of incident coronary heart disease: A meta-analysis. *Journal of the American College of Cardiology* 56:38-46
 108. Rosengren A, Hawken S, Ôunpuu S, Sliwa PK, Zubaid M, et al. 2004. Association of psychosocial risk factors with risk of acute myocardial infarction in 11,119 cases and 13,648 controls from 52 countries (the INTERHEART study): Case-control study. *Lancet* 364:953-62
 109. Rutledge T, Thomas R, Veronica AR, Sarah EL, Barry HG. 2006. Depression in heart failure: A meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *Journal of the American College of Cardiology* 48:1527-37
 110. Saunders E. 1995. Hypertension in minorities: Blacks. *American Journal of Hypertension* 8:115S-9S

111. Scarantino A. 2016. The philosophy of emotions and its impact on affective science. In *Handbook of Emotions*, ed. LF Barret, M Lewis, JM Haviland-Jones:3-48. New York: The Guilford Press. Number of 3-48 pp.
112. Schachter S, Singer J. 1962. Cognitive, social, and physiological determinants of emotional state. *Psychological Review* 69:379-99
113. Sharma A, Colvin-Adams M, Yancy CW. 2014. Heart failure in African Americans: Disparities can be overcome. *Cleveland Clinic Journal of Medicine* 81:301-11
114. Sharp LK, Kimmel LG, Kee R, Saltoun C, Chang C-H. 2007. Assessing the Perceived Stress Scale for African American adults with asthma and low literacy. *Journal of Asthma* 44:311-6
115. Shen B-J, Eisenberg SA, Maeda U, Farrell KA, Schwarz ER, et al. 2011. Depression and anxiety predict decline in physical health functioning in patients with heart failure. *Annals of Behavioral Medicine* 41:373-82
116. Smith TW. 1992. Hostility and health: Current status of a psychosomatic hypothesis. *Health Psychology* 11
117. Smith TW, Smith TW, Frohm KD. 1985. What's so unhealthy about hostility? Construct validity and psychosocial correlates of the Cook and Medley Ho scale. *Health Psychology* 4:503-20
118. Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, et al. 2005. Monitoring clinical changes in patients with heart failure: A comparison of methods. *American Heart Journal* 150:707-15
119. Spielberger CD. 1983. *Manual for the State-Trait Anxiety Inventory (STAI)*. Palo Alto, CA: Consulting Psychologists Press
120. Spielberger CD, Johnson EH, Russell SF, Crane RJ, Jacobs GA, Worden TJ. 1985. The experience and expression of anger: Construction and validation of an anger expression scale. In *Anger and Hostility in Cardiovascular and Behavioral Disorders*, ed. MA Chesney, RH Rosenman:5-30. New York, NY: Hemisphere. Number of 5-30 pp.
121. Spielberger CD, Reheiser EC. 2004. Measuring anxiety, anger, depression, and curiosity as emotional states and personality traits with the STAI, STAXI, and STPI. In *Comprehensive Handbook of Psychological Assessment (Vol. 2): Personality Assessment*, ed. M Hersen, DL Segal, M Hilsenroth:74-80. New York: Wiley. Number of 74-80 pp.
122. Stanek EJ, Oates MB, McGhan WF, Denofrio D, Loh E. 2000. Preferences for treatment outcomes in patients with heart failure: Symptoms versus survival. *Journal of Cardiac Failure* 6:225-32
123. Steptoe A, Brydon L. 2009. Emotional triggering of cardiac events. *Neuroscience and Biobehavioral Reviews* 33:63-70
124. Steptoe A, Kivimaki M. 2012. Stress and cardiovascular disease. *Nature Reviews Cardiology* 9:360-70
125. Suls J. 2013. Anger and the Heart: Perspectives on Cardiac Risk, Mechanisms and Interventions. *Progress in Cardiovascular Diseases* 55:538-47
126. Suls J, Bunde J. 2005. Anger, anxiety, and depression as risk factors for cardiovascular disease: The problems and implications of overlapping affective dispositions. *Psychological Bulletin* 131:260-300

127. System MH. 2018. *Patients by Beneficiary Category*. <https://health.mil/I-Am-A/Media/Media-Center/Patient-Population-Statistics/Patients-by-Beneficiary-Category>
128. Taylor JS, Ellis GR. 2002. Racial differences in responses to drug treatment: Implications for pharmacotherapy of heart failure. *American Journal of Cardiovascular Drugs* 2:389-99
129. Tessler R, Mechanic D. 1978. Psychological distress and perceived health status. *Journal of Health and Social Behavior* 19:254-62
130. The Criteria Committee of the New York Heart Association. 1994. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. pp 253-256. Boston, MA: Little, Brown & Co
131. Tofler G, Hoo SYS, Buckley T, O'Farrell A, Shaw E, et al. 2009. Triggers of acute myocardial infarction: Role of heavy physical exertion, anger and respiratory infection. *Heart, Lung and Circulation* 18, Supplement 3:S127-S8
132. Tousoulis D, Antonopoulos AS, Antoniadis C, Saldari C, Stefanadi E, et al. 2010. Role of depression in heart failure: Choosing the right antidepressive treatment. *International Journal of Cardiology* 140:12-8
133. Upadhyia B, Rocco M, Lewis CE, Oparil S, Lovato LC, et al. 2017. Effect of intensive blood pressure treatment on heart failure events in the Systolic Blood Pressure Reduction Intervention Trial. *Circulation: Heart Failure* 10
134. van der Wal MHL, van Veldhuisen DJ, Veeger NJGM, Rutten FH. 2010. Compliance with non-pharmacological recommendations and outcome in heart failure patients. *European Heart Journal* 31:1486
135. Wan TTH, Terry A, Cobb E, McKee B, Tregerman R, Barbaro SDS. 2017. Strategies to modify the risk of heart failure readmission: A systematic review and meta-analysis. *Health Services Research and Managerial Epidemiology* 4:2333392817701050
136. Wawrzyniak AJ, Dilsizian V, Krantz DS, Harris KM, Smith MF, et al. 2015. High concordance between mental stress-induced and adenosine-induced myocardial ischemia assessed using SPECT in heart failure patients: Hemodynamic and biomarker correlates. *Journal of Nuclear Medicine* 56:1527-33
137. Wexler DJ, Chen J, Smith GL, Radford MJ, Yaari S, et al. 2001. Predictors of costs of caring for elderly patients discharged with heart failure. *American Heart Journal* 142:350-7
138. Williams JE, Couper DJ, Din-Dzietham R, Nieto FJ, Folsom AR. 2007. Race-gender differences in the association of trait anger with subclinical carotid artery atherosclerosis: The Atherosclerosis Risk in Communities Study. *American Journal of Epidemiology* 165:1296-304
139. Williams MT, Chapman LK, Wong J, Turkheimer E. 2012. The role of ethnic identity in symptoms of anxiety and depression in African Americans. *Psychiatry Research* 199:31-6
140. Wirtz PH, Redwine LS, Hong S, Rutledge T, Dimsdale JE, et al. 2010. Increases in B-type natriuretic peptide after acute mental stress in heart failure patients are associated with alcohol consumption. *Journal of Studies on Alcohol and Drugs* 71:786-94

141. Yancy CW. 2005. Heart failure in African Americans. *The American Journal of Cardiology* 96:3-12
142. Zaya M, Phan A, Schwarz ER. 2012. The dilemma, causes and approaches to avoid recurrent hospital readmissions for patients with chronic heart failure. *Heart Failure Reviews* 17:345-53