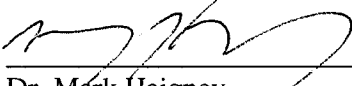## DISSERTATION APPROVAL FOR THE DOCTORAL DISSERTATION IN THE MEDICAL AND CLINICAL PSYCHOLOGY GRADUATE PROGRAM

Title of Dissertation: "The Effect of Dispositional Optimism on Health Outcomes in Patient with Heart Failure"

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Title of Thesis: The Effect of Dispositional Optimism on Health Outcomes

in Patient with Heart Failure

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Approximately 5.8 million people in the United States are living with heart failure (HF). Although improved treatments have increased survival, the overall prevalence, economic burden, morbidity, and mortality associated with the disease remains high. Dispositional Optimism is a trait, characterized by an expectation of good rather than bad outcomes in life, has been associated with better general physical and mental health as well as improved cardiovascular disease outcomes. Just as psychosocial stressors such as depression and anxiety may exert deleterious effects, positive psychosocial factors, such as Optimism, may buffer against negative health outcomes in heart failure patients. Some studies show that levels of inflammatory cytokines are related to heart failure etiology and progression and studies have linked Optimism to lower levels of inflammatory cytokines in healthy adults. The aims of the present study are to assess the relationship of Optimism to various heart failure outcomes (symptoms, functional status, and HF-related hospitalizations), and to determined whether differences in inflammatory cytokines mediate these relationships.

In this study, Optimism was measured (using the Life Orientation Test) in 125 heart failure patients (mean age = 56.7 years; 24% women) and its relationship with heart failure symptoms (Kansas City Cardiomyopathy Questionnaire Overall Summary Score) and functional status (6 Minute Walk Test) at baseline and 3 month follow-up visit was assessed. The relationship between Optimism and likelihood of hospitalizations along with total number of heart failure hospitalizations was also assessed over a mean period of 28 months. The inflammatory cytokines c-reactive protein, interleukin-6, interleukin-10, and tumor necrotic factor – α were also measured at baseline and 3 months and evaluated as potential mediators between Optimism and HF outcomes. Results indicated that Optimism was significantly predictive of fewer HF symptoms and increased functional status at baseline and 3 months after controlling for relevant demographic and medical covariates. Optimists, compared to pessimists had significantly fewer heart failure related hospitalizations and increased all-cause hospitalization-free survival. A trend towards a decreased likelihood of being hospitalized for heart failure and all-causes was observed each one point increase of LOT Total score, although this relationship did not reach statistical significance. Baseline level of interleukin-6 was related HF outcomes, but none of the cytokines were related to Optimism, hence no evidence of a mediation relationship with the inflammatory cytokines was seen.

In summary, Optimism is related to fewer heart failure symptoms, improved functional status, and fewer heart failure hospitalizations. Future research should focus on identifying the mechanisms through which Optimism is operating, as interventions to promote Optimism may prove to be valuable in the treatment of cardiovascular diseases such as heart failure.

The Effect of Dispositional Optimism on Health Outcomes in Patient with Heart Failure

Kerry S. Whittaker

Dissertation submitted to the faculty of the

Department of Medical and Clinical Psychology

Graduate Program of the Uniformed Services University of the Health Sciences

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy, 2013

Dedication

I would like to dedicate this work to my family and friends who have been a source of unwavering support during this monumental journey. Mandy, thank you for always being there to celebrate every achievement, even the smallest ones. Mom, Dad, and Courtney, thank you for believing that I can do anything I put my mind to, even when I didn't believe it myself. Gabe, thank you for keeping me grounded. For supporting me, for believing in me, for loving me. The best part of this journey was finding you along the way. I love you.

individuals who have not only proven to be exceptional colleagues but have become dear

friends.

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Background

Introduction

Approximately 5.8 million people in the United States are living with heart failure (HF), and 670,000 people are newly diagnosed with HF each year (Lloyd-Jones et al., 2010). Heart failure is an enormous economic burden to the health care system, due to repeated hospital visits and rehospitalizations that are common with the condition (Lloyd-Jones, et al., 2010). HF is a progressive clinical syndrome in which the heart is no longer able to pump enough blood and oxygen to meet the bodily demands. Although improved treatments have increased survival, the overall prevalence, morbidity, and mortality associated with HF remains high. Approximately 1 in 5 American will die within one year of being diagnosed with HF (Lloyd-Jones, et al., 2010).

Exacerbations in symptoms occur frequently in HF patients, often resulting in repeated hospitalizations and rapid deterioration in functional status. Thirty-day readmission rates for HF in Medicare beneficiaries are estimated to be over 20% (Ross, et al., 2010) . In addition to the decreased quality of life, such frequent hospitalizations are a large economic burden. The cost of HF (including health care services, medications and loss of productivity) in the United States is projected to reach $39.2 billion in 2010 (Lloyd-Jones, et al., 2010). Given the large social and economic impact of HF, it is important to better understand the multiple factors that contribute to recurrent HF exacerbations.

Despite the high frequency of HF exacerbations, the precipitating factors of such exacerbations remain largely unclear. Psychological factors, such as stress, emotion, and psychological traits, have been shown to predict cardiovascular outcomes in HF patients (Perlman, Ferguson, Bergum, Isenberg, & Hammarsten, 1971; Vaccarino, Kasl, Abramson, & Krumholz, 2001). In HF patients, depression appears to be significant independent risk factor for HF exacerbations, hospitalizations, functional decline, and mortality (Kop & Gottdiener, 2005; Murberg, Bru, Svebak, Tveteras, & Aarsland, 1999; Vaccarino, et al., 2001). In addition, some studies suggest that psychological stress is a significant independent risk factor of developing HF in men (Carels et al., 2004).

In contrast to negative emotions and stress linked to adverse HF outcomes, positive traits and emotions, such as optimism and adaptive coping styles, may offer protection against these deleterious outcomes. For example, evidence suggests that individuals high on the trait of optimism (i.e., dispositional optimism) are less likely to show progression of carotid atherosclerosis during midlife (Matthews, Raikkonen, Sutton-Tyrrell, & Kuller, 2004), and have lower rehospitalization rates after coronary artery bypass graft surgery (Scheier, et al., 1999) .

The focus of the present study is on the possible protective effects of optimism on disease outcomes in patients with heart failure. In this regard, inflammation may play a key role in HF symptom exacerbations and the overall progression of HF. Serum levels of proinflammatory cytokines have been linked to severity of heart failure symptoms and increased risk of cardiovascular events, including death (Blake & Ridker, 2002a, 2002b).

In addition, a range of psychosocial factors (depression, stress, etc.) have been shown to influence immune function (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002).

The primary focus of this literature has been on the effects of stress and negative emotions on inflammatory cytokine levels. For example, a recent meta-analysis of 24 case-control studies has shown that depression is associated with significantly higher levels of some proinflammatory cytokines (e.g., Tumor necrosis factor- alpha (TNF-α) and Interlukin-6 (IL-6)) in medically healthy adults (Dowlati et al., 2010). Type D personality, for instance, characterized by negative affect and social inhibition, has been linked to increased levels of circulating proinflammatory cytokines in cardiovascular disease patients at risk for developing HF (Denollet et al., 2003).

Despite the evidence linking depression and negative emotions with inflammation, few studies have examined the association of positive emotions with immune inflammatory markers. In healthy adults, Positive Affect (e.g., positive emotions and feelings that reflect a level of pleasurable engagement in life (Cohen & Pressman, 2006) have been shown to be inversely associated with certainly proinflammatory cytokines (Roy et al., 2010; Steptoe, O'Donnell, Marmot, & Wardle, 2008). The role of positive emotions and proinflammatory cytokines in HF patients and in cardiovascular disease more generally, is poorly understood. Positive affect has been associated with a reduction of neuroendocrine and inflammatory activity (Steptoe, Wardle, & Marmot, 2005). In addition, there are some studies that suggest that Dispositional Optimism predicts lower levels of proinflammatory cytokines associated with CVD outcomes in adults with and without CVD (Ikeda et al., 2011; Roy, et al., 2010).

The present study was designed to determine whether the positive psychology trait Dispositional Optimism is associated with improved HF outcomes and, whether the effects of Optimism are associated with lower levels of proinflammatory cytokines. In

addition, this study tried to determine whether the effects of Optimism are independent of Positive Affect and adaptive coping styles. The following sections will provide an overview of heart failure pathophysiology, as well as a review of the role of optimism and of proinflammatory cytokines as they relate to cardiovascular disease risk and heart failure and the rationale and hypotheses for the present study.

Cardiovascular Disease Process

Coronary Artery Disease and the Atherosclerotic Process

Coronary artery disease (CAD) is the most common cause of chronic heart failure in the United States, and HF due to CAD is often referred to as ischemic heart failure (Gheorghiade & Bonow, 1998). The CAD process starts with the development of atherosclerosis. The lesions of atherosclerosis can be broken down into three stages: the fatty streak, the intermediate lesion, and the fibrous plaque (R. Ross, 1999a). The fatty streak is made up of monocytes and macrophages (cells that play a key role in both innate and adaptive immune processes), which develop in the intima of the artery. Macrophages give the lesions a yellowish color that resembles adipose tissue, therefore, the lesions are referred to as fatty streaks (R. Ross, 1999b). The intermediate lesion, sometimes referred to as a fibrofatty lesion, is made up of macrophages and T cells which are interspersed among layers of smooth muscle cells. These cells are held together by fine collagen fibrils, elastic fibers, and proteoglycans (R. Ross, 1999b).

As the atherosclerotic process progresses, these lesions often develop into fibrous plaques. These plaques are characterized by the fibrous connective tissue, which cover the advanced atherosclerotic lesion. The fibrous cap can provide stability to the lesion if it is sufficiently thick, but if the fibrous cap is thin; it can become dangerously unstable and rupture. The rupture of a fibrous plaque can lead to occlusion of the lumen of the artery which can result in severe ischemia, myocardial infarction and even sudden death.

According to Ross (1999) the process of atherosclerosis is best described as an inflammatory disease due to the complex cellular and molecular responses it represents. One hypothesis concerning the etiology of atherosclerosis is based in the cellular responses to injury. The response to injury hypothesis suggests that endothelial dysfunction is the first step of atherosclerotic process. The atherosclerotic lesion is the next stage the chronic inflammatory process within the artery. If this process is left unchecked, it will result in advanced lesions and the development of coronary artery disease (R. Ross, 1999b).

Immune Function and Cardiovascular Disease

The recent emphasis on inflammation and infection as potential pathogenic factors in atherosclerosis has lead to increased interest in psychosocial, behavioral, and immune (i.e., psychoneuroimmunological) pathways of coronary artery disease (Fahdi, Gaddam, Garza, Romeo, & Mehta, 2003). Inflammation is an immune mediated response. The immune system in humans is composed of two main cell types known as megakaryocytes and leukocytes, each of which may be further differentiated into a

variety of subtypes. The various immune cells coordinated their response to pathogens via innate or adaptive immune system response. The innate immune system serves as the first line of defense against infection, and depends mostly on monocytes/ macrophages which are mononuclear leukocytes (Fahdi, et al., 2003). The surfaces of these leukocytes have scavenger receptors, which induce endocytosis and lysosomal degradation, as well as toll-like receptors, which activate transcription factors that increase the production of immune cells. The adaptive immune system involves the activation of T-lymphocytes which respond by directly attacking the antigens, or by stimulating antibody production and secreting cytokines (Fahdi, et al., 2003).

Leukocytes play a key role in the process of inflammation. When there is tissue damage, proinflammatory mediators are released resulting in vasodilation. Leukocytes move into the affected tissue which results in swelling. Several different cytokines are also involved in attracting immune cells to the damaged area including interlukin-6 (IL-6) and tumor necrosis factor (TNF). If the tissue damage or infection is not eliminated by the initial immune response then the acute inflammation can turn into chronic inflammation which may promote further penetration of the tissue by monocytes and lymphocytes. Prolonged immune activation, (such as chronic inflammation) can have pathogenic consequences.

Nonspecific markers of systemic inflammation, (such as C-reactive protein (CRP)) have been linked to increased risk of cardiovascular events (Cesari et al., 2003; Kop & Gottdiener, 2005; Vasan et al., 2003). Research has shown that the combined presence of IL-6, TNF-α and CRP levels in the upper tertile is associated with elevated risk of a CAD related event above the risk associated with the elevation of any one of

these markers alone (Cesari, et al., 2003; Kop & Gottdiener, 2005). Furthermore, examination of the cellular composition of atherosclerotic plaque reveals an abundance of T-lymphocytes and monocytes/macrophages (Bosch, Berntson, Cacioppo, Dhabhar, & Marucha, 2003), suggesting that the pathogenesis of atherosclerosis and, by extension, coronary artery disease, has immunological moderators.

Inflammatory cytokines are also associated with the onset of cardiovascular events, including myocardial infarction, even in individuals with non-ischemic heart disease (Cesari, et al., 2003; Vasan, et al., 2003). Proinflammatory cytokines are released in response to myocardial injury (Neumann et al., 1995). Research has shown that when myocardial tissue is reperfused, like after an ischemic event or myocardial infarction, proinflammatory cytokines such as interlukin-8 and interlunkin-6 are released (Neumann, et al., 1995). Chronically increased levels of circulating proinflammatory cytokines such as TNF-α, IL-6, and IL-1, and others, can promote cardiovascular remodeling through their direct and indirect effects on the interstitial matrix (Nian, Lee, Khaper, & Liu, 2004). Cardiovascular remodeling is initially adaptive, allowing the heart to compensate and continue to function after myocardial injury; however continued cardiovascular remodeling can lead to cardiomyopathies and heart failure (Blum & Miller, 2001). In later sections of this thesis, the role of inflammation in heart failure will be reviewed.

Heart Failure

Definition of Heart Failure

Heart failure is the end stage of many forms of cardiovascular disease. It may be characterized as the "pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues," (Remme & Swedberg, 2001); pg 1528). Heart failure is a symptomatic syndrome, clinically manifesting with fatigue, dyspnea (shortness of breath), orthopnea (shortness of breath when lying flat), paroxysmal nocturnal dyspnea (difficulty breathing after laying flat for extended time period), peripheral edema (accumulation of fluid in lower limbs), and right upper quadrant discomfort (due to enlargement of the liver) (Dyer & Fifer, 2003). Most clinicians use a classification system of heart failure symptoms developed by the New York Heart Association (NYHA) to describe a patient's heart failure severity (from Class I to Class IV; see Table 1) (NYHA, 1994).

Epidemiology of Heart Failure

Heart failure is most often a terminal condition, contributing to approximately 287,000 deaths a year (Owen, Khatib, & Morin, 2009). The five-year survival rate after initial diagnosis of HF is only about 50% (Dyer & Fifer, 2003). Approximately 1 in 5 American will die within one year of being diagnosed with HF (Lloyd-Jones, et al., 2010) and patients with more severe symptoms (NYHA Class III or Class IV) have a 1-year survival rate of 40% (Dyer & Fifer, 2003).

Unlike many of the other cardiovascular diseases, the incidence of heart failure appears to be increasing (Dyer & Fifer, 2003). One study of adults 65 years or older

found the age-adjusted incidence of heart failure from 1970-1974 compared to 1990-1994 increased by 14% (Barker, Mullooly, & Getchell, 2006). This increase in HF is likely due to the size of the aging population and the success of therapies and interventions in earlier stages of cardiovascular disease (Dyer & Fifer, 2003). Current reports show that there are approximately 670,000 new cases of heart failure each year (Lloyd-Jones, et al., 2010). While a community-based cohort study found no change in the incidence of HF across two decades (1979-2000), it did show an increase in survival after diagnosis (Roger et al., 2004).

The overall prevalence of heart failure in males aged 20 years and older is 3.1 million (2.4%), which is slightly higher than in females (2.6 million, 2.0%) (Roger et al., 2011). Although the prevalence of heart failure is relatively similar across ethnic groups, there are gender differences among ethnic groups. While the heart failure prevalence in non-Hispanic white males (2.7%) and Mexican American males (2.3%) is slightly higher than in non-Hispanic white females (1.8%) and Mexican American females (1.3%) respectively, heart failure prevalence is highest among in black males (4.5%) and females (3.8%) (Roger, et al., 2011).

Etiology

While 70% of today's heart failure diagnoses are considered to be the result of CAD progression (Gheorghiade & Bonow, 1998), HF can be the result of a number of conditions including: myocardial infarction, arrhythmias, valve abnormalities, myocardial dysfunction, pericardial disease, or induced by renal or thyroid dysfunction (Remme &

Swedberg, 2001). The terms systolic and diastolic are often used to describe heart failure. Systolic dysfunction is most common. Left ventricular systolic dysfunction describes the diminished capacity of the left ventricle to pump blood during systole (contraction). This results in a diminished left ventricular ejection fraction (LVEF). The term ejection fraction (EF) refers to the percentage of blood expelled from ventricle during contraction. Individuals with diastolic heart failure, have an abnormality that occurs during diastole, in the filling or relaxation of the heart (Dyer & Fifer, 2003). Most heart failure patients with diastolic dysfunction also have systolic dysfunction, rarely individuals present with diastolic dysfunction only (e.g. have symptoms of HF with normal EF) (Remme & Swedberg, 2001). Clinically, a patient has systolic heart failure (SHF) if ejection fraction is diminished, and diastolic heart failure (DHF) if ejection fraction is preserved (Chatterjee & Massie, 2007).

There are many common risk factors for SHF and DHF, including old age, hypertension, CAD, diabetes and obesity, however some risk factors are associated more with one type of HF than the other (Chatterjee & Massie, 2007). For example, uncontrolled hypertension is more common in diastolic heart failure patients (Chatterjee & Massie, 2007; Redfield et al., 2003), while the most common etiology of systolic heart failure is CAD or ischemic heart disease (Chatterjee & Massie, 2007). Given the prevalence of CAD and that most heart failure patients with diastolic dysfunction also have systolic dysfunction; the remainder of this review will focus of SHF when referencing HF.

Consequences of Heart Failure.

When the heart is no longer able to pump enough blood to meet the body's demands, it may attempt to compensate through several mechanisms. Once the heart failure process is initiated, a neurohormonal response is triggered (Appleton, 2004; Dyer & Fifer, 2003). This leads to the activation of the renin-angiotension-aldosterone system (RAAS) and the sympathetic nervous system, and also increases the production of antidiuretic hormone (ADH). This increase in ADH leads to vasoconstriction and sodium and fluid retention. If left unchecked this process will cause remodeling of the heart (e.g., stretching of the heart muscle in response to excessive wall stress), resulting in increased heart size or ventricular hypertrophy. Additionally, chronic inflammation is present in heart failure, demonstrated by high levels of tumor necrosis factor alpha (TNF-α) and other pro-inflammatory cytokines (Vescovo, Ravara, Gobbo, & Dalla Libera, 2005). The immune/inflammatory processes associated with chronic inflammation also contribute to remodeling of the heart, and can result in the progression of symptoms and disease in heart failure (Fuchs & Drexler, 2004). Although these compensatory mechanisms promote increases in cardiac output and heart function in the short-term, when chronically activated they become detrimental and can lead to worsening heart failure.

Inflammation and Heart Failure

Elevations in inflammatory cytokines in heart failure patients were first documented in the early 1990's (Levine, Kalman, Mayer, Fillit, & Packer, 1990). Since

this initial report, a great deal of research has been focused on understanding the role of

inflammation in heart failure (Blum & Miller, 2001; Bozkurt, Mann, & Deswal, 2010;

Yndestad et al., 2006, 2007). Although numerous studies have demonstrated persistent

systemic inflammation in HF, the exact mechanism of this is unknown (Yndestad, et al.,

2006). Several theories have been proposed to explain the systemic inflammation seen in

heart failure. Hemodynamic changes and oxidative stress, microbial antigens and

microorganisms, and endotoxins, as well as inappropriate neurohormonal activation have

all been implicated in triggering immune activation in heart failure patients (Yndestad, et

al., 2006, 2007).

Inflammatory markers, such as CRP (c-reactive protein), are significant predictors

of mortality in risk models of HF patient survival (Lee & Tu, 2009). Elevated plasma

levels of proinflammatory cytokines, such as interleukin- 6 (IL-6), tumor necrotic factor -

α (TNF-α), and c –reactive protein (CRP), are associated with increased risk of coronary

artery disease (CAD) related events (Cesari, et al., 2003; Kop & Gottdiener, 2005) and

are elevated in HF (de Virginy, 2006). These proinflammatory cytokines may contribute

to the pathogenesis of HF by directly effecting ventricular dilation, contractile

dysfunction, hypertrophy, apoptosis, and fibrosis (Aukrust, Gullestad, Ueland, Damas, &

Yndestad, 2005; Mann, 2002; Yndestad, et al., 2006). Both IL-6 and CRP have been

shown to play an important role in governing the process of clot formation during acute

phase response as well as fibrosis formation in cardiac tissue (Hirschfield & Pepys, 2003).

TNF-α may also play a crucial role in heart failure as this pro-inflammatory cytokine is

released by the myocardial cells in response to cardiac stressors such as volume overload

and increased left ventricular pressure (Aderka et al., 1992). Increased circulating levels

of TNF-α soluble-receptor (particularly sTNFr1 and sTNFr2) have been shown to have broader actions on the immune system (Aderka, Engelmann, Maor, Brakebusch, & Wallach, 1992; Aderka, Engelmann, Shemer-Avni, et al., 1992). In addition to elevated levels of proinflammatory cytokines, HF patients show an inadequate ratio of anti-inflammatory cytokines such as IL-10 (Bozkurt, et al., 2010). Specifically, in a normal inflammatory response, anti-inflammatory cytokines are released in response to increased levels of circulating pro-inflammatory cytokines as the body attempts to restore homeostasis, resulting in a certain ratio of pro-inflammatory to anti-inflammatory cytokines characterized as a normal response.

A recent systematic review reported that elevated cytokine levels are correlated with disease severity in heart failure patients and also predict poor prognosis (Bozkurt, et al., 2010). In the Framingham Heart Study, levels of CRP, TNF-α, and IL-6 predict the future development of HF in older, asymptomatic adults (Vasan, et al., 2003). Patients with severe heart failure have lower levels of the anti-inflammatory cytokine IL-10 in relation to elevated levels of TNF-α (Vasan, et al., 2003). Recent research suggests that psychosocial factors such as depression and chronic stress may impact inflammatory profiles, resulting in higher levels of inflammatory markers (McDade, Hawkley, & Cacioppo, 2006; Ranjit et al., 2007). In healthy adults, positive emotions are inversely associated with levels CRP and IL-6 (Roy, et al., 2010; Steptoe, et al., 2008).

In one of the only studies to look at positive psychology factors and inflammatory cytokines in a heart failure patient population, Brouwers and colleagues found that positive affect was predictive of lower levels of several key inflammatory markers overtime (Brouwers et al., 2013). A total of 210 heart failure patients in Tilburg, the

Netherlands, took part in an 18-month observational study looking at the effects of positive affect (measured by three different self-report questionnaires) and circulating levels of five pro-inflammatory markers (e.g., IL-6, CRP, TNF-α, sTNFr1, and sTNFr2). Using mixed multivariate modeling, they found that positive affect was significantly predictive of lower average levels of TNF-α and sTNFr2 overtime with two measures of positive affect (The PANAS-positive and negative affect scale, and the GMS-global mood scale), and significantly lower levels of IL-6 with one of the positive affect measures (the GMS). This is one of the first studies to clearly link positive affect to lower levels of pro-inflammatory cytokines in a heart failure patient population, suggesting that other related positive psychology measures may also influence cytokine levels in heart failure.

Positive Psychology and Health Protective Psychological Constructs

In the following section, a brief review of the Positive Psychology constructs of Positive Affect and coping styles and their relationship to cardiovascular outcomes will be presented. Understanding the processes involved in physical and psychological well-being is arguably the essential framework for future research in Health Psychology and Behavior Medicine. These fields are built upon the notion of the mind-body interaction, and the past 40 years of research has been focusing on how psychological stress can influence disease and ill-health.

Rozanski and Kubzansky (2005) propose that positive psychology constructs should be examined as a way that psychological well-being may promote healthy

physiological function, and also buffer against the development of chronic disease. Specifically, they posit that continued physiological hyperarousal resulting from psychosocial stress is one of the common factors through which psychological constructs influence the development of coronary artery disease. They further propose a model that healthy psychological functioning (comprised of vitality, effective coping skills, and emotional competence, which may be influenced by personality traits such as optimism) could reduce chronic hyperarousal of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis seen with chronic stress, depression, anger, and hostility (Rozanski & Kubzansky, 2005). Thus, it is suggested that these positive psychological characteristics may serve as a buffer against the negative effects of stress on disease. Their model builds off the current understanding of the physiological stress response and incorporates the sparse literature available that indicate positive emotion, optimism, and positive social relationships promote positive health outcomes (Giltay, Geleijnse, Zitman, Hoekstra, & Schouten, 2004; Matthews, et al., 2004; Scheier et al., 1989; Scheier, et al., 1999).

Positive Affect

The construct of Positive Affect and its relationship to health have been the focus of several recent reviews (Dockray & Steptoe, 2010; Pressman & Cohen, 2005; Steptoe, Dockray, & Wardle, 2009). Positive Affect is often defined as "feelings that reflect a level of pleasurable engagement with the environment"(Pressman & Cohen, 2005) (pg. 925). As the definition suggests, the state of Positive Affect is more than simply "feeling

happy", but also reflects an individual's level of engagement in his own life. In their systematic review of the Positive Affect literature, Pressman and Cohen (2005) concluded that there was evidence to support that individuals with high positive affect experience fewer negative health symptoms, less pain, and lower morbidity.

Affective states have been associated with cardiovascular functioning through their effect on the sympathetic nervous system(Dockray & Steptoe, 2010), and positive affect may influence a variety of cardiovascular disease outcomes. One recent study of 1739 adult participants in the Nova Scotia Health Survey, demonstrated that individuals with higher positive affect (as rated from structured interviews by trained coders) were less likely to develop CHD during a 10-year follow-up period (adjusted HR: 0.78; (95%CI: 0.63-0.96)(Davidson, Mostofsky, & Whang, 2010). Other research has shown that heart failure patients with low levels of positive affect experience more cardiac symptoms and greater impairment of health status than those with higher levels of Positive Affect (Pelle, Pedersen, Szabó, & Denollet, 2009). It remains unclear how Positive Affect promotes better cardiovascular outcomes, and why these positive emotional states are linked to prospectively to disease. There are a number of plausible explanations for the association of Positive Affect with improved health. Happier people may be more likely to comply with medical advice, engage in health-promoting behaviors, or have reduced stress reactivity. It is possible that measures of positive affect may be tapping into more "chronic" emotions or identifying people who are predisposed to experience trait-like positive affect.

Coping Styles

Coping has been a widely studied construct in psychology and the structure and processes of coping have been implicated in both physical and psychological health (Penley, Tomaka, & Wiebe, 2002). Coping has generally been defined as the cognitive and behavioral efforts of an individual to manage specific external and/or internal demands/events that are seen as stressful (Allman, Berry, & Nasir, 2009). The coping literature is complex and the multitude of measures used in the research in this area makes summarizing the findings difficult. However, coping has been linked to health outcomes (Penley, et al., 2002) and research suggests that optimists use different coping strategies than pessimists (Chang, 2002; Scheier & Carver, 1992). Effective coping strategies may attenuate an individual's stress response which may in turn reduce an individual's risk of adverse health outcomes associated with chronic physiological stress arousal.

Coping styles are often broken into 2 broad categories: Emotion-Focused Coping, and Problem-Focused Coping (Lazarus & Folkman, 1984). Emotion-Focused Coping strategies attempt to change or alter the feelings or emotional response to a stressful situation. In contrast, Problem-Focused Coping strategies attempt to change the stressful situation to make the situation itself less stressful. There does not seem to be one coping strategy that is clearly superior across all situations in mitigating the physiological and psychological effects stress. In fact, being able to change one's coping strategies based on the characteristics of a particular stressor, may confer the most health benefits (Roussi, Krikeli, Hatzidimitriou, & Koutri, 2007). The use of different coping styles has also been shown to have an impact on cardiovascular outcomes (Gleiberman, 2007). Men and

women using "defensive coping styles" (Emotion-Focused Coping) have higher systolic blood pressure than those using less defensive coping styles (King, Barr Taylor, Albright, & Haskell, 1990). CAD patients utilizing Repressive Coping Styles (emotion-focused) are at an increased risk of cardiovascular events (Denollet, Martens, Nyklíček, Conraads, & de Gelder, 2008). In a study of 58 heart failure patients followed for 2 weeks and asked to rate daily HF physical symptoms, coping strategies, mood, and social support, individuals who focused their coping efforts on improving their symptoms (Problem-Focused Coping) and accepting their illness (Emotion-Focused Coping) reported fewer HF symptoms the following day (Carels, et al., 2004).

As previously indicated, there is research to suggest that Optimists and Pessimists may differ in the use of coping strategies. (Scheier, Weintraub, & Carver, 1986).There is one study by Dunbar and colleagues looked at the effect of optimism and coping styles on mood disturbance among 101 patients (84 men and 17 women, mean age: 60 ± 12 years, mean ejection fraction (EF): 34.1%) scheduled to undergo implantable cardioverter defibrillator (ICD) insertion (Dunbar, Jenkins, Hawthorne, & Porter, 1996). Optimism predicted less mood disturbance and was also associated with Challenge Focus Appraisal (r=0.35, p $\leq$ 0.05) and Confrontative Coping Behavior (r=0.35, p $\leq$ 0.05), both of which are associated with the Problem-Focused Coping Style. When entered into a hierarchical multiple regression model predicting total mood disturbance, controlling for sex, age, NYHA classification, history of sudden cardiac arrest, MET level, marital status, and coping and appraisal variables, optimism remained significant predictive (model adjusted R^2=0.47 , p<0.001; F(11,68)=7.44, p<0.0001; β=-0.20, p=0.03) (Dunbar, et al., 1996). This study was cross-sectional in nature and did not use clinical outcomes as dependent

variables, but it is one of the few studies to evaluate optimism and coping in a patient population with low ejection fraction.

In sum, coping and positive affect are two constructs within the field of positive psychology that have been linked to general and cardiovascular health outcomes. Although these constructs are conceptually distinct from Dispositional Optimism, they are most likely related. In addition to using more problem focused coping strategies, Optimists may be more likely to experience Positive Affect than Pessimists. Positive Affect and certain coping strategies may affect health through similar pathways as Optimism. At present, there are no studies looking at coping, Positive Affect and Optimism together as possible predictors of improved outcomes in heart failure patients.

An Introduction to Optimism

The idea of optimism is not new. For as long as we have discussed personality and human relationships, we've been aware of those people who seem to approach the world with a sunny disposition. Those individuals always seem to take things in stride, and expect that things will work out for the best, even when faced with adversity. Until relatively recently that is where our recognition of optimism stopped. Some people just

seem to expect the best, and little work had been done to explore why that might be. After all, optimism does not seem like a problem that needs correcting, so why not focus on pessimists? Focus on the people who always expect something bad to happen, and go around with a dark cloud hanging over them. And for much of the 20th century psychology has focused on those "negative" personality traits, focusing theoretical explanations and research on understanding depression, anxiety, anger and other detrimental psychological factors. The field of health psychology was no exception, and until recently, looking at positive psychological factors as a marker of health and well-being, let alone playing a causal role in good health, is something that has largely been overlooked. In the following sections, the different conceptualizations and ways to measure Optimism will be discussed. After a brief description of Attributional Styles, specifically Optimistic Explanatory Style (OES) and the various ways to measure OES, a general review of the OES literature moving from general health outcomes to more specific cardiovascular disease markers and endpoints will be presented. Following discussion of the OES literature the focus will then move to Dispositional Optimism (DO). A justification for the study focus on Dispositional Optimism will be provided. Dispositional Optimism will be defined and a review of the literature again moving from cardiovascular disease risk factors (including inflammatory markers) to heart failure will be provided.

Optimistic Explanatory Style

The term optimism can refer to a few different constructs even within the positive psychology literature. Some people use the term in a more colloquial sense and this has been translated into research through the multitude of studies that use single item measures of optimism that are rarely compared to the empirically validated optimism scales available. Others use the term optimism to describe an individual's Attributional Style, or how one explains why unpleasant or bad events happen. Attributional Style is rated on 3 dimensions: stability, globality, and internality. Participants with a Pessimistic Explanatory Style will attribute bad events as being stable (with no end in sight), global (extending to all areas of their lives), and internal (their fault); whereas people with an Optimistic Explanatory Style will attribute bad events as being unstable (transient), situational (limited to the specific event), and external (due to forces outside of their control) (Peterson, Seligman & Vaillant, 1988). Questionnaires such as the Attributional Style Questionnaire (ASQ) (Peterson et al., 1982) and coding techniques such as CAVE technique (Content Analysis of Verbatim Explanations) (Peterson, Seligman & Vaillant, 1988) are validated and widely used methods to assess optimism (OES) through people's expectancy for future events based on their interpretation of past events and circumstances. CAVE techniques have also been used on existing personality measures, such as the revised Minnesota Multiphasic Personality Inventory (MMPI-2), to derived optimism measures such as the Optimism-Pessimism Scale (PSM) (Malinchoc, Offord, & Colligan, 1995). The Dutch Scale of Subjective Well-being for Older Persons (SSWO) (Tempelman, 1987) is another example of an existing scale that has been factor analyzed to reveal an optimism subscale (measuring the OES construct).

Taken together, this literature provides a strong basis for the argument that optimism promotes improved cardiovascular outcomes. Optimism has been linked to better physical and mental health (Brenes, Rapp, Rejeski, & Miller, 2002; Carver & Gaines, 1987; Chang & Sanna, 2001; L. Cohen, de Moor, & Amato, 2001; Fournier, De Ridder, & Bensing, 2002; Schou, Ekeberg, Sandvik, & Ruland, 2005; Smith, Pope, Rhodewalt, & Poulton, 1989; Vickers & Vogeltanz, 2000), fewer health risk behaviors and lower health risk factors (Kelloniemi, Ek, & Laitinen, 2005; Taylor et al., 1992), and improved health outcomes in a variety of chronic diseases (see meta-analysis by Rasmussen, Scheier, & Greenhouse, 2009).

Optimistic Explanatory Style and General Health.

In order to establish the argument that optimism is protective against adverse cardiovascular outcomes, it is important to look at the broader literature of optimistic explanatory styles and general health outcomes. In one of the first studies to look at the effects of explanatory style on health outcomes, Peterson, Seligman, and Vaillant (1988) used the CAVE technique (Content Analysis of Verbatim Explanations) to classify the explanatory styles of 99 male participants in the Study of Adult Development at Harvard University. Healthy male members of the 1942-1944 graduating classes at Harvard University were given extensive physical examinations and completed a battery of personality and intelligence tests while undergraduates at the university. After graduation, participants completed annual questionnaires about a variety of topics (including family, employment, health, etc.) and physical examination data from the participants' personal

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physicians were collected every 5 years starting at age 25. The CAVE technique was used to code responses to an open-ended questionnaire completed in 1946 about difficult wartime experience. Health status was rated on a 1(good health) to 5 (deceased) scale by a research internist based on physician reports given at 5 year intervals from age 25 to age 60.

Results indicated that men who had a Pessimistic Explanatory Style at age 25 were less likely to be healthy later in life (Peterson, Seligman, & Vaillant, 1988). While the trend was consistent throughout the 30 year follow-up period, the relationship was only statistically significant at age 45 ($r=.37$, $p<0.001$), 55 ($r=.22$, $p<0.05$), and 60 ($r=.25$, $p<0.001$).

Despite some major methodological limitations (e.g., the subjective measure of health status (ratings were based on participants personal physicians not study physicians), and not accounting for the influence of health behaviors), this was one of the first studies to bring attention to explanatory style, optimism and positive personality constructs in relation to health outcomes. The authors (Peterson, et al., 1988) suggested several theoretical pathways through with an Optimistic Explanatory Style might influence health outcomes which have remained active areas of research over the last 25 years. Although they were unable to assess if physiologic and/or behavioral pathways were the mechanisms through which optimism related to health, they provided a theoretical framework for continued investigations in this area.

Several research groups have built upon this theoretical framework. Maruta and colleagues have published a series of studies using the Optimism-Pessimism scale (PSM) from the MMPI to explore the relationship between optimistic explanatory style and

health (Maruta, Colligan, Malinchoc, & Offord, 2000, 2002). Using data collected from a group of 1145 outpatients self-referred for general medical care to the Mayo Clinic Division of Community Internal Medicine between July 1962 and March of 1965, the relationship between explanatory style, self-rated health, and survival rates were examined. Participants completed the MMPI during the initial baseline visit and as part of a larger MMPI research study (Swenson, Pearson, & Osborne, 1973) and individuals with incomplete or invalid data were excluded from the analyses.

Using a subsample drawn from this population, Maruta and colleagues (2002) looked at the relationship between explanatory style and self-rated health after initial study intake. In 1994, 447 of the surviving 523 initial sample completed the 36-Item Short Form Health Survey (SF-36) (Ware & Sherbourne, 1992). The SF-36 is a self-report questionnaire that assesses 8 health-related quality of life constructs as well as providing 2 summary scores pertaining to overall physical and mental health. The average age of participants completing the SF-36 in 1994 was 60 years. All 8 subscales of the SF-36 as well as the 2 overall summary scales were significantly correlated with the PSM ($p<0.001$), indicating that individuals with optimistic explanatory styles had better self-rated health status (Maruta, et al., 2002).

These are just two examples of studies relating explanatory style to general health. A recent meta-analysis looking at optimism and health found that the mean effect size for measures of optimistic explanatory style and health was 0.28 (*K*=5; *N*=471; 95% CI= 0.05 to 0.47) (Rasmussen, et al., 2009), indicating that the current literature supports the notion that individuals with an optimistic explanatory style are in better health than those with a pessimistic explanatory style.

Optimistic Explanatory Style and CVD Risk Factors.

In addition to establishing a relationship between optimism and general health, several studies have linked optimism (OES) to various physiological and psychosocial CVD risk factors. The Zutphen Elderly Study followed a group of men between the ages of 64-84 and free of cardiovascular disease at baseline for 15 years and assessed variety of health outcomes (Giltay, Geleijnse, Zitman, Buijsse, & Kromhout, 2007; Giltay, et al., 2004; Giltay, Kamphuis, Kalmijn, Zitman, & Kromhout, 2006; Giltay, Zitman, & Kromhout, 2006, 2008). The optimism subscale of the SSWO was used to assess optimism. In one sample of 773 men drawn from the Zutphen Elderly Study, individuals with higher levels of optimism were more likely to be physically active ($\beta=0.15$, $p<0.001$), nonsmokers ($\beta=5.62$, $p=0.02$), drink more alcohol ($\beta=0.05$, $p=0.01$), and consume more fruits, vegetables, and whole grains ($\beta=0.06$, $p=0.01$; $\beta=0.06$, $p=0.01$; $\beta=5.69$, $p=0.01$ respectively), controlling for age, education, living arrangements, self-rated health, cardiovascular disease, diabetes, cancer, BMI, and total energy intake.

In another publication using a subsample of 464 men from this study, participants were split into quartiles based on their responses to the optimism subscale (Giltay, Zitman, et al., 2006). Optimism scores predicted prevalence of depression over the 15-year follow-up period, such that men in the highest tertile of optimism had a lower cumulative incidence of depression compared to men in the lowest tertile (HR: 0.23, 95%CI: 0.15-0.36) and that this relationship remained unchanged after adjusting for age, self-rated health, and presence of cardiovascular disease (Giltay, Zitman, et al., 2006).

These analyses suggest that one mechanism through which optimism may be operating to confer protective effects against cardiovascular disease is through the behavioral pathways such as diet, exercise and other health behaviors as well as reducing the risk of depression, a known psychosocial risk factor for adverse CVD outcome.

Optimistic Explanatory Style, Incident CHD and MI.

In addition to CVD risk factors, optimism has also been linked to the development of coronary artery disease. Kubzansky and colleagues (Kubzansky, Sparrow, Vokonas, & Kawachi, 2001) investigated the effects of optimistic explanatory style in the development of coronary heart disease in a sample of participants from the Normative Aging Study. The Normative Aging Study is a longitudinal study of 2280 community-dwelling men in the greater Boston area between the ages of 21 to 80, started by the Veterans Administration in 1961 (Bell, Rose, & Damon, 1972). Men with chronic health conditions were excluded at baseline, leaving the original cohort composed of initially healthy individuals. Participants in the NAS are followed-up by physical examinations every 3 to 5 years, updating medical histories and measuring clinical risk factors, with morbidity and mortality confirmed through hospital records and death certificates. Optimism was assessed with the revised Optimism-Pessimism Scale (PSM-R), derived from the revised MMPI (MMPI-2) (Malinchoc, et al., 1995).

The MMPI-2 was administered in 1986 to all active NAS study participants and a total of 1306 men (mean age 60.8 years, (SD=8.3 years, range 40-90 years) without pre-existing CHD were included in the analyses. Using the PSM-R as a continuous variable,

men with a more optimistic explanatory style had a relative risk of 0.72 (95%CI: 0.57-0.90) for non-fatal MI, 0.70 (95%CI: 0.55-0.90) for angina pectoris, and 0.75 (95%CI: 0.62-0.91) for total incident CHD after adjusting for age, education, smoking status, blood pressure, cholesterol, BMI, family history of CHD, and alcohol consumption (Kubzansky, et al., 2001). When participants were broken into tertiles according to PSM-R, the most optimistic men had a multivariate-adjusted relative risk of 0.44 (95% CI: 0.26-0.74) for combined non-fatal MI and CHD death. The results of this large epidemiological study suggest that older men who have an optimistic explanatory style have a lower risk of developing CHD, independently of health behaviors such as cigarette smoking and alcohol consumption.

In another large epidemiological study, Boehm and colleagues looked at the development of incident CHD in relationship to optimism in the Whitehall II dataset (Boehm, Peterson, Kivimaki, & Kubzansky, 2011). Using a single item (e.g., "Over the next 5-10 years, I expect to have many more positive than negative experiences,") rated on a 6-point Likert-type scale of 1(strongly disagree) to 6 (strongly agree), participants were categorized into groups of high, medium, and low optimism.

A total of 7,942 participants (5,488 male, 2,454 female) between the ages of 39 to 63 years old were included in the analyses. After adjusting for a host of demographic and disease covariates including; age, gender, ethnicity, marital status, grade of employment, smoking status, alcohol consumption, exercise, fruit and vegetable consumption, systolic and diastolic blood pressure, BMI, cholesterol levels, and diabetes, for every one standard deviation increase in optimism, participants had a 15% reduction in incidence of coronary heart disease (HR=0.85, 95%CI [0.76-0.95]) (Boehm, et al., 2011). Adjusting for

"psychological ill-being" (as derived from the Short-Form General Health Survey items) only slightly attenuated the effects of optimism on incident coronary heart disease (HR= 0.87, 95%CI [0.87-0.97]) (Boehm, et al., 2011). The association of optimism and CHD was similar across men and women and those individuals younger than 55 and older than 55.

Additional analyses splitting CHD outcomes into fatal CHD and nonfatal MI from verified angina showed a similar relationship direction, although high and moderate levels of optimism were only significantly related to verified angina (high optimism: HR=0.58, 95%CI[0.40-0.84]; moderate optimism: HR=0.58, 95%CI [0.42-0.80]) (Boehm, et al., 2011). The extremely large sample size in epidemiological studies like Whitehall II and the Normative Aging Study bring attention to the relationship between higher levels of optimism and lower incident CHD. These studies demonstrate a protective relationship between optimistic life expectations and a reduction in incident CHD that was not explained by health-related behaviors or biological factors

Agarwal and colleagues published a study in 1995 which demonstrated a link between "Positive Life Orientation" and recovery from myocardial infarction (Agarwal, Dalal, Agarwal, & Agarwal, 1995). They defined Positive Life Orientation as "one's ability to emphasize the positive aspects of [a] crisis, make positive comparisons, and maintain a positive attitude towards life in general. Generalized expectancy of successful outcomes is a consequence of positive life orientation," (Agarwal, et al., 1995)(pg. 126).

Researchers in India recruited 70 male patients (average age of 50.9 years) hospitalized with their first MI and used a structured interview schedule to assess Positive Life Orientation. Interviews were conducted 4 to 5 days after initial hospitalization.

Patients with higher Positive Life Orientation were more likely to have improved recovery (both physician rated (r=0.23, p<0.05) and self-rated (r=0.039, p<0.01) after their MI. This study suggests that Positive Life Orientation and by extension optimism, is associated with similar protective effects cross-culturally.

Similar to "Positive Life Orientation", Emotional Vitality been shown to be related to incident CHD. Characterized by a sense of energy, positive well-being, and effective emotion regulation, Emotional Vitality may be influenced by an individual's ability to expect positive outcomes and events from life, (e.g., optimism) (Kubzansky & Thurston, 2007; Rozanski & Kubzansky, 2005). Few studies have looked at Emotional Vitality as a predictor of incident coronary heart disease, but one study found that adjusting for standard cardiovascular disease risk factors and a history of psychological conditions, individuals highest in Emotional Vitality were less likely to develop CHD over a 15 year follow-up period (RR:0.81; 95%CI: 0.69-0.94) (Kubzansky & Thurston, 2007). Overall the literature suggests that individuals who have an optimistic explanatory style have lower incidence of CHD, better physician and self-rated recovery after MI, and are less likely to suffer an MI than their pessimistic counterparts.

Optimistic Explanatory Style and Mortality

Giltay and colleagues (Giltay, et al., 2004) used the SSWO optimism subscale to assess the relationship between optimism (OES) and all-cause and cardiovascular mortality in 941 participants (475 women and 466 men, mean age 74.5 years) in the

Arnhem Elderly Study. Participants were divided into quartiles based on their optimism scores. Compared to the lowest level of optimism, patients with the highest levels of optimism had a decreased risk of all-cause mortality (HR: 0.55, 95%CI: 0.42-0.74; age- and sex-adjusted) and cardiovascular mortality (HR: 0.27, 95%CI: 0.12-0.57). The relationship for all-cause mortality was attenuated when the model was additionally adjusted for smoking, alcohol consumptions, education, total physical activity, socioeconomic status, and marital status (HR: 0.071, 95%CI: 0.52-0.97). However, the relationship with cardiovascular mortality appeared to be strengthened when controlling for age, sex, chronic disease, smoking, education, alcohol consumption, BMI, history of cardiovascular disease or hypertension, and total cholesterol level (HR: 0.23, 95%CI: 0.10-0.55).

Giltay and colleagues also investigated the association between optimism (OES) and cardiovascular mortality (Giltay, Kamphuis, et al., 2006) as well as the association between optimism, high risk cardiovascular disease status and risk of CVD related mortality(Giltay, et al., 2008) in the Zutphen Elderly Study. A total of 545 participants (mean age 71.7 $\pm$ 5.2 years) free of cardiovascular disease and cancer were followed for 15 years (follow-up measures collected in 1990, 1995, and 2000). Over the 15 year follow-up period men in the highest tertile of optimism had a decreased risk of cardiovascular mortality when compared to men in the lowest tertile of optimism when adjusting for age, BMI, diabetes, smoking status, mean arterial pressure, antihypertensive medications, cholesterol, physical activity, alcohol use, family history of CVD, self-rated health, living arrangements, and education (HR: 0.57, 95%CI: 0.36-0.89) (Giltay, Kamphuis, et al., 2006).

In a follow-up study, to assess whether cardiovascular disease risk status was predictive of all-cause and cardiovascular mortality, participants were split into high versus low cardiovascular risk groups based on the presence of at least two of the five traditional risk factors assessed at baseline (BMI $\geq$ 30, current smoking status, hypertension, elevated serum cholesterol, or diabetes) (Giltay, et al., 2008). High risk cardiovascular status was associated with higher cardiovascular mortality (HR: 1.67; 95%CI: 1.25-2.24) and all-cause mortality (HR: 1.48 95%CI: 1:20-182) (Giltay, et al., 2008). Cardiovascular risk factor status was not associated with measures of optimistic explanatory style at any time point and only slightly attenuated the relationship between cardiovascular risk status mortality when included in the Cox regression models. Although the original publication (Giltay, Kamphuis, et al., 2006) suggested that OES was predictive of lower CVD mortality risk, the follow-up publication seems to suggests that when a "high-cardiovascular risk" variable is used in the prediction model, OES does not add to the predictive value of the model. This is one of the only studies that does not demonstrate a relationship with optimism (OES) and cardiovascular risk status. The use of a non-validated measure of optimism may explain why no association was found between optimism and cardiovascular risk factor status in this study.

Other studies have found an association between optimism and decreased risk of mortality. Using data collected from a group of 1145 outpatients self-referred for general medical care to the Mayo Clinic Division of Community Internal Medicine between July 1962 and March of 1965, the relationship between explanatory style, self-rated health, and survival rates were examined. Participants completed the MMPI during the initial baseline visit and as part of a larger MMPI research study (Swenson, et al., 1973) and

individuals with incomplete or invalid data for the PSM optimism scale were excluded

from the analyses (Maruta, et al., 2000). Vital status for the 839 participants (529 women

and 310 men; average age 35 years (ranging from 51-84)) with complete data was

obtained in 1994 by review of Mayo Clinic files, mailed questionnaires, and telephone

interview. For each participant, the 15-year expected survival rate was calculated using

the US West North Central life tables.

Based their PSM scores, participants were divided into 3 categories of

explanatory style: optimistic, mixed, and pessimistic. Individuals who endorsed a more

pessimistic explanatory style had significantly higher-than-expected mortality when

compared to the average 15-year expected survival rate based on age and gender (p=0.01)

(Maruta, et al., 2000). Compared with participants classified as having a mixed

explanatory style, optimists had a significant decreased risk of death (RR: 0.50; 95%CI:

0.29-0.87), whereas pessimists had a significantly increased risk of death (RR: 1.21;

95%CI: 0.88-1.67) (Maruta, et al., 2000). When kept as a continuous variable, a 1

standard deviation increase in PSM scores (higher scores indicating a more pessimistic

explanatory style) was associated with a 19% increase in risk of death controlling for age,

sex, and expected survival (Maruta, et al., 2000). In sum, although there are relatively

few studies in this area, the literature does provide evidence that optimistic explanatory

style and single-item measures of optimism/OES are related to positive health outcomes,

reduced risk of developing cardiovascular disease, improved recovery after a

cardiovascular event, and decreased cardiovascular and all-cause mortality.

Little research has been done looking at optimism in heart failure patients. One study used transcripts from semi-structured interviews with 33 female heart transplant recipients (mean age 62.3 years $\pm$ 5.5) to try to explore the perceptions and meanings women assign to their experiences with heart failure (Evangelista, Doering, & Dracup, 2003). Researchers performed content analysis of linguistic data to identify major theme or concepts occurring in the patient's narrative of her heart transplant which had taken place on average 4.6 ($\pm$4.8) years prior to study participation. Among the factors associated with recovery was "optimism". Women who experience optimism in their relationships with others or who were able to remain optimistic during the worst times of their illness identified these feelings of "hopefulness" or "optimism" as key motivating factors in their recovery.

Without any quantitative way to measure optimism in this sample it is impossible to determine whether optimism impacts recovery from heart transplant, or lessens the burdens associated with heart failure and heart transplant surgery. These qualitative data do suggest the need for quantitative research in this area to assess the physiological and psychological impact of optimism on heart failure patients and patients recovering from heart transplant.

Dispositional Optimism and Cardiovascular Disease

As previously discussed the literature on the effects of optimism on cardiovascular disease encompasses research looking at explanatory styles, dispositional

optimism, and optimism as a situational response to stressors. There is disagreement among researchers as to which conceptual framework best describes the optimism findings, but when taken together these different approaches have added greatly to the literature and raised a number of intriguing questions about optimism and cardiovascular health. Of all the different measures and definitions of optimism, the Life Orientation Test measuring Dispositional Optimism has been the most widely used, especially in relation to health outcomes (Rasmussen, et al., 2009). It is for this reason that the proposed study will focus on Dispositional Optimism (DO), and the term optimism from this point forward will be used to refer to DO unless explicitly stated otherwise.

Dispositional Optimism was introduced by Scheier and Carver in 1985, and came out of their work on behavioral self-regulation (Carver, Blaney, & Scheier, 1979; Carver & Scheier, 1982; Scheier, Carver, & Gibbons, 1979). They were interested in understanding the factors that motivate some individuals to stick with a challenging task while other individuals give up. Their general model of behavioral self-regulation pulls from the theoretical framework that goal-directed behavior is guided by "a hierarchy of closed-loop negative feedback systems" (cf.Heckhausen, 1967; Scheier & Carver, 1985), and that this feedback system is most influential when a person focuses on his own expectancies for this behavior.

Building off the idea that outcome expectancies influence behavior (Klinger, 1975; Kukla, 1972; Rotter, 1952), the model suggests that if an individual holds favorable expectations, he will continue or renew his efforts, whereas holding unfavorable expectations will result in reduced efforts or even behavioral disengagement. Where the concept of dispositional optimism comes into play is through the role of general

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expectancies. Individuals usually evaluate their outcome expectancies for specific situations based on a number of factors (e.g., the difficultly of the task, situational impediments, personal abilities and inabilities (real or imagined)), which are all situation specific. But Scheier and Carver (1985) suggest, that a person's life orientation, or general life expectancies also play a role in behavioral self-regulation. A person who generally expects good, rather than bad things to happen in life is more likely to persist in difficult situations (Scheier & Carver, 1985). This belief, or life orientation, is what Scheier and Carver define as Dispositional Optimism.

In their review of the literature, Scheier and Carver (1985) could find no measure of Dispositional optimism that was not confounded by related constructs such as hope, well-being, meaningfulness, etc.; therefore they developed a self-report questionnaire of optimism that exclusively assessed an individual's generalized outcome expectancies: The Life Orientation Test (LOT). The LOT is a 12-item questionnaire with 8 items assessing optimism and 4 filler items. Half the items are framed in a positive direction and half are framed in a negative direction and respondents are asked to indicate to what degree they agree with each of the items using the following scale: 0= strongly disagree, 1= disagree, 2= neutral, 3= agree, 4= strongly agree. Negatively worded items are reversed scored, filler items are discarded, and responses are totaled to provide an overall Dispositional Optimism score. When this scale was developed, Scheier and Carver conceptualized optimism as existing on a continuum as the bipolar opposite of pessimism. High scores on the LOT indicated an optimist, while low scores on the LOT indicated a pessimist. In their original publication of the scale's psychometric properties, they reported that factor analysis yield both a single and two factor solution. The two factor

solution loaded the 4 negative items (such as "I hardly ever expect things to go my way"

and "If something can go wrong for me, it will") and the 4 positive items (such as "In

uncertain times, I usually expect the best" and "I'm a believer in the idea that "every

cloud has a silver lining") onto separate factors. Despite the fact that a nested test

revealed the two-factor solution to be a somewhat better fit than the one-factor solution,

Scheier and Carver argued in favor of a unidimensional interpretation:

*"[The LOT] may just as reasonably be considered [as] unidimensional. First, all of its
items loaded at least .50 on the first unrotated factor extracted from the initial principle-
factors analysis. Second, there was a high positive correlation between the factors
emerging from the LISREL two-factor solution, r - .64. In sum, though there is
justification for examining the two halves of the scale separately, the available data base
(when taken in its entirety) suggests that it may be most reasonable to treat the scale as
unidimensional for most purposes." (Scheier & Carver, 1985)(pg. 227).*

Since then, a debate on whether optimism, as measured by the LOT, is one end of

the spectrum of the unidimensional construct, Optimism-Pessimism, or if optimism and

pessimism exist as distinct bivariate constructs as measured by the optimism and

pessimism subscales of the LOT (the 4 positively and 4 negatively worded items

respectively) (Herzberg, Glaesmer, & Hoyer, 2006; Kubzansky, Kubzansky, & Maselko,

2004; Robinson-Whelen, Kim, MacCallum, & Kiecolt-Glaser, 1997; Scheier & Carver,

1985). This is more than an interesting theoretical debate. The implications of the

theoretical underpinnings of optimism and pessimism are particularly important when

trying to understand the mechanism through which optimism may affect behavior and

mental and physical health. Research would seem to indicate that optimism is heath

protective (see review Carver, Scheier, & Segerstrom, 2010), but is it optimism or a lack

of pessimism that is really conferring these health benefits? On this, the literature is still

in a state of equipoise.

Dispositional Optimism, Metabolic Syndrome and other CVD Risk Factors

One of the pathways through which dispositional optimism may affect cardiovascular disease is through it's association with cardiovascular disease risk factors. Mezick and colleagues (2010) looked at the effects of positive and negative psychology factors on the sleep-wake mean arterial pressure (MAP) ratio. Prior research has shown that individuals that demonstrate less of a nocturnal decline in blood pressure are at risk for a variety of adverse cardiovascular outcomes, including increased risk of mortality (Mezick, et al., 2010). There is also some evidence to show that positive and negative emotions may affect blood pressure responses otherwise healthy adults (Pieper & Brosschot, 2005; Shapiro, Jamner, & Goldstein, 1997).

A subset of 224 participants enrolled in the Heart Strategies Concentrating on Risk Evaluation (Heart SCORE) study, a single-center prospective community-based cohort study at the University of Pittsburgh, participated in a substudy investigating sleep (Sleep SCORE) (Mezick, et al., 2010). Participants were approximately 50% male (n=113), and 43% African American (n=97), with a mean age of 60 years ($\pm$ 7.2). Over a 10 day period, participants wore an Actigraph at night to record physical movement and nighttime activity. Additionally 24-hour ambulatory blood pressure monitoring was conducted during day/nights 3 and 4. Psychosocial questionnaires, including the LOT, were completed during the study period. Controlling for age, gender, race, BMI, and hypertension, hostility (β=0.15, p=0.03), and low life purpose (β=-0.18, p=0.009), but not optimism (β=-0.08, p=0.22) were associated with attenuated sleep-wake MAP ratios.

This study was cross-sectional in nature, and the participants were drawn from a volunteer sample free from advanced cardiovascular disease and sleep disorders, but despite these limitations the overall methodology was sound. These results suggest that further research in needed to study the effect of optimism on nocturnal blood pressure in other populations, particularly ones with coronary artery disease and other co-morbid diseases. The absence of a relationship between optimism and MAP in this study should not be disregarded as it brings forward the possibility that blood pressure may not be one of the pathways through which optimism affects cardiovascular disease outcomes.

Other studies have found an association between Dispositional Optimism and blood pressure. High blood pressure, particularly ambulatory blood pressure (ABP), is an important risk factor for cardiovascular disease outcomes, including congestive heart failure (Clement et al., 2003; Dolan et al., 2005). Ambulatory blood pressure has been shown to predict the development of CHF in elderly men (Ingelsson, Bjorklund-Bodegard, Lind, Arnlov, & Sundstrom, 2006), with a small, but growing literature, showing that high blood pressure in adolescents predicts subclinical carotid artery disease in adulthood (Li et al., 2003; Raitakari et al., 2003; Vos et al., 2003). Ambulatory blood pressure measurements have also been shown to predict cardiovascular mortality as well as left ventricular mass (Devereux et al., 1983; Perloff, Sokolow, & Cowan, 1983; Raftery, Gould, Altman, Sleight, & Floras, 1981). Raikkonen and colleagues have conducted a series of studies to look at the effects of optimism and pessimism on ABP in adults (Raikkonen, Matthews, Flory, Owens, & Gump, 1999) and in adolescents (Raikkonen & Matthews, 2008).

A total of 50 community dwelling men and 50 women (n=100) between the ages of 30-45 were recruited to participate in a 3-day ambulatory monitoring study, consisting of a baseline laboratory visit followed by two consecutive work days and one non-workday of ambulatory blood pressure monitoring (Raikkonen, et al., 1999). After ambulatory monitoring, participants returned to the laboratory for a final set of assessments. During the baseline visit participants provided demographic data as well as completing a series of psychosocial questionnaires and interviews, some of which were finished during the final laboratory visit. Optimism and pessimism were measured with the LOT and total LOT scores as well as optimism and pessimism subscale scores were calculated for each participant. Using the LOT total score, compared to pessimists, optimists had lower mean systolic and diastolic blood pressure (p<0.05). Optimism, but not pessimism, subscale scores were correlated with lower SBP and DBP.

When contrast comparisons between optimists and pessimists using the overall LOT scores were conducted, only the relationship with DBP was significant (F(1,5267)=8.33, p=0.004), with the same pattern being seen using the subscale scores. When the presence or absence of negative mood was included in the analyses, only Optimists in a negative mood showed elevations in SBP (estimate =.44 t(5267)=2.80, p=0.005) and DBP(estimate =.32 t(5267)=2.83, p=.005) (Raikkonen, et al., 1999). Overall, the findings suggested that Pessimist, particularly those with low optimism subscores, had higher overall SBP and DBP over the ambulatory monitoring period, regardless of their mood. The authors go on to state that "when optimists and low pessimist [experienced a] negative mood, they exhibited BP as high as that observed in pessimists and low optimists" (Raikkonen, et al., 1999).

Almost a decade later, Raikkonen and Matthews (2008) published a study looking at the effects of optimism and pessimism on ABP in adolescents. Using a similar study protocol, 201 healthy adolescent African American and Caucasian boys (n=101; 50 White, 51 African American) and girls (n=100; 52 White, 48 African American), aged 14-16 were recruited from Pittsburgh area high schools to participate in ambulatory blood pressure monitoring during 2 consecutive school days. Prior to the ambulatory monitoring, participants came into the laboratory to provide baseline measurements, demographic information, and complete a number of psychosocial questionnaires, including the LOT. No significant relationship was found between ABP and total LOT score or the optimism subscale. The pessimism subscale was predictive of ABP such that, for every 1 standard deviation increase in pessimism systolic ABP increased 1.86mmHg during the day and 2.58mmHg at night, with a 24-hour systolic load increase of 3.54%. A similar relationship was found with daytime diastolic blood pressure and (1.28mmHg increase per standard deviation) and 24-hour diastolic load (2.73% increase per standard deviation) (Raikkonen & Matthews, 2008).

These relationships remained significant controlling for gender, ethnicity and BMI. Additional analyses revealed that when adolescents were broken into quartiles using their pessimism scores, the least pessimistic quartile had the lowest systolic ABP for day and night as well as for 24-hour load (p<0.05). Taken together the results of these two studies by Raikkonen and colleagues suggest that pessimism may have more of an effect on ABP than optimism in healthy adolescents and adults.

Cohen and colleagues (2010) conducted a cross-sectional analysis of 1024 patients (840 males and 184 females) with stable coronary heart disease from the Heart

and Soul Study to determine whether several psychosocial factors were associated with

the presence of metabolic syndrome. They used several validated measures to assess

psychological functioning including: the Patient Health Questionnaire (PHQ) (Spitzer,

Kroenke, & Williams, 1999) for Depression, the Cynical Distrust Scale (Greenglass &

Julkunen, 1989) for hostility, the Hospital Anxiety and Depression scales (HADS)

(Zigmond & Snaith, 1983) for Anxiety, the State-Trait Anger Expression Inventory

(STAXI) (Spielberger, 1988) for anger, and The Life Orientation Test (LOT) (Scheier &

Carver, 1985) for pessimism. Despite being able to code the LOT in such a way to

produce two separate measures of optimism and pessimism, the authors only chose to talk

about the pessimism scale from the LOT. Their results showed that individuals higher on

trait pessimism were more likely to have metabolic syndrome (adjusted for age, sex, and

race β=0.044 95%CI [0.01-0.07]; p$\leq$0.05.). No regression analyses were presented for

optimism despite indicating in a table presenting psychological characteristics that

patients' without metabolic syndrome had higher scores on the LOT indicting greater

optimism (mean $\pm$ S.D. without metabolic syndrome 15.5 $\pm$ 4.0 (n=609) versus with

metabolic syndrome 14.7 $\pm$ 4.0 (n=415)). Unfortunately, this is just one of many

examples in which positive psychology constructs are not reported in the literature.

Dispositional Optimism, Atherosclerosis, and CAD

Optimism has also been shown to protect against progression of carotid

atherosclerosis in post-menopausal women (Matthews, et al., 2004). As a part of the

Healthy Women Study (HWS), 209 peri-menopausal women between the ages of 42-50

years recruited from Allegheny County, Pennsylvania between 1983 and 1984 were studied to see the effects of optimism on intima medial thickness (IMT). Upon study entry a variety of clinic and psychosocial data were collected including measures of optimism (LOT). After menstruation had ceased for 12 successive months, women returned for follow-up examinations and continued to receive follow-up examinations every 3 to 5 years. In 1993 carotid ultrasound was added to the follow-up protocol for women who were 5 to 8 years post-menopause. Intima medial thickness was measured across 1-cm segments of the distal common carotid, carotid bulb, and internal carotid artery using B-mode ultrasound scans with a 5MHz linear array probe (Matthews, et al., 2004). Measures from each location were averaged to provide a measure of average IMT and maximal IMT for each of the locations. Woman underwent a follow-up carotid scan an average of 3 years after the first scan was completed.

The Life Orientation Test was administered at baseline and at the time of the first carotid scan and were highly stable over the 10 year period (Pearson $r= 0.71$, $p<0.0001$). During the 3-year time period, changes in mean IMT were comparable to changes observed in other studies with a similar population, with an average increase of 0.032mm ($t=6.85$, $p<0.0001$). Smoking status, higher systolic blood pressure, and longer duration between scans significantly predicted progression of IMT ($p<0.05$). As a continuous variable, pessimism measured at study entry was significantly predictive of increase in mean IMT ($\beta=0.10$, $t=2.71$, $p<.007$) but not of maximum IMT. However, when women were broken into quartiles based on LOT score distribution, optimists had less atherosclerotic progression (average percent increase = 1.3 for mean IMT and -0.25 for maximum IMT) compared to pessimists (average percent increase = 6.0 for mean IM and

3.1 for maximum IMT; $F= 15.4$, $p<0.001$ and $F= 5.6$, $p<0.02$). Controlling for baseline

systolic blood pressure, waist circumference, fasting glucose, triglycerides, smoking

status, physical activity, alcohol consumption, lipid-lowering and hypertension

medication, optimists had less atherosclerotic progression than pessimists ($\beta=0.14$,

$p<0.03$) (Matthews, et al., 2004). In the final stepwise regression model, LOT scores

accounted for 2.2% of the variance in change of IMT as compared with 1.5% for

smoking, 2.2% for time from baseline scan to study entry, 3.1% for systolic blood

pressure, and 15.3% for initial mean IMT($p<0.04$ for final step of the model).

Furthermore, depressive symptoms, measured by the BDI, were not related to

IMT at any time point. This study highlights the protective nature of optimism against the

progression of carotid disease in a sample of healthy middle-aged women. When

compared to pessimists, optimists showed almost no increase in carotid IMT over the 3

years of study follow-up (Matthews, et al., 2004). Although the study is limited in

generalizability due to its relatively non-diverse sample, it provides important

information about the effects of optimism in the early stages of the cardiovascular disease

process. The fact that optimists had less progression of atherosclerosis even when

controlling of biological and lifestyle factors and medication use suggests that there is a

unique protective component provided by optimism.

Optimism has been associated with improved outcomes after coronary artery

bypass graft surgery (CABG). A total of 51 male patients undergoing CABG at

Allegheny General Hospital in Pittsburgh, Pennsylvania between February and August

1984, participated in the study (Scheier, et al., 1989). Patients filled out a series of

psychosocial questionnaires (including the LOT) and provided a variety of demographic

and medical data on the day they were admitted to the hospital for the CABG procedure. The second follow-up occurred in person 6-8 days post surgery with the final patient follow-up occurring 6 months postoperatively by mail and telephone interviews. The mean age of the participants was 48.5 years (SD=6.5) and 48% (n=24) of the patients had two diseased vessels (50% occlusion). Dispositional optimism was not significantly related to extensiveness of surgery however it was significantly related to physiological evidence of MI during the surgical procedure, such that optimists were less likely than pessimists to develop new Q-waves ($F(1,46)=7.82$, $p<0.01$), and less likely to have a clinically significant release of AST (greater than 100mU.ml of an enzyme indicative of general muscle damage and seen released in response to MI; $F(1,46) = 4.70$, $p<0.05$) (Scheier, et al., 1989).

Following surgery, optimists took fewer days to begin to walk around their hospital rooms and were rated by hospital staff as having more favorable physical recovery than pessimists ($F(1,44)=6.67$, $p<0.02$; and $F(1,44)=6.25$, $p<0.02$ respectively) (Scheier, et al., 1989). Six months postoperatively optimists were more likely to have resumed vigorous physical exercise than pessimists ($F(1,43)=5.13$, $p<0.03$), and had higher self-reported quality of life ($F(1,43)=34.16$, $p<0.0001$). Optimists also reported more satisfaction with their level of medical care ($F(1,45)=10.54$, $p<0.003$) and were more likely to have returned to a variety of "normal life activities" (e.g. working, exercise, sex, socializing, and hobbies) (Fs ranged from 5.14 to 8.24, p's <0.05) and to have done so more quickly than pessimists (Fs ranged from 4.12 to 7.48, p's <0.05). The extensive analyses performed in the study, seem to suggest that optimism has a broad reaching effect on a number of physical health outcomes in patients undergoing CABG surgery.

Additional analyses focusing on optimism's effects on patient mood and coping strategies suggest that optimism provides a number of mental health benefits as well (Scheier, et al., 1989).

Optimism has also been shown to predict future rehospitalizations in cardiovascular disease patients, a costly burden to the health care system. Scheier, Matthews, Owens, Schulz, Bridges, Magovern, and Carver (1999) used the 10-item Revised Life Orientation Test (LOT-R) (Scheier, Carver, & Bridges, 1994) to measure trait optimism during a baseline interview 1 to 20 days prior to coronary artery bypass graft surgery in 309 patients (69.9% male, 62.8 ± 10.4 years); the Center for Epidemiological Studies Depression Scale (Radloff, 1977) and the Eysenck Personality Questionnaire (Eysenck, 1958) assessed depression and neuroticism, respectively, as known correlates of individual differences in optimism. Demographics were recorded at intake along with physiological variables obtained from medical records to determine covariates; rehospitalization was measured up to 6 months post surgery.

The study found that controlling for age, education level, and serum cholesterol, optimistic patients were significantly less likely to be rehospitalized for CHD related causes (b = -.16 $\pm$ .06; $P < .01$; OR = 0.53, 95% CI = 0.33 – 0.83); more specifically, greater optimism reduced rehospitalizations due to underlying CAD-specific reasons (b = -.31 $\pm$ .09; $P < .001$; OR = 0.29, 95% CI = 0.14 – 0.60) (Scheier, et al., 1999). Furthermore, optimism was predictive over depression and neuroticism in a model adjusting for gender and serum cholesterol (b = -.14 $\pm$ .07; $P < .05$; OR = 0.58, 95% CI = 0.34 – 0.99) (Scheier, et al., 1999). This methodologically sound study clearly

demonstrates that after CABG surgery, rehospitalizations rates were lower in optimistic patients, suggesting that fostering positive expectations can facilitate recovery.

In one of the few studies to look at Optimism as both a bipolar and unipolar trait in CAD patients, Tindle and colleagues (2012) investigated the effect of Optimism on response to depression treatment and risk of rehospitalization after CABG surgery. A total of 430 post-CABG patients (284 of whom made up a depressed cohort categorized by Patient Health Questionnaire scores) were split into quartiles using the LOT-R Total score with the lowest quartile representing Pessimism and the highest quartile representing Optimism. Depressed patients were randomized to a collaborative care intervention for depression or treatment as usual, and at 8 month follow-up optimistic depressed patients were more three times more likely to respond to treatment overall, and more likely than pessimists to respond to either treatment modality. Optimists were also less likely to be rehospitalized for any reason after the CABG procedure. Looking at the Optimism and Pessimism Subscales, Optimism and not Pessimism was associated with response to depression treatment and lower risk of rehospitalization in the adjusted models. This suggests that Optimism may be protective against negative health outcomes even in patients with psychological risk factors.

Dispositional Optimism and Inflammatory Markers in CAD

One mechanism through which optimism may affect cardiovascular health is immune/inflammatory pathways. In one of the first studies to look at the association of optimism, pessimism and immune/inflammatory markers, Roy and colleagues (Roy, et al.,

2010) collected data as part of the NHLBI sponsored Multi-Ethnic Study of

Atherosclerosis (MESA) to explore these associations. MESA is a six-center,

longitudinal cohort study consisting of 6814 men and women between the ages of 45-84,

free from clinical cardiovascular disease during study baseline enrollment (July 2000

through August 2002)(Bild et al., 2002). The main study purpose is to investigate and

identify risk factors for subclinical atherosclerosis and its progression.

Follow-up data collection is on-going, collected every 1.5 to 2 years, and started

in September 2002. Sociodemographic information was collected at baseline along with

Dispositional Optimism (measured using the LOT-R (Scheier, et al., 1994) and scored to

provide an overall Dispositional Optimism score and an optimism and pessimism

subscale score). Each score was derived from the LOT-R was split into quartiles.

Inflammatory and hemostasis markers including IL-6, CRP, fibrinogen, homocysteine,

Factor VIIIc, D-dimer, and plasmin-antiplasmin were also measured at baseline and log-

transformed for statistical analyses. The mean age of participants was 62.1 years with

52% of the sample being female, and 38.5% white, 27.8% African American, 22%

Hispanic, and 11.8 Chinese. Of the 6814 participants, 5220 to 5358 (depending on the

outcome measure) had complete data to be included in the analyses (Roy, et al., 2010).

Preliminary analyses revealed no gender differences in levels of optimism and also

showed that optimists were more likely than pessimists to be non-smokers, more

physically active, have a diet with more whole grains and vegetables, have lower BMI,

and less likely to have diabetes.

Dispositional optimism was associated with lower levels of IL-6, fibrinogen, and

homocysteine (p- value for trend: p=001, p<.001, p=.03, respectively). CRP

demonstrated the same trend but was not statistically significant (p=.39) (Roy, et al., 2010). No clear pattern was seen in the other 3 markers. When looking at the optimism and pessimism subscales of the LOT-R, it appeared that these relationships were driven by the pessimism subscale. After adjusting for age, sex, current infection, current medication use, fasting state, opposing subscale a two standard deviation increase in pessimism was associated with a 6.01% increase in IL-6 (p=.001), 10.31% increase in CRP (p=.001), and a 2.47% increase in fibrinogen (p<.001). Additionally adjusting for race, education, income, depression, cynical distrust, smoking, exercise, and diet, a two standard deviation increase in pessimism was associated with a 8.25% increase in CRP(p=.02) and a 1.86% increase in fibrinogen(p=.002). Further adjusting for BMI, diabetes, and hypertension, only the association with fibrinogen and pessimism remained significant (1.36% increase p=.02) (Roy, et al., 2010). An association with optimism and higher CRP levels was also found but only in the models adjusted for age, sex, current infection, current medication use, fasting state, opposing subscale (7.67% increase p=.02), and additionally adjusting for race, education, income, depression, cynical distrust, smoking, exercise, and diet (7.80% increase p=.02), however this association was not consistent across models and may be a statistical artifact (Roy, et al., 2010).

This study is among the first to look at the association of optimism and pessimism with hemodynamic and inflammatory markers, and indicates that dispositional optimism (overall LOT-R scores) were associated with lower levels of CRP IL-6, fibrinogen, homocysteine, but not D-dimer, Factor VIIc, nor plasmin-antiplasmin. When divided into subscales the pessimism subscale was more consistently associated with the inflammatory markers indicating that pessimism may have a stronger physiological effect

than optimism. However, since the pessimism subscale is made up of the negatively worded items in the LOT which are reversed scored and combined with the positively worded items to obtain a dispositional optimism score, the author suggest that the negatively worded items might be a better measure of dispositional optimism. The key finding remains that the LOT-R was found to be predictive of a number of inflammatory markers associated with cardiovascular disease in participants free of CVD at enrollment (Roy, et al., 2010). Although the cross-sectional nature of this study prohibits drawing causal inferences, it demonstrate an important association between optimism and a biological mechanism through which this psychosocial construct may affect the progression and etiology of CVD.

In the only longitudinal study found to date to look at the association between optimism and endothelial dysfunction, Ikeda and colleagues demonstrated the optimism was associated with lower levels of IL-6 and soluble intercellular adhesion molecule-1(Ikeda, et al., 2011). A total of 340 men free from CAD (mean age 70.9 years) participating in the Normative Aging Study were administered the LOT before collecting serum markers of inflammation and endothelial dysfunction for up to 4 follow-up visits (e.g., high-sensitivity CRP, IL-6, soluble intercellular adhesion molecule-1(sICAM-1), soluble vascular adhesion molecule-1 (sVCAM-I), soluble tumor necrosis factor receptor II(sTNF-RII)). Optimism was associated with lower baseline levels of IL-6, sTNF-RII, sICAM-1, and sVCAM-I (p's<0.05)(Ikeda, et al., 2011). Optimism was also associated with lower levels of these markers at follow-up time points, but no significant relationship was found with optimism and changes in these markers over time. When adjusting for depression, BMI, physical activity, hypertension, abnormal glucose

tolerance, cholesterol levels, statin use, alcohol intake, smoking status, and age, Optimism was only associated with lower levels of IL-6 and sICAM-I (Ikeda, et al., 2011). When the optimism and pessimism subscales of the LOT were looked at separately, the associations were stronger with the pessimism subscale than the optimism subscale.

Findings from this study are in-line with the findings from the previous described MESA study. Both studies show that optimism is associated with lower levels of some proinflammatory cytokines. And although, there are still many questions regarding the relationship between optimism and inflammatory processes, these studies suggest that this might be one mechanism through which optimism promotes improved cardiovascular outcomes.

Dispositional Optimism and Mortality

In the largest epidemiological study to date to look at the effects of optimism on cardiovascular outcomes, Tindle and colleagues (Tindle et al., 2009) found that optimism was predictive of incident coronary heart disease and all-cause mortality. A subset of 97,253 women who were participants in the Women's Health Initiative study (Anderson et al., 2003; Hays et al., 2003) were included in the analyses. Participants in the Women's Health Initiative were between the ages of 50-79 years and recruited from 40 centers across 24 states from September, 1994 through December 1998 to participate in either a long-term clinical trial or an observational study. Women with a previous cancer diagnosis or a history of cardiovascular disease were excluded from the analyses.

Optimism was measured at baseline using the LOT-R and participants were followed for 8 years to assess incident coronary heart disease and all-cause mortality. Women were split into quartiles of optimism based on LOT-R score distributions and analyses were stratified by race (African American n=7,994, White=89,259). African American and White women had similar distributions of optimism.

Optimists were less likely to be hostile (p for linear trend >0.0001) and, as compared to pessimists, were more likely to be younger, live in the Western United States, have higher education and income, be employed and have health insurance. As compared to pessimists, optimists were less likely to smoke, have diabetes, hypertension, high cholesterol, depression, lead a sedentary life style, have higher BMI or waist circumference (Tindle, et al., 2009). Age-adjusted incident CHD rates (per 10,000 women) decrease in a stepwise fashion with increasing levels of optimism (from 60 per 10,000 among pessimists to 43 per 10,000 among optimists; p for trend <0.0001). A similar pattern was seen for all-cause mortality with 63 deaths per 10,000 among pessimists decreasing to 46 deaths per 10,000 deaths among optimistic women (p for trend <0.0001). This trend was more pronounced in black women (85 vs 47 per 10,000, p for trend <0.0001) (Tindle, et al., 2009).

Optimism was predictive of incident CHD and all-cause mortality independent of hostility levels. Adjusting for age, race, education, income, diabetes, hypertension, high cholesterol, depressive symptoms, alcohol consumption, smoking, physical activity, use of hormone replacement therapy, BMI, and cohort membership, optimist were less likely to experience incident myocardial infarction (HR:0.84, 95%CI: 0.73-0.96), incident CHD (HR:0.91, 95%CI: 0.83-0.99), and had lower all-cause mortality (HR:0.86, 95%CI: 0.79-

0.93), CHD-related mortality (HR:0.70, 95%CI: 0.55-0.90), and CVD-related mortality
(HR:0.76, 95%CI: 0.64-0.90) (Tindle, et al., 2009). All of these relationships were
replicated in white women, but only the relationship between optimism and all-cause
mortality was significant among black women (HR:0.67, 95%CI: 0.50-0.90). This is the
largest study to date to use a validated measure of Dispositional Optimism (the LOT-R)
to evaluate the effects of optimism on incident CHD and all-cause mortality. Even after
adjusting for standard risk covariates optimism accounted for a 30% reduction in all-
cause mortality and a 9% reduction in incident CHD. Although the results of this study
cannot be generalized to men, it lends strong support to the health protective effects of
optimism in adults.

Dispositional Optimism and Heart Failure

In at least one study of heart failure patients, optimism has not been shown to
predict survival (Rohrbaugh, Shoham, & Coyne, 2006). A total of 189 heart failure
patients (139 men, 50 woman) and their spouse were recruited to take part in a study
investigate the effects of marital quality on all-cause mortality. Participants were
recruited from University of Michigan Medical Center HF clinics between 1993 and 1995
and were followed for all-cause mortality over the next 8 year. The average age at study
enrollment was 52 years with couples having been married an average of 25 years. Most
psychosocial measures were collected through patient interview and from a 10-minute

video-taped partner interaction coded for positive and negative affect by trained raters. Participants also completed several questionnaires (including the LOT) mailed to them 1 to 2 days after participating in the interview portion of the protocol. Results indicated that the strongest predictor of 8-year survival was NYHA classification at the time of study enrollment (gender adjusted relative risk ratio for survival were 0.57 per unit of NYHA class.) Marital quality was also strongly related to patient survival (gender-adjusted RR=2.01, 95% CI: 1.37-2.93). No interaction was found between marital quality and HF severity, nor was there any relationship between optimism and 8-year survival.

Although results of this study show that optimism does not have an effect on long-term survival in this sample, the generalizability of the particular population is limited. Participants were all married and had spouses willing to participate in the study and tended to be younger than other heart failure patient community samples. It is unclear as to whether optimism would have an effect on long-term survival in unmarried patients with HF who live alone or with a non-spousal caregiver. Additional research is needed to explore the relationship of optimism and long term survival in heart failure patients. At the time of this review, no study was found looking at the effects of optimism and pessimism on immune/inflammatory markers in heart failure patients.

Overall Summary

Dispositional Optimism and Optimistic Explanatory Style are often used interchangeably in the literature despite the fact that they are born out of different theoretical backgrounds and that the two most widely used measures, the Life Orientation

Test and the Attributional Style Questionnaire, are not consistently correlated with each other. While some studies have found moderate to high correlations between the ASQ and the LOT (from 0.41 (Hjelle, Busch, & Warren, 1996) to 0.69 (Gillham, Shatté, Reivich, & Seligman, 2001) others have found them to be only modestly correlated (Reilley, Geers, Lindsay, Deronde, & Dember, 2005), while some have found them to not be correlated at all (Isaacowitz & Seligman, 2001). Given the inconsistent association between the measures of dispositional optimism and optimistic explanatory style it seems prudent to take account of findings in the explanatory style literature, especially when information about correlations with the LOT is provided.

In summary, although several studies demonstrate a relationship between optimism and cardiovascular health, relatively few studies have been conducted in the area of Optimism and heart failure. In a 2004 review article by O'Keefe and colleagues (O'Keefe, Poston, Haddock, Moe, & Harris, 2004), the authors outline some theoretical groundwork of how different psychosocial factors may influence the progression and etiology of cardiovascular disease. It is generally accepted that anything that causes chronic and excessive sympathetic nervous system activation results in a worsened cardiovascular prognosis by way of the adrenergic receptors becoming down-regulated causing the system to lose its normal responsiveness (O'Keefe, et al., 2004). Often times this is the result of physical stressors on the cardiovascular system, however psychosocial stress may be a powerful and chronic influence on cardiovascular health and autonomic nervous system dysregulation. Just as psychosocial stressors may exert deleterious effects, positive psychosocial factors, such as Dispositional Optimism, Positive Affect, and coping styles, may buffer against autonomic dysregulation and negative cardiovascular

health outcomes. In addition to a healthier neurohormonal and inflammatory profile, Optimists may be more likely to engage in positive health behaviors such as regular exercise, healthy diet and less likely to engage in negative health behaviors such as substance abuse and cigarette smoking.

The studies reviewed above establish a relationship between Dispositional Optimism and improved cardiovascular outcomes (See Table 2). Additionally, A meta-analytic summary of the optimism and health literature conducted in 2009 incorporates studies using both measures of optimistic explanatory style and dispositional optimism clearly shows that optimism is a significant predictor of positive physical health outcomes (Rasmussen, et al., 2009). In terms of cardiovascular health outcomes, cross-sectional and longitudinal studies show that optimism is related to better cardiovascular health outcomes (K=8, N=589; weighted mean ES=0.25, 95% CI=0.12 – 0.37, p=0.0002) (Rasmussen, et al., 2009). Prospective studies of optimism and cardiovascular health also show optimism is associated with improved cardiovascular outcomes (K=4, N=761; weighted mean ES=0.15, 95% CI=0.03 – 0.27, p=0.01) (Rasmussen, et al., 2009). The relationship with optimism and immune function is less clear, but in prospective studies, optimism was shown to predict improved immune function (K=7, N=251; weighted mean ES=0.21, 95% CI=0.05 – 0.36, p=0.01) (Rasmussen, et al., 2009). The relationship in cross-sectional and longitudinal studies was in the same direction but did not reach statistical significance. Research published since the release of this meta- analysis has demonstrated a relationship between optimism and immune markers in cardiovascular patients (Roy, et al., 2010).

Despite a growing literature, there are still many questions as to what role Dispositional Optimism may play in the etiology and progression of cardiovascular disease. Almost no studies look at the effects of Dispositional Optimism on heart failure in general. Little is known on how DO may affect heart failure exacerbations, heart failure prognosis, heart failure hospitalization, or even quality of life in heart failure patients. With more than half a million Americans being diagnosed with heart failure (HF) each year (Lloyd-Jones, et al., 2010), looking at the effects of protective psychosocial factors such as optimism in this patient populations is of great importance. Most research in heart failure has focused on negative psychological traits such as depression. However, examination of possible protective factors like Dispositional Optimism may inform potential interventions for heart failure.

Elevated levels of proinflammatory cytokines have been linked to the risk of developing heart failure and its progression (Dunlay et al., 2009; Seta, Shan, Bozkurt, Oral, & Mann, 1996; Suzuki et al., 2008), and Positive Affect and Dispositional Optimism have been linked to lower levels of proinflammatory cytokines in health adults (Ikeda, et al., 2011; Steptoe, et al., 2008). There is at least one study that has linked optimism to lower levels of these cytokines in CAD patients (Roy, et al., 2010).

Furthermore, evidence suggests that Positive Affect and adaptive coping styles, while conceptual distinct from Dispositional Optimism, may affect cardiovascular health through the same mechanisms (Pressman & Cohen, 2005). However the relationship between these three positive psychology constructs and cardiovascular outcomes have been largely unexplored.

Study Rationale

Taken as a whole, there is sufficient evidence to support the further investigation into the relationship between Dispositional Optimism, immune function, and heart failure exacerbations, and to see whether this relationship is independent of Positive Affect and Coping. Therefore the study will assess the relationship between Dispositional Optimism, cytokines, and heart failure outcomes. Specifically, this study will examine whether Dispositional Optimism, and not a lack of pessimism, predict heart failure exacerbations as determined by patient functional status, symptom burden, and hospitalizations, and whether the hypothesized relationship between Dispositional Optimism and heart failure exacerbations operates in part through the inflammatory pathway. Additionally, exploratory analyses focus on whether the effects of Dispositional Optimism on HF exacerbations are independent of Positive Affect and coping styles. The specific aims of the study are:

Specific Aim 1: To determine whether Dispositional Optimism is associated with heart failure exacerbations, defined via self-reported symptom status, functional status, and likelihood of HF hospitalization.

Hypothesis 1a: It is hypothesized that patients with higher levels of Dispositional Optimism (higher total LOT scores) will have fewer reported symptoms, better functional status, and decreased likelihood of hospitalizations.

<u>Hypothesis 1b:</u> It is hypothesized that these effects will best be accounted for by the optimism subscale of the LOT and not the pessimism subscale.

Specific Aim 2: To determine whether immune/inflammatory markers are related to Dispositional Optimism levels and HF exacerbations.

<u>Hypothesis 2a:</u> It is hypothesized that baseline levels of proinflammatory cytokines and lower levels of anti-inflammatory cytokines will predict increased likelihood of HF hospitalizations and symptom exacerbations such that higher levels of proinflammatory cytokines Interleukin-6 (IL-6), tumor necrotic factor-α (TNF-α), and C-reactive protein (CRP), and lower levels of the anti-inflammatory cytokine Interleukin-10 (IL-10) will predict increased likelihood of hospitalizations, decreased functional status, and HF symptom worsening.

<u>Hypothesis 2b:</u> It is hypothesized that Dispositional Optimism (higher LOT scores) will be associated with lower levels of proinflammatory cytokines Interleukin-6 (IL-6), tumor necrotic factor-α (TNF-α), and C-reactive protein (CRP) and higher levels of the anti-inflammatory cytokine Interleukin-10 (IL-10).

Specific Aim 3: To determine if relationships between Dispositional Optimism and HF exacerbations are partially mediated by proinflammatory cytokines in HF patients.

<u>Hypothesis 3a:</u> It is hypothesized that levels of proinflammatory cytokines will partially mediate the relationship between Dispositional Optimism and HF worsening such that high levels of optimism (higher total LOT scores) will be associated with lower levels of

proinflammatory cytokines. These cytokines, will, in turn predict fewer hospitalizations, better functional status, and fewer HF symptoms.

Hypothesis 3b: It is hypothesized that this relationship will best be accounted for by the optimism subscale and not the pessimism subscale of the LOT.

Specific Aim 4: To determine if the relationship between Dispositional Optimism and HF exacerbation is independent of other positive psychosocial variables.

Hypothesis 4: It is hypothesized that patients with higher levels of dispositional optimism (higher total LOT scores) will have fewer reported symptoms, better functional status, and decreased likelihood of hospitalizations independent of Positive Affect and coping styles.

Methods

The present study is an observational study of Optimism in HF patients and how it relates to levels of proinflammatory cytokines and HF worsening. It was run in conjunction with the NHLBI funded (R01 HL085730-01 A1) prospective study of Biobehavioral Precipitating Factors of Worsening in Heart Failure BETRHEART; (PI David Krantz, Ph.D.). Data for the present study were collected during the initial phase of the ongoing BETRHEART study. The overall aim of the BETRHEART Study is to evaluate the relationship between HF biomarkers, psychosocial stress, and clinical and functional outcomes in heart failure patients. The BETRHEART protocol consists of an in-person baseline and a three-month follow-up visit, where psychosocial questionnaires are completed, blood samples drawn and processed, biomarkers are assessed and clinical data recorded (including functional status and symptoms). During the three month period participants are contacted by telephone every two weeks to gather information on psychosocial stressors they may have encountered over the previous two weeks. A subset of these participants are brought into the hospital for a short visit for repeated testing for medication and dietary compliance, functional and symptom status and HF biomarkers testing. All measures taken during the baseline visit are repeated at the three-month follow-up visit. Participants are then contacted once every six months for three years for additional follow up and hospital records are reviewed for cardiovascular events and mortality. The design and procedure for the present study are as follows:

Study Participants/Patients

Study participants (N=125) were recruited from the Heart Failure Clinic at the University of Maryland Medical Center (UMMC) in Baltimore, MD, which is directed by Stephen Gottlieb, MD. This clinic serves patients at both UMMC and the adjoining Baltimore VA Hospital. Patients with HF who were currently medically stable (as defined by their treating physician) were eligible to enter the study. Recruitment was facilitated by Stephen Gottlieb, MD., at the UMMC in Baltimore, MD.

Eligibility Criteria

Eligibility criteria for participation were: (1) diagnosis of heart failure (with a New York Heart Association (NYHA) classification of II-IV) for at least 3 months; (2) left ventricular ejection fraction < 40% as determined by echocardiogram within the past year; (3) Age > 21. Exclusion criteria were as follows: (1) clinically significant mitral valve disease; (2) documented myocarditis in the past 6 months; (3) alcoholism or thyroid dysfunction as primary etiological factor of HF; (4) implanted left ventricular assist device; (5) planned heart transplantation; (6) active cancer treatment; (7) living in nursing home; (8) cognitive impairments interfering with consent or questionnaire completion. Additionally, patients had to be at least one month post-hospitalization. Because we were interested in assessing emotional precipitants of worsening of HF status during usual treatment, patients enrolled in the study were not withdrawn from usual medications. It should be noted that some medications used by HF patients (e.g., anti-inflammatory medications and statins) may reduce circulating levels of proinflammatory cytokines

(Tsirpanlis, 2005; Tsirpanlis, Boufidou, Alevyzaki, & Psimenou, 2005) . Therefore, the use of these medications was controlled for when appropriate during statistical analyses. Given the demographic characteristics associated with HF diagnosis, a significant number of patients had comorbid disorders (e.g., diabetes, cancer history, etc). Unless these comorbid disorders interfered substantially with the patients' participation in the study (e.g., stroke, recent or current cancer, etc.), these patients were not excluded. A detailed medical history was taken during the baseline visit and comorbid conditions were controlled for as appropriate in statistical analyses.

Procedures

Patients were screened for inclusion and exclusion criteria by Stephen Gottlieb, MD, or by a staff member from the UMMC Heart Failure Clinic. After receiving approval from the patients' treating physician, patients were approached during a routine follow-up visit to the UMMC Heart Failure Clinic where informed consent for study participation was obtained and the initial baseline visit was scheduled.

During the baseline visit, participants came to the cardiovascular research clinic and completed a series of psychosocial and physical health related questionnaires, general clinical information, and had a blood sample taken. Measurements of HF symptoms and functional status, clinical and demographic variables, current medications, resting blood pressure, and history of comorbid disorders (e.g., diabetes, arthritis, HIV, etc.) were assessed. Additional psychosocial data were collected during biweekly phone interviews as part of the larger BETRHEART study protocol. The reason for collecting additional

psychosocial data during the telephone interview phase of BETRHEART was to decrease the patient burden during the initial baseline visit. The measure of trait Optimism (Life Orientation Test) was administered during the telephone interview phase.

At the three-month follow-up visit, all measurements obtained during the baseline visit were reassessed (with the exception of the initial medical history). HF symptoms and functional status were assessed, blood samples obtained, and psychosocial questionnaires were repeated.

Participants then entered the long term follow-up phase of the study. During this phase, participants were contacted by a research team member every six months for the next three years to obtain information regarding current health status and cardiovascular events that occurred. Participants are asked about all hospitalizations and/or procedures that they have undergone in the prior six months and their current symptoms were assessed. Long-term follow-up data was collected through telephone interviews using the contact information provided by the participants during the three-month follow-up visit, or in person at one of their routine visits to the heart failure clinic. During that time the participant was also asked to provide a contact number for a friend or family member who may be contacted in the event that study personnel are unable to contact them during the long term follow-up phase. Verification of any reported cardiovascular events (hospitalization due to CV events, MI, stroke, etc.) was obtained through the participants' hospital records. Mortality was verified using hospital records. Participants who could not be contacted for long-term follow-up had their hospital records verified for mortality status. Permission for this record review was obtained from the participants during the initial study consent process. The present study used long-term follow-up data from at

least the first 6 months after the 3 month visit for all participants, although some participants had longer follow-up available due to the prospective nature of data collection for this study.

Measurements

Psychological

Optimism was assessed using the Life Orientation Test (LOT) (Scheier & Carver, 1985). The LOT is one of the most commonly used measures of dispositional optimism. It has 12 items, four optimism items (e.g., in uncertain times, I usually expect the best), four pessimism items (e.g., If something can go wrong for me it will), and four filler items (e.g., I enjoy my friends a lot). Participants are asked to indicate the extent to which they agree with each of the items using a five-point scale ranging from 0 (strongly disagree) to 4 (strongly agree). The total score ranges from 0-32 with higher scores indicating higher levels of optimism (pessimism items are reverse coded). The high four-week, test-retest reliability correlation ($r = .79$) supports the assumption that optimism is a relatively stable trait over time (Scheier & Carver, 1985). Stability of LOT scores over time has also been shown in a heart failure population (Luskin, Reitz, Newell, Quinn, & Haskell, 2002). The LOT has been used in numerous studies and is well validated (Burke, Joyner, Czech, & Wilson, 2000). Given that optimism is stable over time, the administration of the LOT during the phone interview phase was not believed to have a serious impact on the study findings.

Scheier and Carver (1985) reported the original fit indices for a one factor solution as χ^2 (18)=28.50, p<.11, delta=.99, and for a two factor solution as χ^2 (17)= 24.32, p<.12, delta=.99, with nested test showing the two factor solution slightly superior

to the one factor solution χ^2 (1)=4.18, p<.05. Since the original publication of the LOT, other studies have found support for the two factor solution being superior to the one factor solution χ^2 (1,N=292)=58.76, p<.005 (Kubzansky, et al., 2004). Given that both an unipolar and bipolar conceptualization of Optimism-Pessimism are supported in the literature, and no consensus exists regarding the preferred approach, this study evaluated both. The LOT Total score measures Optimism and Pessimism as anchoring ends of a bipolar construct; with higher scores representing optimistic individuals and lower scores representing pessimistic individuals. The Optimism and Pessimism Subscales measure Optimism and Pessimism as distinct unipolar constructs. Previous research has also used LOT Total scores dichotomized by median split to look at optimists versus pessimists and differential outcomes (Kivimäki et al., 2005). Additional regression analyses looking at the relationship between heart failure outcomes and Optimism using median split LOT Total scores were performed.

Optimism-Pessimism has been shown to be a distinct construct from depression (Kubzansky, et al., 2004; Scheier & Carver, 1985); still many researcher worry about the possibility that these variables are confounded. To address this concern depressive symptoms were measured using, the Beck Depression Inventory-II (BDI-II; (Beck, Steer, Ball, & Ranieri, 1996), and used as a covariate in the final models. The questionnaire contains 21 items, each of which lists four statements arranged in order of increasing depression severity. Higher scores on the BDI-II indicate greater depressive symptomatology. Mild depression scores range between 14-19, moderate 20-28, and severe 29 and above (Beck, et al., 1996). This measure has been extensively used and is well validated (Richter, Werner, Heerlein, Kraus, & Sauer, 1998). The internal

consistency of the scale is high (0.86 to 0.88 among psychiatric patients and 0.81 with non-psychiatric subjects) and it has been successfully used in HF patient populations (Gottlieb et al., 2004). This questionnaire was administered during baseline and three-month follow-up visits.

Positive affect describes an overall positive emotional style and was measured by an 18-item modified version of the Positive and Negative Affect Scale (PANAS)(S. Cohen, Doyle, Turner, Alper, & Skoner, 2003). Consisting of 9 positive adjectives representing calm, well-being, and vigor, and 9 negative adjectives representing hostility, depression, and anxiety, patients are asked to rate each adjective on how they have felt over the past 24-hours on a 5-point Likert scale ranging from "you haven't felt that way at all" to "you've felt that way a lot"(S. Cohen, et al., 2003). The questionnaire has adequate validity and reliability with Cronbach's alpha ranging from 0.89 to 0.93 for the positive affect scales and from 0.87 to 0.92 for the negative affect scales (Cohen et al., 2003). Patients were administered this questionnaire at baseline and 3-month follow-up.

Several different inventories are available to measure an individual's coping style, many of which are time-consuming and are associated with an increase in patient burden (Carver, 1997). In the initial 30 patients the COPE was used to assess patient coping styles. To reduce patient burden the Brief COPE (Carver, 1997) will be used to assess coping styles for all other participants. Consisting of 28-items reflecting 14 distinct coping strategies, patients are asked how much they usually engage in a certain coping strategy when faced with a stressor on a 4-point scale from 1 – "I usually don't do this at all" to 4 – " I usually do this a lot" (Carver, 1997). The factor structure of the Brief COPE is comparable to that of the full COPE (Carver, Scheier, & Weintraub, 1989) and has

been successfully used with a heart failure patient population (Klein, Turvey, & Pies, 2007). The Brief COPE uses two questions to assess each coping style cutting out two of lowest loading four questions from each scale of the full COPE. The Brief COPE has been shown to have adequate internal reliability in heart failure samples, ranging from 0.72 – 0 .81(Bean, Gibson, Flattery, Duncan, & Hess, 2009). Given that coping styles are seen as stable over time, they were assessed during the phone interview phase.

To address the issues created by switching from the COPE to the Brief COPE during the course of the study, Z-scores were calculated for each of the individual coping subscales in the COPE and Brief COPE. These subscales were then grouped together to represent two distinct styles of coping: Problem Focused Coping and Emotion Focused Coping. Using the procedure outlined by Ben-Zur and Yagil (2005), the Z-scored subscales of Active Coping, Positive Reframing, Planning, and Use of Instrumental Support were added together to create a composite score representing Problem Focused Coping styles. Likewise, Venting, Behavioral Disengagement, Denial, Acceptance, Humor, and Self Distraction, were combined to create a composite score representing Emotion Focused Coping. By following the approach outlined by Ben-Zur and Yagil (2005) only the subscales that were consistent in both the Brief COPE and COPE were used to create the two composite coping styles.

Immune/Inflammatory

Inflammatory markers were measured from the blood samples collected at the baseline and three-month follow-up visits. Samples were collected in vacuum tubes (EDTA 4.5 mmol/l), mixed gently for 30 seconds, and sat at room temperature for 45 minutes. Separation of plasma was performed by temperature-controlled centrifugation at 3000 g for 15 minutes. Aliquots of plasma and serum were stored at -80^0 C until the final patient completed the 3 month visit. Measurement of C- reactive protein (CRP) was obtained via standard procedures used in other studies conducting immunological assessments (deFilippi et al., 2003; Denollet, et al., 2003; Miller, Freedland, Carney, Stetler, & Banks, 2003). CRP was analyzed using a high sensitivity analyzer (Behring Nephelometer Analyzer II; detection range > 0.15 mg/L). Similar to the procedure used by deFilippi et al. (2003), a BN-100 nephelometer was used with a high-sensitivity immunoassay to measure CRP levels. This measurement system allows for detection of CRP at lower circulating levels and has intra-assay and inter-assay coefficients < 3% (deFilippi, et al., 2003; Denollet, et al., 2003). Assays measuring CRP were performed at the University of Maryland Medical Center in the laboratory of Robert H. Christenson, Ph.D., by an experienced laboratory technician.

Measurements of Interleukin 6 (IL-6), Interleukin 10 (IL-10), and Tumor Necrotic Factor alpha (TNF-α), were performed by Singulex® using their proprietary Erenna® Immunoassay System, which utilizes a patented digital single-molecule counting detection system. The remaining blood samples were packed in dry ice and shipped overnight to Singulex® laboratories in Alameda, California. Detailed information regarding the Erenna® system and the procedures used to test IL-6, IL-10,

and TNF-α can be found in the Erenna ® immunoassay kit package insert, downloadable from the Singulex website (http://www.singulex.com/assays.html).

The technique used by Singulex for measuring each of the three cytokines utilizes a quantitative "florescent sandwich immunoassay technique" to measure the levels of the cytokine present in the sample. A capture antibody specific to the cytokine being tested is pre-coated onto paramagnetic microparticles. Samples along with standards, and the microparticles were pipetted into microplate wells and allowed to incubate for 1 hour at $25^{o}C$ on Boekel Scientific, The Jitterbug ™ setting 5 (IL-6 requires an incubation time of 2 hours). During the incubation process the cytokine present in the sample binds to the capture antibody on the microparticles, and any unbound particles are washed away during the buffer exchange and washing process. After which point Fluor-labeled detection antibodies are added to the wells and a separate incubation and wash cycle are completed. The microparticles are then transferred to a clean plate where the elution buffer is added and the plates are incubated for a final time. During the final incubation, the elution buffer dissociates the bound protein sandwich for the microparticle surface, which relesse the labeled antibodies, which are then separated during the final microplate transfer. Erenna® System detects and counts the labeled molecules which are directly proportional to the amount of the cytokine in the sample.

Several studies have demonstrated that these cytokines are relevant to general cardiovascular disease risk and HF exacerbation (Dunlay, et al., 2009; Kaur, Sharma, & Singal, 2006; Sato et al., 1999; Stumpf, Lehner, Yilmaz, Daniel, & Garlichs, 2003; Suzuki, et al., 2008). These cytokine were chosen because research indicates that elevations in IL-6, TNF-α, and CRP are more predictive of cardiovascular events than

anyone of these cytokines alone (Kop & Gottdiener, 2005). Other research suggests that

the ratios of IL-10 to TNF-α are important to predict adverse outcomes in HF patients,

therefore IL-10 levels was also assessed (Bolger et al., 2002).

Measures of Heart Failure Severity

A standard clinical severity index of HF symptom severity, the New York Heart

Association (NYHA) classification, was initially used to assess HF symptom severity and

health status in terms of physician-rated physical limitation and symptoms. NYHA

classifications were obtained at both baseline and 3-month follow-up visits. Left

ventricular ejection fraction obtained as part of study inclusion criteria was used as a

measure of disease severity and as a covariate in all analyses. The Kansas City

Cardiomyopathy Questionnaire (KCCQ) (Green, Porter, Bresnahan, & Spertus, 2000)

was also used to access HF symptom severity. The KCCQ is a self-administered 23-item

questionnaire that has been found to be highly sensitive to clinical changes. The KCCQ

is a valid and reliable measure of HF symptom status (Green, et al., 2000). Scores range

from 0 – 100, and lower scores on the KCCQ represent more severe HF symptoms.

Functional status was assessed using the American Thoracic Society's Six Minute

Walk Test (6MWT) at both baseline and three month visits. This test uses a primary

measurement of total distance walked in 6 minutes. Patients were taken to a minimally

used hallway in the University of Maryland Cardiovascular Research Unit and instructed

to walk back and forth between the two marked points (60 feet apart) without stopping

for 6 minutes. They were instructed to walk at a comfortable pace and told that they

could stop to rest or terminate the test if it they could no longer walk. The total distance walked by each patient was calculated at the end of the 6 minute test. The 6MWT is safe, easier to administer, and better reflects activities of daily living than other walk tests (Solway, Brooks, Lacasse, & Thomas, 2001).

Total number of hospitalizations and heart failure related hospitalizations were recorded at the three-month follow-up visit and at every six month interview during the long-term follow-up period. The average length of follow-up time from baseline visit for this study was 875 days (approximately 28 months) with a maximum of 1300 days (approximately 42 months). Information on all hospitalization was initially collected as self-report data and then verified by review of participants' medical records. Once verified, all hospitalizations were classified into two categories: heart failure-related or all-cause hospitalization. Heart failure hospitalizations were classified as hospitalizations with a primary diagnosis of heart failure exacerbation, which was characterized by a diagnosis of pump failure or fluid overload. All hospitalizations after participation in the baseline visit were counted for each category of hospitalizations. A dichotomized (hospitalized yes/no) variable for both heart-failure and all-cause hospitalization was made and the total number of heart-failure hospitalizations was used as an outcome variable.

A total of 18 participants died during the long term follow-up phase of the study. Of these 18 people, 6 died prior to any all-cause or HF-related hospitalizations. All regression models for hospitalizations were run with and without these 6 individuals, and no significant differences were seen in the results. Follow-up time was adjusted for these

18 participants to reflect time from study baseline until date of death and was controlled for in all logistic and linear regression analyses evaluating hospitalization endpoints.

Statistical Analyses

SPSS Statistics Version 19.0.1 (IBM, Chicago, Illinois) was used for data analysis. The primary analytic strategy utilized regression modeling to assess the relationship between Optimism, inflammatory cytokines, and HF exacerbations based on the hypothesized research models (Figures 1 and 2).

Pearson's Product Moment Correlations were run between the LOT Total score, LOT Optimism Subscale, and LOT Pessimism Subscale, number of HF hospitalizations, functional status (as measured by the 6MWT at baseline and 3 months), heart failure symptoms (as measured by the KCCQ overall summary score which combines the clinical summary, quality of life, and social limitations scales, at baseline and 3 months), and cytokines (measured at baseline and 3 months). Specific Aim 1: Linear regression models were run to assess the relationship between Optimism and the continuous dependent variables; the 6MWT and KCCQ scale scores. These analyses were repeated with the Optimism and Pessimism Subscales scores in place of the LOT Total score. Logistic regression analyses were used to assess the relationship with the LOT Total Score and the Optimism and Pessimism Subscales and dichotomized heart failure and all-cause hospitalization as the dependent variables.

Time to hospitalization was assessed for both heart failure-related and all-cause hospitalizations and Cox regression analyses were used to evaluate the relationship

between Optimism and time from baseline to first hospitalization. Finally the relationship between Optimism and total number of heart failure-related hospitalizations was assessed using linear regression modeling.

Covariates for all the regression models were chosen a priori based on the literature for their relationship with one or more of the outcome variables (i.e., age, gender, race, household income, smoking history, NYHA Class, left ventricular ejection fraction, hypertension, baseline creatinine, current anti-inflammatory use, and current statin use). Each of these variables was then tested in univariate models to determine if they were related to the outcome variables in this study sample. The number of covariates used in the adjusted models was narrowed down by including only the variables that were significantly predictive of at least one of the outcome measures (i.e., age, gender, baseline creatinine level, hypertension, income, and ejection fraction). This was done in an effort to conserve power.

Specific Aim 2: Linear regression modeling was also used to assess the relationship between IL-6, IL-10, TNF- α, and CRP, with 6MWT and KCCQ Overall Summary scores at baseline and 3 months. The cytokines were log transformed to obtain a more normal distribution of data (Brouwers, et al., 2013; Ikeda, et al., 2011). Linear regression models using baseline levels of IL-6, IL-10, TNF- α, and CRP as predictors (independent variables) were used to assess the relationship with baseline 6MWT and KCCQ Overall Summary scores. Additional linear regression models were run testing whether baseline cytokine levels were predictive of 3 month 6MWT , KCCQ Overall Summary score, or the number of heart failure hospitalizations. Linear regression models assessing the relationship between 3 month cytokine levels and 3 month 6MWT and

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KCCQ Overall Summary scores were also run. Variables for the ratio of TNF-α to IL-10 levels at baseline and 3 months were calculated and used as independent variables for the above analyses. Logistic and Cox regression analyses were used to assess the relationship between inflammatory cytokines and likelihood of heart failure-related and all-cause hospitalizations.

The cytokines were also used in some analyses as outcome variables. Linear regressions were used to assess whether Optimism was associated with any of the cytokines at either baseline or 3 months. These models were repeated using the Optimism and Pessimism Subscales in place of the LOT Total scores.

Specific Aim 3: To test whether inflammatory cytokines mediate the relationship between Optimism and HF outcomes the four steps outlined by Baron and Kenny (1986) were followed. If a statistically significant relationship between Optimism and HF exacerbation, or Optimism and inflammatory cytokines, or inflammatory cytokines and HF exacerbations exists, the Sobel test (Sobel, 1982) will be used to estimate the size of the indirect effect. The analyses performed to address specific aims 1 and 2 are the preliminary step in determining whether inflammatory cytokines mediated the relationship between Optimism and HF exacerbations. If statistically significant relationships between Optimism and HF exacerbation, Optimism and inflammatory cytokines, or inflammatory cytokines and HF exacerbations are not found, then no further mediational test will be conducted as it can be concluded that no mediational relationship exists.

Specific Aim 4: Finally, to determine if the relationship between Optimism and HF exacerbation was independent of other psychosocial variables a step was added to

each of the regression models, containing scores for Positive and Negative Affect,

Problem Focused and Emotion Focused Coping styles, and baseline depression

symptoms (BDI scores) before entering the final step containing the LOT Total scores.

Power analyses:

Sample size calculations were based on conservative estimates derived from

logistic regression models. The smallest effect size was anticipated to be between

optimism and cytokine levels and the study was powered to the smallest effect size of the

cytokines seen previously in the literature (which was between IL-10 and LOT scores

(effect size=0.24) (Kohut, Cooper, Nickolaus, Russell, & Cunnick, 2002; Rasmussen, et

al., 2009)). Given an α = .05, effect size = 0.24, power = 0.8, and 7 predictors/covariates,

a total of 119 participants were needed to adequately power the present study (Hsieh,

Bloch, & Larsen, 1998).

Results

Sample Characteristics

A total of 150 heart failure patients were initially recruited from the University of Maryland Medical Center and Baltimore VA heart failure clinics. Of the 150 participants consented for study participation, 146 individuals completed baseline demographic information. The sample was predominately African American (68.7%), male (75.3%), with a median income of under $30,000 a year. Using New York Heart Association (NYHA) classifications, 97.9% of patients had mild to moderate heart failure (NYHA class II: n=73; NYHA class III: n=50) and 44.7% had a history of coronary artery disease. The majority of patients (55.3%) had non-ischemic cardiomyopathy, such as dilated cardiomyopathy (DCM), with a range of etiologies (including but not limited to: alcohol and drug abuse, or consequences from uncontrolled diabetes). Of the 146 patients that completed baseline demographic information, 125 also completed the Life Orientation Test, making it possible to calculate Optimism scores for 85.6% of the sample. Demographic characteristics for the full sample and the reduced sample with Optimism scores did not differ in a meaningful way. Of the 125 patients included in the final sample, 59 patients (47%) were hospitalized during study follow-up, and 35 (28%) of these

hospitalizations were classified as heart-failure related. The sample characteristics are outline in Table 3.

The Life Orientation Test (Scheier & Carver, 1985) was scored using both the one factor (LOT Total score), and two factor (Optimism Subscale and Pessimism Subscale) approach. LOT total scores in this sample were fairly normally distributed, with a range from 7 to 32 (scale range 0-32) and a mean of 21.86 $\pm$ 5.63(SD) which is similar to the mean LOT score found in the Normative Aging Study (Mean= 21.5, $\pm$ 4.33); (Achat, Kawachi, Spiro, DeMolles, and Sparrow, 2000). There were no significant differences in the sample mean for the LOT Total Scores between men (21.64 $\pm$ 5.54) and women (22.53 $\pm$ 5.96) or African American (22.08 $\pm$ 5.00) and Caucasians (21.47 $\pm$ 6.64) participants. Looking at Optimism and Pessimism as distinct constructs, the sample mean for the Optimism Subscale was 11.87 $\pm$ 3.12 and 6.02 $\pm$ 3.77 for the Pessimism Subscale. Similarly, no gender or race differences were observed in the sample means for the Optimism and Pessimism subscales. An examination of the distribution of the cytokines measured in this study revealed that none of the inflammatory markers were normally distributed. The decision to log transform the data for CRP, TNF- α, IL-6, and IL-10 was made before any additional analyses were undertaken. The means and standard deviations of key variables are outlined in Table 4.

Univariate correlations Among Variables

Full results of correlation analyses are depicted in Table 5. As expected, the psychosocial variables were moderately correlated with one another (See Table 5). LOT Total scores were negatively correlated with depressive symptoms (BDI; r=-0.46,

p<0.001), Negative Affect (PANAS Negative Mood; r=-0.35, p<0.001), and Emotion Focused Coping (r=-0.18, p=0.05), and positively correlated with Positive Affect (PANAS Positive Mood; r=0.31, p<0.001) and Problem Focused Coping (r=0.34, p<0.001). The same pattern was seen with the LOT Optimism Subscale however the magnitude of the correlations was reduced. The LOT Pessimism Subscale was positively correlated with depressive symptoms (BDI; r=0.43, p<0.001), Negative Affect (PANAS Negative Mood; r= 0.36, p<0.001), and Emotion Focused Coping (r=.31, p=0.001), and negatively correlated with Positive Affect (PANAS Positive Mood; r=-0.16, p=0.07) and Problem Focused Coping (r=-0.19, p=0.04). LOT Total Scores were positively correlated with baseline (r=0.43, p<0.001) and 3 month (r=0.26, p=0.004) KCCQ Overall Summary scores indicating that greater Dispositional Optimism was associated with fewer HF symptoms. LOT Optimism (r=0.34, p<0.001) and Pessimism (r=-0.37, p<0.001) Subscales scores were significantly associated with baseline KCCQ Overall Summary Scores in the expected directions, whereas the Pessimism Subscale (and not the Optimism Subscale) was associated with 3 month symptom status (r=-0.26, p=0.005). Greater Dispositional Optimism was also associated with fewer heart failure hospitalizations (r=-0.19, p=0.03). Only the Optimism Subscale was associated with total number of all-cause hospitalizations (r=-0.21, p=0.02). Neither the LOT Total score, nor the Optimism and Pessimism Subscales were significantly associated with any of the inflammatory markers.

Specific Aim 1

Specific Aim 1 was to determine whether Dispositional Optimism was associated with heart failure exacerbations; specifically self-reported symptom status, functional status, and HF hospitalization. The hypotheses for this aim were divided into two parts: (a) patients with higher levels of Dispositional Optimism (higher LOT Total scores) would have fewer reported symptoms, and better functional status at baseline and 3 months, and be less likely to be hospitalized during the study follow-up period; (b) The protective effects of Optimism would best be accounted for by the Optimism Subscale of the LOT and not the Pessimism Subscale.

Hypothesis 1a

Optimism (LOT Total Score) and Symptoms at Baseline and 3 Months

The relationship between the LOT Total score and the Kansas City Cardiomyopathy questionnaire (KCCQ) was evaluated. The overall summary score of the KCCQ (KCCQ-OS) was used as the dependent variable representing HF symptoms in the research model. Univariate linear regression modeling revealed that the LOT Total score was predictive of fewer HF symptoms at baseline (R^2=.19, $F(1,123)$ =28.30, $p< 0.001$, β = 0.43, $p< 0.001$) and at 3 months (R^2=.07, $F(1,119)$ = 8.51, $p = 0.004$, $\beta = 0.26$, $p =$ 0.004). After controlling for relevant demographic and medical variables (i.e., gender, age, ejection fraction (ef), baseline creatinine level, hypertension, and household income), the LOT Total score was still significantly predictive of fewer HF symptoms at baseline (Model R^2=0.25, $F(7,110)$ = 5.19, $p< 0.001$, change in R^2=0.19, $\beta = 0.45$, $p< 0.001$) and at 3 months (Model R^2=0.14, $F(7,106)$ = 2.46, $p= 0.02$, change in R^2=0.07, $\beta = 0.26$, $p=$ 0.005; See Table 6).

Optimism (LOT Total Score) and Functional Status at Baseline and 3 Months

The relationship between the LOT Total score and the 6 minute walk test was evaluated. The total distance (in feet) walked by the patient in 6 minutes was used as the dependent variable measuring functional status in the study protocol. Results from univariate models indicated that the LOT Total score did not predict total distance walked (in feet) at baseline (R^2=.02, $F(1,111) = 1.91$, $p= 0.17$, $\beta = 0.13$, $p= 0.17$) or at 3 months (R^2=.02, $F(1,106) = 2.12$, $p= 0.15$, $\beta = 0.14$, $p= 0.15$). When controlling for demographic and medical covariates, the LOT Total score was significantly predictive of greater distance walked at baseline (Model R^2=0.20, $F(7,100) = 4.52$ $p< 0.001$, change in R^2=0.04, $\beta = 0.20$, $p= 0.03$), but the relationship at 3 months was only marginally significant (Model R^2=0.23, $F(7,94) = 5.34$, $p< 0.001$, change in R^2=0.02, $\beta = 0.15$, $p= 0.09$; See Table 6).

Optimism (LOT Total Score) and Hospitalizations During Study Follow-Up

Study participants were followed up to 3 years after completion of the 3 month visit and information about hospitalizations is collected via telephone interview at 6 month intervals. Each patient had at least 6 months of follow-up after completion of the 3-month visit. The average length of follow-up time from baseline visit for this study was 875 days (approximately 28 months) with a maximum of 1300 days (approximately 42 months).

Likelihood of Heart Failure Hospitalization: Logistic regression analyses were used to evaluate whether the LOT Total score predicted whether the patients were or were not hospitalized (i.e., likelihood of being hospitalized) due to a heart failure- related incident

over the follow-up period. In the univariate model, LOT Total score was not predictive of heart failure hospitalizations ($\chi^2_{(1)}$=2.78, N=125, Exp(B)=0.94, 95%CI: 0.88-1.01, p=0.10). The LOT Total score was only marginally significantly predictive of HF hospitalizations when demographic and medical covariates, and length of follow-up time were added to the model ($\chi^2_{(8)}$=23.91.34, N=118, Exp(B)=0.93, 95%CI: 0.86-1.01, p=0.08). Cox regression analyses determined that in both the univariate (HR=0.96, 95%CI: 0.92-1.01, p=0.08) and multivariate (HR=0.95, 95%CI: 0.89-1.00, p=0.07) models greater LOT Total score was only marginally significantly related to greater heart failure hospitalization-free survival. Using a median-split to categorized the LOT Total scores into two groups representing optimists and pessimists, optimists were 51% less likely to be hospitalized than pessimists (HR= 0.49, 95%CI: 0.25- 0.95, p=0.03; See Figure 3). Controlling for disease covariates Optimists were 53% less likely to be hospitalized than pessimist (HR=0.47, 95%CI: 0.23-0.96, p=0.04; See Table 7).

Number of Heart Failure Hospitalizations: In addition to likelihood of hospitalization, the relationship of Dispositional Optimism to the number of heart failure hospitalizations during the study was explored. The distribution of HF hospitalizations was examined and patients with more than 5 heart failure hospitalizations were excluded from the analyses as outliers because they fell more than 3 standard deviations above the mean (n=2). However, including patients with more than 5 heart failure-related hospitalizations did not change the pattern of results. The linear regression analyses showed that greater LOT Total score was predictive of fewer HF related hospitalization during the follow-up period (R^2=.04, $F(1,123) = 4.77$, $p= 0.03$, $\beta = -0.19$, $p= 0.03$) and the relationship remained significant after controlling for relevant demographic and medical covariates

(Model R^2=0.19, $F(7,110)$ = 3.57, p= 0.002, change in R^2=0.04, β = -0.25, p= 0.02). An additional regression model was run to take into account the varying lengths of follow-up for participants by adding a time in study variable as an additional covariate. Although length of time in the study was significantly related to number of hospitalizations (β = 0.19, p= 0.04), the addition of this variable to the model only slightly attenuated the relationship with the LOT Total score (Model R^2=0.22, $F(8,109)$ = 3.77, p= 0.001, change in R^2=0.04, β = -0.20, p= 0.02), which remained a significant predictor of fewer total number of HF hospitalizations (See Table 7).

Likelihood of All-Cause Hospitalization: Using logistic regression analysis, LOT Total score was not predictive of being hospitalized during follow-up using a univariate model ($\chi^2_{(1)}$=2.61, N=125, Exp(B)=0.95, 95%CI: 0.89-1.01, p=0.11). Controlling for demographic and medical covariates, LOT Total score was significantly predictive of being hospitalized during follow-up, such that Optimism was related to reduced likelihood of hospitalization ($\chi^2_{(8)}$=33.22, N=118, Exp(B)=0.93, 95%CI: 0.86-1.00, p=0.05) . Results from Cox regression analyses indicated that LOT Total scores were marginally predictive of time to first hospitalization in univariate (HR=0.96, 95%CI: 0.92-1.01, p=0.10) and multivariate models (HR=0.96, 95%CI: 0.92-1.01, p=0.09). However, optimists, when compared to pessimists were 50% less likely to be hospitalized during follow-up when using the dichotomized LOT Total score variable (HR= 0.50, 95%CI: 0.29-0.85; See Figure 4). This relationship was only slightly attenuated when demographic variables were controlled for (HR= 0.51, 95% CI: 0.29-0.92; See Table 7).

Hypothesis 1b

Optimism and Pessimism Subscales and Symptoms at Baseline and 3 Months

To address whether Optimism and Pessimism relate to heart failure symptoms differently, the LOT was broken into Optimism and Pessimism Subscales. The relationships between the two subscales and the KCCQ-OS were evaluated (Results are summarized in Table 8). Univariate linear regression modeling revealed that the LOT Optimism Subscale was significantly predictive of fewer HF symptoms at baseline ($F(1,123) =15.73$ $p< 0.001$, $\beta = 0. 34$, $p< 0.001$) and marginally predictive at 3 months ($F(1,119) = 2.96$, $p = 0.09$, $\beta = 0.16$, $p = 0.09$). The Pessimism Subscale was significantly predictive of more heart failure symptoms at baseline ($F(1,123) =19.20$ $p< 0.001$, $\beta = -0. 38$, $p< 0.001$) and at 3 months ($F(1,119) =8.27$ $p= 0.005$, $\beta = -0. 26$, $p= 0.005$). Controlling for demographic and medical covariate set the LOT Optimism Subscale was still significantly predictive of fewer HF symptoms at baseline ($F(7,110) =3.60$ $p= 0.002$, change in $R^2=0.13$, $p<0.001$, $\beta = 0. 37$, $p<0.001$) and marginally predictive at 3 months ($F(7,106) =1.79$ $p= 0.10$, change in $R^2= 0.03$, $\beta = 0. 18$, $p=0.054$). The Pessimism Subscale was still significantly predictive of more heart failure symptoms after controlling for the covariates at baseline ($R^2=0.18$ $F(7,110) = 3.48$ $p= 0.002$, change in $R^2= 0.13$, $\beta = -0.37$, $p<0.001$) and 3 months ($R^2=0.07$, $F(7, 106) =2.20$ $p= 0.04$, change in $R^2= 0.05$, $\beta = -0.24$, $p=0.01$).

Optimism and Pessimism Subscales and Functional Status at Baseline and 3 Months

The relationship between the LOT Optimism and Pessimism Subscales and the 6 Minute Walk Test were evaluated and results from univariate models indicated that

neither the LOT Optimism Subscale nor the LOT Pessimism Subscale predicted total

distance walked at baseline (Optimism Subscale: $\beta = 0.12$, $p= 0.19$; Pessimism Subscale:

$\beta = -0.09$, $p=0.36$) or at 3 month (Optimism Subscale: $\beta = 0.11$, $p= 0.24$; Pessimism

Subscale: $\beta = -0.11$, $p= 0.25$). However, when demographic and medical covariates were

entered into the model the LOT Optimism Subscale was significantly predictive of

distance walked at baseline ($F(7,99) =5.00$ $p< 0.001$, change in $R^2= 0.05$, $\beta = 0.23$,

$p=.01$) and at 3 months ($F(7,94) = 5.89$ $p<0.001$, change in $R^2= 0.04$, $\beta = 0.21$, $p=0.02$).

In the multivariate model the LOT Pessimism Subscale was not predictive of distance

walked either at Baseline ($\beta=-0.09$, $p=0.31$) or at 3 months ($\beta=-0.05$, $p=0.59$) (See Table

8).

Optimism and Pessimism Subscales and Hospitalization During Study Follow-up

 Likelihood of Heart Failure Hospitalization: As was done for Hypothesis 1a,

logistic regression analysis was used to evaluate whether the LOT Optimism and

Pessimism Subscales predicted whether patients were hospitalized for a heart failure-

related incident. Univariate logistic regression analyses showed that neither the Optimism

or Pessimism Subscales were predictive of HF hospitalizations (Optimism Subscale:

$\chi^2_{(1)}=1.38$, N=125, Exp(B)=0.93, 95%CI: 0.82-1.05, p=0.24; Pessimism Subscale: $\chi^2_{(1)}=$

2.26, N=125, Exp(B)=1.08, 95%CI: 0.98-1.20, p=0.13). These results did not differ in the

multivariate model (Optimism Subscale: $\chi^2_{(8)}=22.67$, N=118, Exp(B)=0.91, 95%CI: 0.79-

1.04, p=0.16; Pessimism Subscale: $\chi^2_{(8)}= 23.15$, N=118, Exp(B)=1.11, 95%CI: 0.98-1.24,

p=0.12). Univariate Cox regression analyses also failed to reveal a significant

relationship between time to first HF hospitalization and the Optimism Subscale

(HR=0.96, 95%CI: 0.89-1.04, p=0.35). However in the multivariate model, the analyses indicated that participants scoring higher on the Optimism Subscale had marginally greater HF-related hospitalization –free survival (HR=0.91, 95%CI: 0.82-1.01, p=0.08). The univariate Cox regression model for the Pessimism Subscale was marginally related to reduced HF-related hospitalization-free survival (HR=1.06, 95%CI: 0.995-1.13, p=0.07), whereas the relationship in the multivariate model was greatly attenuated (HR=1.06, 95%CI: 0.97-1.16, p=0.21) (Table 8).

$\quad$ *Number of Heart Failure Hospitalizations:* Looking at the total number of HF Hospitalizations, both the Optimism and Pessimism Subscales were found to be marginally significantly predictive of HF hospitalizations in univariate analysis with the Optimism Subscale predicting fewer HF hospitalizations ($F(1,123) = 2.79$, $p = 0.10$, $\beta = -0.15$, $p = 0.10$) and the Pessimism Subscale predicting more HF hospitalizations ($F(1,123) = 3.37$, $p = 0.07$, $\beta = 0.17$, $p = 0.07$). The pattern of results remained unchanged after controlling for medical and demographic covariates (Optimism Subscale: $F(7,110) = 3.25$, $p = 0.004$, change in $R^2 = 0.03$, $\beta = -0.16$, $p = 0.07$; Pessimism Subscale: $F(7,110) = 3.27$, $p = 0.003$, change in $R^2 = 0.03$, $\beta = 0.17$, $p = 0.06$).

$\quad$ *Likelihood of All-Cause Hospitalization:* Logistic regression analyses were used to evaluate whether the LOT Optimism and Pessimism Subscales predicted the likelihood of being hospitalized for any reason during the follow-up period. The LOT Optimism Subscale was not predictive of being hospitalized during follow-up in a univariate model ($\chi^2_{(1)}=0.35$, N=125, Exp(B)=0.97, 95%CI: 0.86-1.08, p=0.55), but the LOT Pessimism Subscale was marginally predictive of greater likelihood of being hospitalized for any reason during follow-up ($\chi^2_{(1)}=0.35$, N=125, Exp(B)=1.10, 95%CI: 0.996-1.21, p=0.059).

Controlling for demographic and medical covariates, the LOT Optimism Subscale was still not significantly predictive of being hospitalized during follow-up ($\chi^2_{(8)}$=29.98, N=118, Exp(B)=0.95, 95%CI: 0.83-1.08, p=0.40), while the LOT Pessimism Subscale was significantly predictive of greater likelihood of being hospitalized ($\chi^2_{(8)}$=34.61, N=118, Exp(B)=1.16, 95%CI: 1.02-1.29, p=0.02). Results of Cox regression analyses indicated that neither the LOT Optimism or Pessimism Subscales were significantly predictive of time to first all-cause hospitalization in univariate (Optimism Subscale: HR=0.96, 95%CI: 0.89-1.05, p=0.40; Pessimism Subscale: HR=1.06, 95%CI: 0.99-1.13, p=0.09) or multivariate models (Optimism Subscale: HR=0.94, 95%CI: 0.87-1.02, p=0.15; Pessimism Subscale: HR=1.05, 95%CI: 0.98-1.12, p=0.20) (See Table 8).

Summary of Results for Specific Aim 1

The hypotheses for Specific Aim 1 were largely confirmed. Dispositional Optimism (LOT Total Score) was predictive of fewer HF symptoms (KCCQ-OS Scores) at baseline and 3 months. LOT Total Scores were also predictive of functional status at baseline as measured by the 6 minute walk test when controlling for demographic and medical covariates, but this relationship was only marginally significant at 3 months. Finally, LOT Total Scores were significantly predictive of fewer total number of HF hospitalizations, but the relationships between continuous LOT Total Scores and the likelihood of HF hospitalization and all cause hospitalization were found to be only marginally statistically significant. Categorizing patients as optimists or pessimists based on a median-split of the LOT Total scores, showed that Optimists were less likely than pessimists to be hospitalized for a heart failure-related or all-cause hospitalization.

Using the Optimism and Pessimism Subscales of the LOT only differentially predicted outcomes in functional status, with the Optimism Subscale predicting greater distance walked, while the Pessimism Subscale did not yield a significant relationship. Neither the Optimism nor Pessimism Subscales were statistically significantly related to hospitalizations of any kind.

Specific Aim 2

The focus of Specific Aim 2 was to determine whether immune/inflammatory markers were related to Dispositional Optimism levels and HF exacerbations. The hypotheses for this specific aim were also broken into two parts. Hypothesis 2a predicted that higher baseline levels of the proinflammatory cytokines C-reactive protein (CRP), Interleukin-6 (IL-6), and Tumor Necrotic Factor-α (TNF-α) would predict greater likelihood of hospitalization, decreased functional status, and HF symptom worsening. It was further predicted that lower levels of the anti-inflammatory cytokine Interleukin-10 (IL-10) would show an inverse relationship to that of the pro-inflammatory cytokines. Hypothesis 2a also predicted that the same pattern of relationships would be seen with the HF outcome variables and 3 month levels of these cytokines. Hypothesis 2b stated that Dispositional Optimism (higher LOT Total scores) would be associated with lower levels of proinflammatory cytokines Interleukin-6 (IL-6), tumor necrotic factor-α (TNF-α), and C-reactive protein (CRP) and higher levels of the anti-inflammatory cytokine Interleukin-10 (IL-10).

Hypothesis 2a

Cytokine Levels and Symptom Status at Baseline and 3 Months

Univariate linear regression models with log-transformed cytokine data revealed no relationship between baseline log-transformed CRP and KCCQ-OS baseline (R^2=.003, $F(1,132) = 0.46$, *p*= 0.50, β = -0.06, *p*= 0.50)or 3 month scores (R^2=.001, $F(1,115) = 0.08$, *p*= 0.80, β = 0.03, *p*= 0.80). LogCRP at 3 months was not related to symptoms at 3 months (KCCQ-OS 3 month; R^2=.003, $F(1,119) = 0.40$, *p*= 0.53, β = -0.06, *p*= 0.53). Controlling for relevant demographic and medical variables did not change the pattern of results[1]. Univariate linear regression analyses did not demonstrate a relationship between baseline logTNF-α levels and KCCQ-OS scores at baseline (R^2=.002, $F(1,132) = 0.29$, *p*= 0.59, β = 0.05, *p*= 0.59) or at 3 months (R^2=.01, $F(1,113) = 1.18$, *p*= 0.28, β = 0.10, *p*= 0.28). LogTNF-α at 3 months was also not related to KCCQ-OS scores at 3 months (R^2<.0001, $F(1,110) = 0.003$, *p*= 0.96, β = -0.01, *p*= 0.96). Multivariate models for logTNF- α did not yield significant results.

A significant univariate relationship was found between logIL-6 and baseline KCCQ scores, such that at baseline higher logIL-6 was related to greater HF symptoms (R^2=.07, $F(1,136) = 10.42$, *p*= 0.002, β = -0.27, *p*= 0.002). This relationship remained significant when controlling for demographic and medical covariates (R^2=.11, $F(7,123) = 2.25$, *p*= 0.04 change in R^2= 0.074, β = -0.28, *p*= 0.002). However neither univariate or multivariate models for logIL-6 at baseline or 3 months were related to KCCQ-OS scores

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[1] Statin use and anti-inflammatory use were initially controlled for in models with the inflammatory cytokines, however neither were found to impact the outcome variables in a meaningful way. The results of the regression analyses controlling for statin and anti-inflammatory use in addition to the demographic and medical covariates (age, ef, creatinine, gender, hypertension, and income) did not differ from the models using just the demographic and medical covariates. Therefore, to conserve statistical power and to keep the covariates consistent with the other analyses presented, results presented for the inflammatory cytokines do not control for statin or anti-inflammatory use.

at 3 months (logIL-6 baseline univariate: R^2=.01, $F(1,115)$ = 1.04, p= 0.31, β = -0.10, p= 0.31; logIL-6 3 month univariate: R^2=.01, $F(1,117)$ = 0.77, p= 0.38, β = -0.08, p= 0.38). Contrary to the hypothesis, univariate and multivariate models for baseline logIL-10 were marginally significantly related to baseline KCCQ-OS, such that higher levels of logIL-10 were predictive of more HF symptoms (univariate: R^2=.03, $F(1,134)$ = 3.79, p= 0.054, β = -0.17, p= 0.054; multivariate: R^2=.07, $F(7,121)$ = 1.42, p= 0.29, change in R^2=0.03 β = -0.17, p= 0.08). No significant relationship was seen in the univariate or multivariate models for logIL-10 at baseline or 3 months and KCCQ-OS scores at 3 months.

Finally the ratio of logTNF- α to logIL-10 was examined as this relationship has previously been shown to be predictive of adverse HF outcomes (Bolger et al., 2002). Only the univariate model of baseline logTNF- α to logIL-10 was significantly related to baseline KCCQ-OS scores, such that larger logTNF- α to logIL-10 ratio was predictive of fewer HF symptoms (R^2=.04, $F(1,132)$ = 4.89, p= 0.03, β = 0.19, p= 0.03). Baseline logTNF- α to logIL-10 ratio was also marginally significantly predictive of 3 month KCCQ-OS scores (R^2=.03, $F(1,113)$ = 3.34, p= 0.07, β = 0.17, p= 0.07). Multivariate models for baseline logTNF- α to logIL-10 ratios were not significantly predictive of either baseline or 3 month KCCQ-OS, and neither were multivariate models for 3 month logTNF- α to logIL-10 ratio and KCCQ-OS 3 month scores (See Table 9).

Cytokine Levels and Functional Status at Baseline and 3 Months

Univariate linear regression models revealed no relationship between baseline logCRP and 6MWT at baseline (R^2=.01, $F(1,120)$ = 1.59, p= 0.21, β = -0.11, p= 0.21) or

3 months (R^2=.002, $F(1,104) = 0.19$, p= 0.66, β = -0.44, p= 0.66). LogCRP at 3 months was not related to symptoms at 3 months (6MWT 3 month; R^2=.01, $F(1,106) = 1.14$, p= 0.29, β = -0.10, p= 0.29). Controlling for relevant demographic and medical variables revealed a significant relationship between baseline logCRP and baseline 6MWT (R^2=.20, $F(7,108) = 3.84$, p= 0.001, change in R^2= 0.03, β = -0.19, p= 0.04), but did not change the pattern of results for the 3 month variables. A significant univariate relationship was found between baseline logTNF-α levels and the 6MWT at baseline (R^2=.12, $F(1,120) = 16.33$, p< 0.001, β = -0.35, p<0.001) and 3 months (R^2=.06, $F(1,100) = 6.23$, p= 0.01, β = -0.24, p= 0.01) such that higher levels of logTNF-α predicted shorter distance walked. LogTNF-α at 3 months was also significantly related to 6MWT at 3 months (R^2=.10, $F(1,100) = 6.04$, p= 0.02, β = -0.24, p= 0.02) . The multivariate models, however, only yielded a significant relationship for baseline logTNF- α and baseline 6MWT (R^2=.20, $F(7,108) = 3.91$, p= 0.001, change in R^2=0.02, β = -0.26, p= 0.01).

Significant relationships were seen in both univariate (R^2=.11, $F(1,122) = 14.62$, p< 0.001, β = -0.33, p< 0.001) and multivariate (R^2=.21, $F(7,110) = 4.13$, p< 0.001, change in R^2=0.05, β = -0.24, p= 0.01) models for baseline logIL-10 and 6MWT, but no significant relationship was found between baseline or 3 month log IL-10 and 3 month 6MWT. When the ratio of logTNF- α to logIL-10 was examined, only the univariate model for 3 month logTNF- α to logIL-10 ratio and 3 month 6MWT was found to be significant (R^2=.04, $F(1,100) = 4.10$, p= 0.05, β = -0.20, p=0.05). The relationship was attenuated to marginal significance when demographic and medical covariates were added to the model (R^2=.23, $F(7,89) = 3.87$, p= 0.001, change in R^2=0.03, β = -0.17, p= 0.08).

The only cytokine found to have a consistent relationship with the 6MWT was logIL-6. Higher levels of logIL-6 were predictive of less distance walked on the 6MWT both cross-sectionally (baseline logIL-6 predicting baseline 6MWT: R^2=.15, $F(1,124)$ = 21.39, $p< 0.001$, β = -0.38, $p<0.001$; 3 month logIL-6 predicting 3 month 6MWT: R^2=.19, $F(1,105)$ = 24.03, $p< 0.001$, β = -0.42, $p<0.001$) and prospectively (baseline logIL-6 predicting 3 month 6MWT: R^2=.10, $F(1,102)$ = 10.59, $p= 0.002$, β = -0.31, $p=0.002$). These relationships remained significant even after controlling for relevant medical and demographic covariates (baseline logIL-6 predicting baseline 6MWT: R^2=.28, $F(7,112)$ = 6.21, $p< 0.001$, change in R^2= 0.13, β = -0.36, $p<0.001$; 3 month logIL-6 predicting 3 month 6MWT: R^2=.32, $F(7,93)$ = 6.31, $p< 0.001$, change in R^2= 0.10, β = -0.33, $p=0.001$; baseline logIL-6 predicting 3 month 6MWT: R^2=.35, $F(7,90)$ = 6.80, $p< 0.001$, change in R^2=0.10, β = -0.29, $p=0.001$) (See Table 9).

Cytokines and Hospitalizations During Study Follow-up

Likelihood of Heart Failure Hospitalization: To examine the relationship between heart failure hospitalizations and levels of cytokines, logistic regression analyses were again conducted (See Table 10). No significant relationship was found between HF-related hospitalization and logIL-10 at baseline or 3 months in either the univariate (baseline: $\chi^2_{(1)}$=0.1, N=137, Exp(B)=1.30, 95%CI: 0.26-6.51, p=0.75) or multivariate models (baseline: $\chi^2_{(8)}$=15.82, N=130, Exp(B)=1.93, 95%CI: 0.28-13.39, p=0.51). Similarly levels of logCRP at baseline and 3 months were not significantly predictive of greater likelihood of hospitalization in univariate (baseline: $\chi^2_{(1)}$=1.40, N=135,

Exp(B)=0.82, 95%CI: 0.41-1.60, p=0.57) or multivariate model (baseline: $\chi^2_{(8)}$=19.67, N=128, Exp(B)=1.74, 95%CI: 0.73-4.12, p=0.21).

Univariate logistic regression models indicated that for both baseline and 3 months levels of logIL-6 (baseline: $\chi^2_{(1)}$=5.32, N=139, Exp(B)=3.08, 95%CI: 1.18-8.10, p=0.02; 3 month: $\chi^2_{(1)}$=3.96, N=120, Exp(B)=3.39, 95%CI: 1.01-11.36, p=0.05), logTNF-α (baseline: $\chi^2_{(1)}$=6.63, N=135, Exp(B)=7.49, 95%CI: 1.46-38.31, p=0.02; 3 month: $\chi^2_{(1)}$=11.10, N=113, Exp(B)=25.37, 95%CI: 3.25-197.84, p=0.002), and the ratio of logTNF-α to log IL-10 (baseline: $\chi^2_{(1)}$=5.84, N=135, Exp(B)=6.76, 95%CI: 1.31-34.99, p=0.02; 3 month: $\chi^2_{(1)}$=4.72, N=113, Exp(B)=7.55, 95%CI: 1.11-51.30, p=0.04) were significantly predictive of greater likelihood of being hospitalized due to HF during the study follow-up period. However, when these relationships were examined in multivariate logistic regressions, only baseline levels of logIL-6 ($\chi^2_{(8)}$=21.52, N=132, Exp(B)=4.04, 95%CI: 1.40-11.69, p=0.01), 3 month logTNF-α ($\chi^2_{(8)}$=24.77, N=107, Exp(B)=11.33, 95%CI: 1.01-126.95, p=0.05) were still significantly predictive baseline levels of TNF-α ($\chi^2_{(8)}$=18.90, N=107, Exp(B)=6.95, 95%CI: 0.93-51.69, p=0.06) were marginally significant and all other models did not reach statistical significance. When these relationships were tested in Cox regression models most of the findings remained unchanged. Differences were seen in the multivariate models for logTNF- α and the ratio of logTNF-α to log IL-10 using Cox regression. Baseline and 3 month logTNF- α (Baseline: HR=6.51, 95%CI: 1.24-34.29, p=0.03; 3 month: HR=6.13, 95%CI: 1.04-36.23, p=0.05) were found to be significantly related to reduced HF hospitalization-free survival, and the ratio of logTNF-α to log IL-10 at baseline (HR=3.87, 95%CI: 0.78-19.30, p=0.10) was marginally significant.

Likelihood of All-Cause Hospitalization: Results of logistic regression analyses indicated that neither baseline ($\chi^2_{(1)}$=0.33, N=135, Exp(B)=0.82, 95%CI: 0.42-1.60, p=0.57) nor 3 month ($\chi^2_{(1)}$=0.05, N=122, Exp(B)=0.92, 95%CI: 0.45-1.89, p=0.82) levels of logCRP were predictive of whether patients were hospitalized for any cause during the study period. These findings reminded unchanged after controlling for relevant covariates. Levels of logIL-10 were not predictive of likelihood of hospitalization in the univariate models (baseline: $\chi^2_{(1)}$=0.01, N=137, Exp(B)=0.94, 95%CI: 0.28-3.88, p=0.93) or multivariate models (baseline: $\chi^2_{(8)}$=22.21, N=130, Exp(B)=2.70, 95%CI: 0.47-15.56, p=0.27).

Univariate and multivariate logistic regression models showed marginally significant or significant prediction of being hospitalized by baseline levels of logIL-6 (univariate: $\chi^2_{(1)}$=3.44, N=139, Exp(B)=2.26, 95%CI: 0.94-5.43, p=0.07; multivariate: $\chi^2_{(8)}$=26.52, N=132, Exp(B)=3.57, 95%CI: 1.28-10.01, p=0.02), baseline levels of logTNF-α (univariate: $\chi^2_{(1)}$=4.94, N=135, Exp(B)=4.30, 95%CI: 1.11-16.73, p=0.04; multivariate: $\chi^2_{(8)}$=31.83, N=128, Exp(B)=14.13, 95%CI: 2.40-83.32, p=0.003), and the ratio of logTNF-α to log IL-10 at baseline (univariate: $\chi^2_{(1)}$=6.17, N=135, Exp(B)=5.39, 95%CI: 1.30-22.36, p=0.02; multivariate: $\chi^2_{(8)}$=26.70, N=128, Exp(B)=5.64, 95%CI: 1.10-28.96, p=0.04). These results indicated that higher levels of logIL-6, logTNF- α, and a higher ratio of logTNF-α to log IL-10, increased the likelihood of all-cause hospitalization during the study and follow-up period (See Table 10). The results from the Cox regression analyses mirrored the results of the logistic regressions with one exception, univariate baseline logIL-6 (HR=2.29, 95%CI: 1.23-4.27, p=0.01) went from

marginal significance to statistical significance, such that higher levels of IL-6 at baseline were significantly related to reduced hospitalization-free survival.

Hypothesis 2b

Dispositional Optimism and Cytokine Levels at Baseline and 3 months

To evaluate the relationship between Dispositional Optimism and levels of cytokines at baseline and 3 months a series of linear regressions were run. In both the univariate and multivariate models, LOT Total scores were not related to baseline or 3 month levels of any of the cytokines (Table 11). No significant univariate or multivariate relationships were found with any of the cytokines when the LOT was broken into Optimism and Pessimism Subscales (See Table 12 for summary of regression models).

Summary of Results for Specific Aim 2

Dispositional Optimism was not related to baseline or 3 month levels of CRP, IL-6, IL-10, TNF-α or the ratio of TNF-α to IL-10. The relationship between cytokines and symptoms, functional status, and hospitalizations is complex. No consistent significant relationships were found between 3 month levels of any of the cytokine and the outcome variables. Baseline levels of IL-6 were predictive of symptoms, functional status and hospitalizations. Baseline TNF-α and IL-10 were predictive of functional status (6MWT) but not symptoms. Baseline TNF-α was related to all-cause hospitalizations and HF hospitalizations in univariate models, but only all-cause hospitalizations in the multivariate model. Neither CRP nor the ratio of TNF-α to IL-10 demonstrated any

consistent relationship to the outcome variables. Only baseline levels of IL-6 were consistently predictive of all the heart failure outcomes tested.

Specific Aim 3

The focus of the third Specific Aim was to determine if the relationship between Optimism and HF exacerbations were partially mediated by inflammatory cytokines in HF patients. Two hypotheses were put forth regarding this relationship: Hypothesis 3a stated that levels of inflammatory cytokines would partially mediate the relationship between Optimism and HF worsening such that higher LOT Total scores would be associated with lower levels of proinflammatory cytokines, and that lower levels of these cytokines, would, in turn predict fewer hospitalizations, better functional status, and fewer HF symptoms (mediation model outlined Figure 1). Hypothesis 3b stated that the meditational relationship would hold true for the Optimism Subscale and not the Pessimism Subscale of the LOT (mediation model outlined in Figure 2).

Hypothesis 3a

Cytokine Levels Mediating the Relationship Between Optimism and HF Outcomes

In order to evaluate whether or not a variable is acting as a mediator between the independent variable (in this case, LOT Total Scores) and the dependent variable (KCCQ-OS, 6MWT, and likelihood of hospitalizations) certain criteria must be met. According to Baron and Kenny (1986), (1) the independent variable must predict the dependent variable; (2) the independent variable must predict the mediator variable; (3) the mediator variable must predict the dependent variable (while controlling for the independent variable), and (4) the independent variable cannot predict the dependent

variable when controlling for the mediator variable (although for partial mediating this particular criterion does not have to be satisfied). The findings outlined under hypothesis 1a, show that the first criterion was satisfied: LOT Total Scores predicted KCCQ-OS score, 6MWT distance, and hospitalizations (number of HF hospitalization and likelihood of all-cause and HF hospitalizations when LOT Total scores were dichotomized). However, the second criterion was not met, as LOT Total Score did not predict any of the cytokines at either baseline or 3 months (results presented under hypothesis 2b). Therefore no test of mediation was performed, as the criteria for cytokine mediation were not fully met.

Hypothesis 3b

Cytokine Levels Mediating the Relationship Between Optimism and Pessimism Subscales and HF Outcomes

The requirements for mediation were described in the previous paragraph. Since the Optimism Subscale was only predictive of the 6MWT at baseline and 3 months, and the KCCQ-OS at baseline, criterion 1 was only satisfied for these 3 models. However, as with the LOT Total score, the LOT Optimism Subscale was not predictive of any of the cytokine measures and therefore the second criterion for mediation was not satisfied. Similarly, the LOT Pessimism Subscale was only predictive of the KCCQ-OS (satisfying criterion 1 for this outcome measure), but did not predicted any of the cytokines (failing to fulfill criterion 2). Therefore, cytokines were not found to mediate the relationship between Optimism or Pessimism Subscales and HF outcomes.

Summary of Results for Specific Aim 3

The Sobel Test for cytokine mediation in the relationship between Optimism and HF Outcomes was not conducted as the criteria for mediation was not met (Baron and Kenny, 1986). No evidence was found relating Optimism to levels of inflammatory cytokines at either baseline or 3 months. Levels of CRP, IL-6, IL-10, and TNF-α did not mediate the relationship between Optimism and the HF outcomes of self-reported symptoms, functional status, or likelihood of hospitalizations in this sample.

Specific Aim 4

The focus of the fourth and final specific aim was to determine if the relationship between Dispositional Optimism and HF exacerbation was independent of other psychosocial variables. Hypothesis 4 stated that the relationship between Optimism and symptoms, functional status, and hospitalizations would remain significant when controlling for depressive symptoms (Beck Depression Inventory; BDI), positive and negative affect (Positive and Negative Affect Scale; PANAS), and Problem and Emotion Focused Coping Styles.

Hypothesis 4
Optimism, Symptom, and Functional Status Controlling for Psychosocial Variables

To determine whether the effects of Optimism on HF symptoms (KCCQ-OS) and functional status (6MWT) were independent of other psychosocial variables, an additional step was added to the covariate adjusted linear regression models reported in Specific Aim 1. Results indicated that, although the effect was attenuated, greater LOT Total Scores were still predictive of fewer HF symptoms at baseline (Model R^2=0.47,

$F(12,102) = 7.54$, $p < 0.001$, $\beta = 0.17$, $p = 0.05$). However LOT Total score was no longer predictive of HF symptoms at 3 months (Model $R^2 = 0.36$, $F(12,106) = 4.67$, $p < 0.001$, $\beta = 0.02$, $p = 0.83$). In both the baseline and 3 month models, greater baseline BDI scores were significantly predictive of more HF symptoms ($\beta = -0.34$, $p = 0.002$, and $\beta = -0.59$, $p < 0.001$, respectively).

In the final model for functional status, LOT Total scores were not significantly predictive of total distance walked on the 6MWT at baseline (Model $R^2 = 0.34$, $F(12,91) = 3.82$, $p < 0.001$, $\beta = 0.07$, $p = 0.53$) or at 3 months(Model $R^2 = 0.38$, $F(12,86) = 4.30$, $p < 0.001$, $\beta = 0.04$, $p = 0.71$). In the second step of the model, greater Problem Focused Coping was significantly predictive of baseline 6MWT ($\beta = 0.24$, $p = 0.03$, but not after the final step was added). Only Positive Affect was significantly predictive of greater distance walked at baseline ($\beta = 0.22$, $p = 0.03$) and 3 months ($\beta = 0.24$, $p = 0.03$) in the full model (reference Model 3 in Table 6).

Each of these models was rerun using the LOT Optimism and Pessimism Subscales in the final to evaluate whether these subscales differentially predicted the outcomes. When controlling for psychosocial covariates, neither Optimism Subscale scores nor Pessimism Subscale scores were predictive of KCCQ-OS at baseline (Optimism Subscale: $\beta = 0.15$, $p = 0.08$; Pessimism Subscale: $\beta = -0.12$, $p = 0.18$) or at 3 months (Optimism Subscale: $\beta = 0.06$, $p = 0.54$; Pessimism Subscale: $\beta = 0.02$, $p = 0.85$). Similarly, neither the Optimism or Pessimism Subscale scores were predictive of 6MWT at baseline (Optimism Subscale: $\beta = 0.06$, $p = 0.54$; Pessimism Subscale: $\beta = -0.04$, $p = 0.73$) or 3 months (Optimism Subscale: $\beta = 0.05$, $p = 0.63$; Pessimism Subscale: $\beta = -0.01$, $p = 0.90$) in the final model.

Optimism and Hospitalizations Controlling for Psychosocial Variables

The logistic and Cox regression models reported for Specific Aim 1 were rerun in the same manner, adding the block of psychosocial covariates in the second step.

Likelihood of Heart Failure Hospitalization: In the final logistic regression model for HF-related hospitalizations, the continuous LOT Total score was not a significant predictor(Exp(B)=0.95, 95%CI: 0.85-1.05, p=0.30). Emotion Focused Coping (Exp(B)=1.23, 95%CI: 1.02-1.48, p=0.03) was significantly predictive of greater likelihood of HF hospitalization in the second step of the model (before LOT Total scores were added). In the full model (after adding LOT Total scores), greater BDI score ($\chi^2_{(13)}$=30.08, N=115, Exp(B)=0.89, 95%CI: 0.82-0.98, p=0.01) and Problem Focused Coping (Exp(B)=0.78, 95%CI: 0.62-0.98, p=0.03) were significantly predictive of reduced likelihood of HF-related hospitalizations. LOT Total scores were also not significant in the Cox regression model (HR=0.95, 95%CI: 0.88-1.02, p=0.16), although BDI scores BDI (HR=0.92, 95%CI: 0.86-0.98, p=0.01) were significantly predictive of reduced HF hospitalization-free survival.

When patients were categorized as either optimists or pessimists using the median-split of LOT Total scores, Cox regression analyses showed that optimists were 50% less likely than pessimists to be hospitalized for a heart failure-related incident independent of other psychosocial factors (HR=0.50, 95%CI: 0.23-1.09; p=0.08). Although this Optimism was only marginally statistically significant, the magnitude of the relationship was only slightly attenuated from the demographic and medical covariate adjusted model (See Table 7).

Number of Heart Failure Hospitalizations: The block of psychosocial variables was added to the linear regression model assessing the relationship between number of HF hospitalizations and LOT Total scores. When the psychosocial variables were added, continuous LOT Total score was no longer significantly predictive of the number of HF Hospitalizations during follow-up (Model R^2=0.22, $F(13,101) = 2.24$, p=0.01, β = -.16, p= 0.15), none of the psychosocial variables were predictive number of HF Hospitalization in the full model. However, when the dichotomized LOT Total Score was used in the full model, optimists had significantly fewer heart failure hospitalizations than pessimism, independent of the psychosocial models (Model R^2=0.27, change in R^2=0.03, p=0.05, $F(13, 101)$ =2.41, p=0.007; β = -0.20, p= 0.05) (See Table 7).

Likelihood of All-Cause Hospitalization: In the logistic regression model, neither the continuous LOT Total scores ($\chi^2_{(13)}$=35.32, N=115, Exp(B)=0.93, 95%CI: 0.84-1.03, p=0.15) nor any of the psychosocial variables were significantly predictive of all-cause hospitalizations. However, in the second step of the model (before LOT Total Scores were added), greater Problem Focused Coping (Exp(B)=0.83, 95%CI: 0.68-1.00, p=0.05) was predictive of reduced likelihood of all-cause hospitalization, and Negative Affect was predictive of increased likelihood of all-cause hospitalizations (Exp(B)=1.05, 95%CI: 1.00-1.10, p=0.05) . In the Cox regression models Negative Affect (HR=1.05, 95%CI: 0.97-1.10, p=0.05) was predictive of reduced all-cause hospitalization survival and Problem Focused Coping (HR=0.89, 95%CI: 0.80-0.99, p=0.04) was predictive of higher all-cause hospitalization-free survival, however when LOT Total Score was added as the final step, only the BDI (HR=0.96, 95%CI: 0.91-1.00, p=0.05) was significantly predictive of reduced all-cause hospitalization-free survival.

When the dichotomized LOT Total score variable was used in the full model instead of LOT Total continuous scores, both logistic and Cox regression analyses showed that optimists were 49% less likely than pessimists to be hospitalized independent of other psychosocial factors (HR=0.51, 95%CI: 0.28-0.92; p=0.03) (See Table 7).

Optimism and Pessimism Subscales and Hospitalizations: The Optimism and Pessimism Subscales were not significantly predictive of all-cause, HF, or number of HF hospitalizations, when the analyses were run with the psychosocial variable block (substituting either the Optimism or Pessimism Subscale for the LOT Total score in the final step) in the Cox and linear regression models. In the logistic regression model for all-cause hospitalization, the Pessimism subscale was significantly predictive of greater likelihood of all-cause hospitalization (Exp(B)==1.18, 95%CI: 1.01-1.37, p=0.03).

Summary of Results for Specific Aim 4

When BDI scores, Positive and Negative Affect scores, and Problem Focused and Emotion Focused Coping scores were added to the regression models evaluating the relationship between Optimism and HF symptoms, functional status, and hospitalizations, Optimism (continuous LOT Total score) was only significantly predictive of baseline symptoms (KCCQ-OS). Across all the heart failure outcome variables there was no consistent pattern in the relationship of the additional psychosocial variables (See Table 6). The relationship between continuous LOT Total score and HF outcomes was not found to be independent of other psychosocial variables. However, when patients were categorized as either optimists or pessimists using a median-split of the LOT Total scores, Cox regression analyses found that optimists had higher hospital-free survival than

pessimist (all-cause hospitalizations). Linear regression analyses revealed that optimists had fewer heart failure-related hospitalizations then pessimists, independent of the additional psychosocial variables (See Table 7).

Additional Analyses

In light of the findings described in the previous section, some additional exploratory analyses were conducted. Because no relationship was seen with the inflammatory cytokines and Optimism, possible behavioral mediators for the relationship between Optimism and heart failure outcomes were explored. Dietary compliance (adapted from the Dietary Compliance Survey (Sneed & Paul, 2003)), medication adherence (taken from the Brief Medication Questionnaire (Svarstad, Chewning, Sleath, & Claesson, 1999)), and physical activity level over a 30 day period (measured using a one-item Likert-type question on amount of physical activity over the previous 30 days) were assessed in the BETRHEART Study. LOT Total scores were not significantly correlated with any of these health behavior measures (Dietary Compliance: r =-0.01, p=0.95; Medication Compliance: r= -0.13, p=0.18; Physical Activity: r=-0.08, p=0.39). The relationship between Optimism and baseline and 3 month levels of B-type Naturetic Peptide (BNP) was also assessed. BNP is released in response to wall stretch in the ventricles and is related to vascular remodeling and poor outcomes in heart failure patients. Optimism was not significantly related to levels of BNP at either time-point (baseline: r=0.2, p=0.84; 3 month: r=0.03, p=0.75).

Finally, the combined endpoint of HF related hospitalization and death was examined using Cox regression modeling. Adjusting for demographic and medical

covariates, continuous LOT Total scores were significantly predictive of greater even-free survival (HR=0.94, 95%CI: 0.89-0.99, p=0.03). Dichotomized LOT Total scores were marginally significant (HR=0.56, 95%CI: 0.30-1.06, p=0.07), while the Optimism Subscale was significantly predictive of greater event-free survival (HR=0.89, 95%CI: 0.81-0.98, p=0.02). In the final model adjusting for demographic and disease covariates as well as the other psychological variables, Cox regression analyses showed that continuous LOT Total scores (HR=0.94, 95%CI: 0.88-1.01, p=0.09), dichotomized LOT Total Scores (HR=0.59, 95%CI: 0.29-1.17, p=0.13), and LOT Optimism Subscales scores (HR=0.89, 95%CI: 0.79-1.01, p=0.06) were marginally associated with greater event-free survival.

Discussion

Summary and Study Findings

Relatively few studies have explored the relationship between Optimism and positive health outcomes in patients with heart failure (see Table 2). The present study found that Optimism, as measured by the LOT Total score, was related to fewer heart failure symptoms, better functional status at both baseline and 3 months, and fewer total number of heart failure related hospitalizations. Optimism significantly predicted better outcomes even while controlling for relevant medical and demographic factors. Optimism when dichotomized using a median-split was also related to decreased likelihood of being hospitalized in general and for a heart failure related event (See Figure 5).

Another goal of this study was to examine the construct of Optimism in relation to heart failure outcomes. Specifically, it is unclear as to whether Optimism and Pessimism exist on opposite ends of the same spectrum, representing one construct, or if they operate separately as two distinct but related constructs. The present study found that when looking at Optimism and Pessimism as two distinct constructs by using the LOT Optimism and Pessimism Subscales, the predictive relationships to heart failure outcomes were less consistent, and there were differences in predictive ability in the same outcome measures between the Optimism and Pessimism Subscales. These findings might suggest that Optimism and Pessimism exist as two distinct constructs. However the greater consistency seen when using the LOT Total score indicates that Optimism/Pessimism as a single construct may be more useful in HF patients.

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Additionally the present study evaluated Optimism in light of other potentially relevant psychosocial variables. After controlling for baseline depressive symptoms, positive and negative affect, and emotion and problem focused coping styles, Optimism was only significantly associated with baseline HF symptoms. However the dichotomized Optimism score was still significantly predictive of fewer numbers of HF-hospitalizations and increased all-cause hospitalization-free survival when the psychosocial variables were added. Lastly, this study sought to evaluate levels of inflammatory cytokine as a possible mechanism through which Optimism may be operating. No evidence of such a mediational relationship was found in this study, thereby suggesting that Optimism does not influence HF outcomes via inflammatory pathways.

Optimism and Heart Failure Outcomes

Symptoms

Hypothesis 1a (that optimists would have improved heart failure outcomes) was generally supported by the data. When demographic and medical variables that could influence symptom reporting or symptom perceptions were accounted for, more optimistic individuals still reported fewer overall HF-related symptoms than their more pessimistic counterparts. This relationship was independent of left ventricular ejection fraction which served as a measure of heart failure severity in this study. The relationship with Optimism and HF symptoms was seen both at baseline and 3 months, which suggests that Optimism may exert an influence over future symptom severity, and not just present symptom status. The meta-analysis published by Rasmussen and colleagues in (2009), clearly showed that Optimism was associated both cross-sectionally and prospectively to improved cardiovascular outcomes. The present study findings not only

support the current literature, but also illustrate that the health benefits associated with

Optimism are present in a heart failure population, which represent a unique and more

severe subset of cardiovascular diseases.

It has been suggested that optimists may report fewer symptoms due to a

perception or recall bias (Hamid, 1990). Since Dispositional Optimism is characterized

by the expectation of good rather than bad events happening in one's life; optimists may

be predisposed to paying attention to the good rather than the bad. This may mean that

optimists minimize the amount of symptoms they experience or that they focus on the

things that they can do, rather than their limitations. In terms of a recall bias, because

optimists are primed to see the good in things (Segerstrom, 2001a), it may be harder for

them to recall the negative symptoms or limitations they have experienced in relation to

their disease. However, at least one study has shown that in chronically ill patients,

Optimism was not associated with a biased interpretation of their health status (de Ridder,

Fournier, & Bensing, 2004). Optimistic patients with insulin dependent diabetes mellitus

reported less fatigue, less unstable blood glucose (self report), and better physical

functioning at 6 month follow-up. Optimism had no relationship with hemoglobin A1c

levels (an objective measure of blood glucose levels over time) or duration of illness.

This pattern is replicated in the present study, as Optimism predicted symptoms

independently of the medical covariates. This study adds support to the evidence that

optimistic individuals are not simply attending away from or ignoring physical symptoms.

Symptoms and Other Psychosocial Variables
It should be noted that when depressive symptoms were added to the model, the

relationship between Optimism and HF symptoms as measured by the KCCQ-OS

disappeared. This is particularly interesting in light of the previous discussion of attention and recall bias. Simply stated, just as being happy makes it harder to recall bad feelings and events, being sad makes it harder to recall good feelings and events. In fact, in the study by de Ridder and colleagues (2004) mentioned above, Negative Affect was found to mediate the relationship between Optimism and symptom reporting. This is in line with a large body of research showing that negative affectivity increases perception of physical sensations and often leads to the recall and interpretation of health status being worse than it would be, if measured objectively (Feldman, Cohen, Doyle, Skoner, & Gwaltney Jr, 1999; Larsen, 1992; Watson & Pennebaker, 1991).Similarly, there is a large body of literature linking depression to a variety of deleterious outcomes in cardiovascular disease in general and among heart failure patients (Rutledge, Reis, Linke, Greenberg, & Mills, 2006), it is therefore not surprising that this study found a strong relationship between depression and HF symptoms at both baseline and 3 months. However Optimism seemed to have no effect on symptom reporting when depression was added to the model (See Table 6). This is probably due to the fact that in these patients depression is a more powerful predictor of symptoms than Optimism. The Optimism construct and depression are not mutually exclusive, and it may be that depression is moderating the relationship seen between Optimism and HF symptoms. This would not be inconsistent with previous literature.

Other possible explanations for this particular finding should also be considered. For instance, given that all of the psychosocial variables were at least moderately correlated with one another, the addition of all of them to the model may have lead to model instability due to problems with multicollinearity. However, the Variance Inflation

Factors for the psychological variables entered into the final step of the regression models ranged from 1.44 to 2.24, which would seem to indicate that multicollinearity is not an issue in these models. It is also possible that the study is under -powered to detect the effect sizes of the psychosocial variables that were observed in this particular sample. These limitations will be discussed in greater detail later in the Discussion. With these limitations in mind, the findings in present study would suggest that the subjective nature of self-reported symptoms are influenced more by negative emotions and depressive symptoms, than by positive affect or Optimism.

Functional Status

It is particularly interesting that, in addition to symptoms, Optimism also predicted greater distance walked on the 6 Minute Walk Test at baseline. One could argue that the 6MWT, in addition to being an assessment of functional status, is a more objective measure of symptoms than the KCCQ-OS, because if a patient were experiencing particularly severe HF symptoms he or she would have a very difficult time completing the 6MWT. Although differences in disease severity cannot be completely ruled out, the fact that Optimism predicted greater distance walked on the 6MWT illustrates a relationship with better overall functional status in optimistic heart failure patients. The 6 minute walk test may also be thought of as a measure of motivation, effort, or even mood, and Optimism predicting greater distance walked may be an artifact of an individual being less depressed, in a better mood, or simply more engaged in the test. Carver and Scheier suggest that Optimism may be working through behavior self-

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regulation, and cite that an optimistic attitude about one's health may result in continued engagement in health promoting or health protective behaviors(Carver & Scheier, 2001).

Although there was no way to objectively measure effort on the part of the patient during the 6 minute walk test, a vast majority of patients appeared to be engaged in the test and exerting themselves in a manner consistent with reasonable effort to complete the task at hand. The data seem to indicate that patients in a positive mood (PANAS Positive Mood Score) and patients using more Problem-Focused coping (usually associated with more active coping styles) did walk greater distances on the test. Interestingly, there was no significant association between the 6MWT and depressive symptoms (baseline BDI scores) or negative mood (PANAS Negative Mood Score), suggesting that it was not the presence or absence of negative emotions affecting the distance walked on the test. Positive mood and Problem-Focused coping were both positively correlated with Optimism, indicating that these positive psychology constructs, and not negative emotions, are driving the relationship with functional status. In fact, Positive Affect was found to be predictive of greater distance walked at both baseline and 3 months independent of all other variables. This particular finding would support the idea that a patient's positive mood may in fact influence his/her performance on assessments of functional status.

These results should not overshadow the finding that Optimism was able to predict distance walked when disease-related and medical covariates were accounted for at baseline, and trended towards significance at 3 months. Despite their disease status, optimists may believe that they are better able to perform daily life task (such as walking) because of their general positive expectancies. This belief in turn may then translate into

persisting at tasks longer (as has been shown in previous research (Segerstrom, 2005; Sieber et al., 1992)), and in this case actually walking greater distances. Even if the relationship between functional status and Optimism is not causally direct, the association of Optimism with better functional status may result in an improved functional status overtime, as heart failure patients who continue to remain active tend to have better outcomes than those who are not active (Belardinelli, Georgiou, Cianci, & Purcaro, 1999). The trend towards significance at 3 months is most likely explained by a decrease in sample size and the resulting loss of power to detect a statistically significant relationship, and perhaps not a lack of a prospective relationship between Optimism and functional status.

The Relationship Between Symptoms and Functional Status

It was not terribly surprising to see the modest correlations between the different heart failure outcomes. In fact, one of the reasons that three different domains of heart failure outcomes were evaluated was due to the differences in subjective and objective measure of disease and symptom severity (Baker, Stabile, & Deri, 2001; Juenger et al., 2002). The correlation between baseline and 3 month symptoms was reasonably high (although these patients appeared to be improving over the study duration) as was the correlation between baseline and 3 month distance walked, however the magnitude of the correlations between symptoms and distance walked were much lower. In fact they appeared to correlated no more strongly with one another than either of them correlated with Optimism. This finding could suggest that these measures of symptoms and functional status are also tapping into some underlying dimensions associated with psychosocial constructs. It also highlights the need to further investigate how these

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different aspects of heart failure related to each other, and suggests that psychosocial factors may play a substantial role in these two widely used measures how heart failure symptom and functional status.

Hospitalizations

The hypotheses regarding Optimism and hospitalizations were partially confirmed. Optimism using both the continuous LOT Total score and a dichotomized median-split variable were used in the hospitalization analyses which consisted of: likelihood and time to all-cause and HF Hospitalizations (examined using examined using logistic and Cox regression modeling) and total number of heart failure-related hospitalizations (examined through linear regression modeling). A clear relationship existed between Optimism and the number of times a patient was hospitalized for a heart failure-related incident during the follow-up time frame. Although it was hypothesized in this study that Optimism was related to a decreased number of HF hospitalizations over time, the mechanisms through which Optimism is operating remain unclear. There was no evidence that Optimism was operating through inflammatory pathways as had been hypothesized. It is possible that Optimism is working through different biological pathways not tested in the present study. Or Optimism could be operating through behavioral pathways. For example previous literature demonstrates that optimists engage in more health protective behaviors (Giltay, et al., 2007; Shepperd, Maroto, & Pbert, 1996), which could lead to fewer HF exacerbations and subsequently fewer total HF-related hospitalizations as was seen in this sample.

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Also of note, the demographic and medical variables tested, only creatinine was significantly predictive of whether or not patients had a HF-related hospitalizations. This suggests that Optimism was a better predictor of number of HF hospitalizations in this sample than, age, gender, baseline ejection fraction, or hypertension.

It is important to note that length of follow-up time was controlled for in these analyses. Greater length of follow-up time was significantly predictive of more HF hospitalizations, and it is possible that when all participants have completed the 3 year follow-up period for the BETRHEART Study that the results may differ. However, length of time in the study was a less potent predictor of HF hospitalizations than Optimism. With repeated hospitalizations being one of the hallmarks of the heart failure syndrome, demonstrating that Optimism is related to fewer HF hospitalizations highlights a possible area of psychosocial intervention to improve patient quality of life and decrease the financial burden associated with repeated hospitalizations. While Optimism is considered to be a stable trait over time, changes are possible (Segerstrom, 2007). Currently there are no specific "Optimism Interventions", but a few studies using multi-modal psychological interventions have been able to increase Optimism or a decrease in Pessimism (Carver, et al., 2010).

Continuous LOT scores versus the median-split
Optimism, when measured as a continuous variable, was not significantly associated with likelihood of being hospitalized for an HF-related event, nor was it significantly related to all-cause hospitalization in the study, however it was significantly predictive of greater event-free survival of the combined outcome of HF hospitalization and death. There was a trend toward a decreased likelihood of HF and all-cause

hospitalization for patients with higher Optimism levels (*p's* < 0.10). This same pattern was seen in the time to event models, showing that over time, Optimism was associated with increased likelihood of hospital-free survival (*p's* < 0.10), and taken in combination with the significant findings for total number of heart failure related hospitalizations, a pattern seems to emerge. Using a median-split to categorize patients as either optimists or pessimists revealed that optimists were significantly less likely to be hospitalized for both HF-related and all-cause hospitalizations, independent of medical and disease covariates. Furthermore the reduced likelihood of all-cause hospitalization (p<0.05) and a trend towards reduced HF-related hospitalization (p<0.10) remained even after controlling of other psychosocial factors. Using the dichotomized variable optimists also had significantly fewer heart failure related hospitalizations than pessimists in the fully adjusted model; further suggesting that the effect of Optimism on the number HF-related hospitalizations is independent of other depressive symptoms, negative affect, and coping styles.

Splitting patients into two groups using the LOT Total score seems to be capitalizing on some underlying difference in the data. Seeing a significant relationship with the dichotomized variable and not the continuous scores may be a statistical artifact. However when plotting the predicted probabilities of the continuous LOT Total score against number of hospitalizations, a slight chance in the slope of the line is seen around the mean/median of the LOT Total scores. In fact, when linear, quadratic, and cubic fit lines are applied to the scatter plot of HF related hospitalizations and LOT Total scores the linear model has the poorest fit (Figure 6). Therefore splitting the sample into

optimists and pessimists at the median may actually be highlighting an underlying

relationship between Optimism and all-cause and HF-related hospitalization.

Alternative explanations as to why continuous LOT Total scores did not reach

statistical significance in the HF and all-cause hospitalization models and why the

significant relationship seen with the dichotomized LOT Total score variable and HF-

related hospitalizations was attenuated when the psychosocial variables were add to the

final model, needs to be explored further. Perhaps, the study population was simply too

sick to have the likelihood of being hospitalized strongly influenced by a psychosocial

factor such as Optimism. At some point in the disease process, it seems unlikely that an

optimistic outlook would be able to over-ride the pathophysiological mechanisms of heart

failure. When dealing with a heart failure population, the protective benefits of Optimism

may act more strongly on the frequency of hospitalization. In other words, most heart

failure patients will be hospitalized at some point during the course of their illness, but

optimistic heart failure patients will be hospitalized less often. Of course the lack of a

statistically significant relationship between Optimism and likelihood of HF

hospitalizations might also be due to the small number of HF hospitalizations seen. Only

35 patients (28%) experienced a HF-related hospitalization. While a total of 59 patients

were hospitalized during the study (reflecting all-cause hospitalizations, with that number

including the 35 HF-related hospitalizations), it is possible that the effect of Optimism is

simply not strong enough to be seen in this number of patients or with this number of

events.

The combined endpoint of HF hospitalization and death support the general

conclusion that Optimism is protective against this deleterious outcome. When

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controlling for demographic and medical covariates both the continuous LOT Total score and the Optimism Subscale predicted greater event-free survival. Although the relationship was attenuated when the block of psychological variables were added to the model, these findings suggest that Optimism and not a lack of Pessimism is associated with decreased risk of the combined heart failure hospitalization and death endpoint. Despite the overall pattern of results for the combined endpoint looking similar to those for all-cause and HF-related hospitalizations, there are some subtle differences. In the combined endpoint the dichotomized LOT Total score is not significant while the continuous LOT Total score and the Optimism Subscale are. Including deaths in this endpoint increases the number of events to 43 up from just 35 HF-related hospitalizations, which does increase the statistical power in the Cox regression analyses, and may explain why the relationships that were marginally significant in the HF hospitalization endpoint are now statistically significant in the combined endpoint. It could also suggest that the nature of the relationship between Optimism and HF-related hospitalization and all-cause mortality are inherently different. Perhaps higher levels of Optimism alone (and not simply a lack of Pessimism) are enough to increase survival time in heart failure patients. Unfortunately the limited number of deaths observed in this study makes it impossible to further explore these differences at present, but may be able to be addressed as more deaths are recorded in the larger BETRHEART Study.

Hospitalizations and Other Psychosocial Variables

Taking a closer look at the variables in the psychosocial block and hospitalizations revealed some interesting findings. In both HF and all-cause hospitalization Cox regression models, Problem-Focused Coping was associated with a

higher hospitalization-free survive before Optimism was added to the model. In this study, Problem Focused Coping encompassed a range of coping styles including, Active Coping, Positive Reframing, Planning, and Use of Instrumental Support. These coping strategies reflect more active approaches to dealing with stressors. Previous research suggests that optimists may utilize more Problem-Focused Coping Styles (Dunbar, et al., 1996; Scheier, et al., 1986), and Problem Focused Coping was positively correlated with Optimism in this sample. Perhaps HF patients who use more Problem Focused Coping Styles are more likely to be adherent to their medical treatments. They also could be less likely to use denial in dealing with their heart failure diagnosis, which could lead to a decrease in hospitalizations. This might suggest that Problem Focus Coping Styles operate through behavioral pathways, the same type of behavioral pathways that Optimism may be operating through.

One of the aspects of this set of analyses that is particularly difficult to explain is the inverse relationship found for baseline depressive symptoms. Depression is widely accepted as a cardiovascular disease risk factor, conferring increased risk of adverse outcomes (Van der Kooy et al., 2007). However, in this study it would appear that depression is actually related to a decreased likelihood of hospitalization for any reason, including for heart failure. It is possible that these findings could be attributed to a statistical artifact or to Type I error, especially considering the number of analyses performed in this study. However, this explanation does not seem sufficient considering that even when not statistically significant the nature of the relationship with depression was consistently in the same (inverse) direction. Rerunning the models with BDI scores dichotomized at 10 (a cut point found to be relevant in clinical research (Frasure-Smith et

al., 2000; Rutledge et al., 2009)), still showed an inverse relationship, although it did not reach statistical significance. Furthermore, depression was found to be associated with greater symptom burden, negatively correlated with Optimism, and positively correlated with Negative Affect (all as expected). And at least in the Cox regression models for all-cause hospitalization, Negative Affect (PANAS Negative Mood) was associated with reduced hospitalization-free survival before Optimism was entered into the model. BDI scores were not significantly associated with all-cause or HF-related hospitalizations in univariate or disease covariate models, but the odds ratios associate with BDI scores were in the expected direction (i.e., $OR > 1.0$). This could indicated that one of the other psychosocial variables in the model could be influencing the relationship with depression and hospitalizations.

Taking all of these aspects into account, another explanation for the inverse relationship found with BDI and hospitalizations (likelihood of both all-cause and HF-related) that seems plausible is that, in this sample, BDI scores are highlighting a lack of medical attention seeking among depressed heart failure patients. It is also well documented in the literature that depressed individuals are less likely to take care of themselves, often neglecting to take medications, follow treatment regimes, or engage in positive health behaviors(Allgöwer, Wardle, & Steptoe, 2001; Frederick, Frerichs, & Clark, 1988). Depression is also a risk factor for medical noncompliance (Carney, Freedland, Eisen, Rich, & Jaffe, 1995; DiMatteo, Lepper, & Croghan, 2000). This line of reasoning could be extended such that these depressed individuals are less likely to seek medical attention (i.e., go to the hospital) even if they are experiencing greater symptoms. This could explain why depression predicted greater symptom burden on the KCCQ and

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also predicted a decreased likelihood of hospitalizations in this study. However, it the relationship seen with depressive symptoms and hospitalization outcomes should be interpreted with extreme caution as it is most likely a statistical artifact.

The interpretation of the final models with the block of psychological variables can be conceptually difficult depending on the theoretical approach used to guide one's understanding of the results. It could be argued that these models "over-control" for the effects associated with Optimism, and make it more difficult to understand the true nature of the relationship between these heart failure outcomes and Optimism. A strict interpretation of the final model would suggest that the effects of Optimism on the outcome variable are with all other psychological variables in the model being held constant. This is probably not an accurate to assume that levels of depression, affect and coping strategies can all be held constant with regard to one another and in relation to Optimism and the heart failure outcome being evaluated. However, interpreting these models from a more epidemiological approach helps to evaluate the independence of Optimism from these other psychological constructs, and that was one of the larger goals of the present study. Future studies ought to reduce the number of psychological covariates included in the regression models and should also explore how these other psychological variables may interact or moderate the relationship between Optimism and heart failure outcomes.

Inflammatory Cytokines

Cytokines and Heart Failure Outcomes

Hypotheses 2a and 2b were largely disconfirmed. It had been hypothesized that the proinflammatory cytokines CRP, IL-6, TNF-α, and the anti-inflammatory cytokine IL-10 would be predictive of heart failure outcomes. However, none of the cytokines tested were predictive of symptoms, functional status, and hospitalizations at both baseline and 3 month. Only one of the cytokines, IL-6, was predictive of more than one outcome at both time points while controlling for demographic and disease covariates. Baseline measurement of IL-6 was the only cytokine found to be predictive of baseline symptoms, functional status, and likelihood of all-cause and HF hospitalizations. The significant relationships that were found between the proinflammatory cytokines and the HF outcomes as a whole were in the direction expected. For instance higher levels of IL-6 were related to greater HF symptoms, decreased distance walked on the 6MWT and a greater likelihood of being hospitalized for all-cause or HF-related events. This makes sense within the frame work of the existing literature, as it is believed that a proinflammatory state (e.g., higher levels of circulating proinflammatory cytokines) is related to negative health outcomes in general and specifically in regards to cardiovascular disease. By extension, it was hypothesized that higher levels of the anti-inflammatory cytokine IL-10 would be related to fewer HF symptoms, better functional status, and decreased likelihood of hospitalization. In this population, IL-10 showed little predictive value for any of the outcomes, however for the one outcome it was associated with (Baseline 6MWT) the direction of the relationship was in the opposite direction. Higher IL-10 was associated with less distance walked. One explanation could be that since IL-10 is an anti-inflammatory cytokine that is released in response to a pro-inflammatory state, higher levels of IL-10 is really reflective of greater levels of

proinflammatory cytokines, and indicative of an overall proinflammatory state instead of being indicative of a protective anti-inflammatory response as had been hypothesized.

The results of the current study suggest a complex relationship between cytokine levels and heart failure outcomes. It further illustrates the dynamic and multifaceted nature of heart failure. A simple direct relationship between increased levels of proinflammatory cytokines and worse health status in heart failure patients does not seem to exist, and given the complexity of the inflammatory cascade this is not surprising. Perhaps these cytokines are more consistently related to symptoms and worsening earlier in the heart failure disease process and as patients live longer with the disease these cytokine levels become less reliable as markers of worsening. The findings of the present study illustrate the need for further research investigating the relationship between cytokine levels and heart failure exacerbations.

Cytokines and Optimism

The hypothesis that Optimism would be related to cytokine levels at baseline and 3 months was not supported by the data. No significant relationships were found in any of the analyses with LOT Total Scores or the Optimism and Pessimism Subscales and the cytokines. Given the current literature, it is a little surprising that no association was found in this study. Although there is not a great depth of literature in the area, a clear relationship between Optimism has been shown to be predictive of some inflammatory cytokines like IL-6 and CRP in patients with cardiovascular disease (Roy et al., 2010). There are many possible explanations for the lack of association found in this study, the most parsimonious of which is that Optimism (LOT Total or Optimism Subscales) simply

does not operate through the inflammatory pathway to affect heart failure outcomes. If this is the case, an alternative mechanism of action for Optimism should be explored. The current literature would suggest the effects of Optimism on health outcomes may operate through health behaviors (Boehm & Kubzansky, 2012; Giltay, et al., 2007). When no relationship between Optimism and inflammatory cytokines were found a preliminary investigation into health behaviors was launched. No relationship was seen between Optimism and measures of baseline dietary compliance, medication adherence, or physical activity in this study. This would suggest that Optimism is not acting through these behavioral pathways either. Other studies also have failed to find a relationship between Optimism and physical activity in a cardiovascular disease population (Rius-Ottenheim et al., 2012). However, many studies have consistently linked Positive Psychological Well-Being (a construct that encompasses a number of positive psychology constructs including Optimism) with positive health behaviors and inversely associated with negative health behaviors (Boehm & Kubzansky, 2012). It should be noted that since the present study was not designed to look at health behaviors as a mediator between Optimism and heart failure outcomes, the measures of these health behaviors are not ideal and have their own limitations. Therefore, while it would appear that Optimism is not acting through health behaviors to influence heart failure outcomes in this study, this pathway cannot be dismissed without further investigations.

As was previously discussed in review of the relationship between inflammatory cytokines and heart failure outcomes, perhaps the effect of Optimism on cytokine levels is seen earlier in the cardiovascular disease process. It could be that when patients reach the final stages of cardiovascular disease (i.e., heart failure), that the underlying

pathophysiology of the disease is too great to be altered by personality traits such as Optimism. Likewise, it could also indicate that the cytokines investigated in this study (CRP, IL-6, Il-10, and TNF-α) no longer show reliable changes in this stage of the disease process. In other words, when patients have been living with heart failure for a period of time, their bodies may not respond with the same type or intensity of inflammatory cascade response that it would have in earlier disease stages. It could very well be a combination of these factors that led to the lack of an observed relationship between Optimism and inflammatory cytokines in present study.

Another possible explanation for the lack of observed relationship between Optimism and the inflammatory cytokines is the method used to measure the levels of the cytokines in the patient blood samples. The assays for this study were run by Singulex® using their proprietary Erenna® Immunoassay System, which utilizes a patented digital single-molecule counting detection system. This immunoassay system has greater sensitivity and specificity than the traditional ELISA technique utilized by most academic laboratories. It is possible that the increased specificity in the measurement of these cytokines revealed a true lack of relationship between the cytokines and optimism, something that the traditional ELISA technique was not able to demonstrate. Future research should seek to clarify this finding by using the Singulex® system to look at these cytokines in heart failure patients while collecting more comprehensive data on disease course and severity, as well as health behaviors.

Optimism: Bipolar or Unipolar Construct?

The underlying theme of this investigation was focused on demonstrating a protective relationship between Optimism and heart failure outcomes. More broadly, the intent was to focus on Positive Psychology constructs, and show that these constructs, though less mainstream in the health and medical psychology literature, can be important predictors of health outcomes in heart failure patients. It was also important to look at the LOT (one of the most widely used instruments to measure Optimism) and the different ways to code the scale to try to identify the most useful approach in this population. As outlined previously, the LOT can provide a total score, which measures Optimism/Pessimism as opposite ends of a single construct, often referred to as Dispositional Optimism. However, the LOT can also be broken out into separate Optimism and Pessimism Subscales, totaling the questions worded in a positive frame (e.g., "every cloud has a silver lining") to create an Optimism scale, independent of the Pessimism scale (created from totaling items with a negative frame: e.g., "if something can go wrong it will"). Although the LOT can easily be scored either way, very few studies have compared the two to see if they differentially predict outcomes.

This study hypothesized that Optimism would predict better health outcomes in heart failure patients when characterized at as a bipolar trait (Dispositional Optimism, i.e., LOT Total Scores), and that evaluating Optimism and Pessimism as unipolar traits would show Optimism and not Pessimism to be related to improved heart failure health outcomes. Fundamentally, what this would mean is that Optimism and Pessimism are not mutually exclusive, and that being optimistic and not simply an absence of Pessimism would be driving the relationship with health outcomes. However, the findings of the current study do not lend themselves to such a straightforward conclusion.

Dispositional Optimism demonstrated a consistent protective relationship across the different heart failure outcomes that the Optimism and Pessimism Subscales did not. For example, the Optimism Subscale was predictive of fewer HF symptoms at baseline, but only marginally significant at 3 months when medical and demographic covariates were added in the model. The Pessimism Subscale however, was predictive of greater HF symptoms at both time points. Whereas the Pessimism Subscale showed no significant relationship with functional status at either time point in the adjusted models, the Optimism Subscale was predictive of greater distance walked. Furthermore both the Optimism and Pessimism Subscales were only marginally significantly predictive of number of HF hospitalizations.

The disaggregation of Optimism and Pessimism into unipolar traits could be supported by the fact that the Optimism and Pessimism Subscales were only moderately correlated with one another (r= -0.33, p<0.001). Taken together with the fact that only the Optimism Subscales demonstrated a relationship with the 6 Minute Walk Test would further support the idea of Optimism and Pessimism being unipolar constructs. This is particularly interesting because it would appear to lend credence to the idea that it is Optimism that is related to favorable health outcomes rather than Pessimism being related to poorer ones. However, given that this type of relationship was only seen in regards to the functional status outcome, a unipolar view of Optimism and Pessimism does not appear to be strongly supported. In fact the current study findings seem to suggest that Dispositional Optimism is a better predictor of HF outcomes, because it was clearly associated with fewer symptoms, better functional status, and fewer number of heart

failure related hospitalizations. These findings indicate that one needs Optimism, as well as a lack of Pessimism, to see health protective benefits in this population.

This study suggests that Optimism is a bipolar rather than unipolar construct. It would be an overgeneralization to argue that Optimism and Pessimism are mutually exclusive (as a bipolar conceptualization would suggest) given that in at least one set of analyses they were differentially predictive of outcomes, but this study does highlight the need for continued research in this area. This study indicates that Dispositional Optimism (LOT Total Scores) should continue to be explored in relationship to heart failure outcomes as a possible protective factor.

Study Limitations

The hypotheses in the present study were tested using data collected through the NHLBI-funded BETRHEART Study. Given that the BETRHEART study tested a wide range of psychosocial variables, many of the trait measures were broken up over the biweekly telephone interviews. The current study protocol focused on the baseline and 3 month relationship with Optimism and heart failure outcomes, however the LOT scale was not administered until the 3rd phone interview (approximately halfway between baseline and 3 month follow-up). Although this backwards time relationship violates one assumption for determining causation, there is strong evidence that Optimism is stable overtime. Additionally causation is not being assumed. Ideally, the relationship between the baseline heart failure measures would be tested against LOT scores also obtained at baseline. However, despite these limitations the findings from the study provide an important foundation for future research.

Statistical Power

Although the study was sufficiently powered to test the relationship between Optimism and heart failure symptoms and functional status, it was underpowered to accurately detect the modest effect of Optimism in predicting hospitalizations. The initial power calculation were based on the effect sizes for optimism and cytokines seen previously in the literature (IL-10 and LOT scores effect size=0.24; (Kohut, et al., 2002; Rasmussen, et al., 2009), which indicated that a total of 119 participants would be needed for adequate power (Hsieh, et al., 1998). The relationship between Optimism and the cytokines was expected to have the smallest effect size which is why the study sample size was based on these calculations. However, the relationship between Optimism and likelihood of hospitalizations was greatly underpowered. Using the methodology proposed by Hsieh & Lavori (2000) to calculate the sample size needed for the effect size found for Optimism in the Cox regression models 126 hospitalizations would be needed to see a 10% reduction in events .This assumes 80% power to detect a 10% decrease in risk (a hazard ratio of .90) associated with a 1-unit increase in LOT total score, based on Cox proportional hazards regression with a 5% two-sided significance level, using the standard deviation of the LOT scores ($\pm$ 5.63). The hazard ratios seen with the continuous LOT scores reflected a very small difference and would need to be studied in a much larger sample size in order to be adequately powered.

Study Sample

Another limitation of the current study is the possibility of the lack of generalizability to a larger population of patients with coronary artery disease. Although limiting the study sample to patients with heart failure addressed a specific population often overlooked in cardiovascular behavioral medicine research, it also limits the generalization of findings to other populations. Heart failure is the end stage of many cardiovascular disease processes and it is impossible to tell whether the protective effects of Optimism seen in heart failure patients would also be seen in patients in earlier stages of the cardiovascular disease process, although the extant literature suggests it does. Another factor limiting the generalizability of the study is the demographic make-up of the study sample. This sample was distinctive in that it consisted of predominantly male African American patients, with non-ischemic cardiomyopathy. The sample was also comprised largely of individuals of low socioeconomic status. Several of the participants were receiving care for their heart failure diagnosis through the VA system, further contributing to the uniqueness of this sample. Furthermore, most patients had several comorbidities, which could have influenced any of the study outcomes. An effort was made to control for these potential confounders, but it is possible that all of these factors together had an influence on the outcome measures that was not anticipated. There were no significant differences in mean LOT total scores based on gender or race, but it is unclear if the results would differ in sample more reflective of the general heart failure population.

Study Implications and Future Directions

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One important implication of the study is that optimists with heart failure may have better outcomes than their pessimistic counterparts, independent of their disease severity. Evaluating heart failure outcome with measures from three different domains was a unique aspect of this study. Few studies have looked at the effects of Optimism in heart failure patients, and this is the first study to the author's knowledge to look at Optimism as it relates to symptoms, functional status, and hospitalizations in a population comprised of heart failure patients. Given the large economic burden associated with heart failure, highlighting a psychosocial factor that could potentially be used to reduce health care utilization in this population is particularly valuable. Since Optimism is associated with fewer symptoms, better functional status, and fewer HF hospitalizations, it could be implied that optimists utilize the traditional health care system less often, as they do not perceive their limitations or symptoms related to heart failure to be as severe or troubling. However this was not specifically evaluated in the present study.

Another implication from the study findings suggests that Optimism may not be acting through inflammatory pathways, at least in the present study population. This is particularly interesting given that other studies have shown a relationship between Pessimism and biomarkers related to immunosenescence as well as inflammation (Tindle et al., 2010; O'Donovan et al., 2009; Roy et al.2010). It is possible that the small sample size or more sensitive assay technique used in this study contributed to these findings; however it also highlights the importance of exploring other mechanisms through which optimism may confer health benefits. As existing literature would suggest, perhaps optimists practice better health behaviors (Giltay et al., 2007). Optimists may also have better compliance with medical treatment, or perhaps have fewer psychosocial risk

factors associated with adverse cardiovascular outcomes. Although a preliminary look into level of physical activity of the patients, and their medication and dietary compliance did not appear to be related to Optimism, a more in depth study of these behavioral pathways is warranted.

Exploring the pathways through which Optimism is operating to influence heart failure outcomes is very important. This study looked at one possible pathway (inflammatory cytokines) of Optimism but left many others unexplored. Marker of sympathetic function and more importantly sympathetic dysregulation have been linked to adverse outcomes in heart failure patients (Baker, et al., 2001). Although not within the scope of the present investigation, the effects of Optimism on sympathetic function might be a mechanism through which health outcomes are influence. Previous literature has demonstrated a relationship between Optimism and lower 24-hour ambulatory blood pressure in adolescence and young adults (Raikkonen & Matthews, 2008; Raikkonen, et al., 1999), although Optimism has not been related to lower mean arterial pressure in an older population (Mezick, et al., 2010). Preliminary analyses with the BETRHEART sample did not show any correlation between baseline systolic (r=0.03, p=0.8) or diastolic blood pressure (r=0.03, p=0.75) and Optimism or with Optimism and baseline resting heart rate (r= -0.14, p=0.12); however these sympathetic pathways warrant more in depth investigation.

This study also conceptualized the directionality of the relationship between Optimism and heart failure outcomes as one in which Optimism is acting in some way to change or influence heart failure outcomes. The bidirectionality of this relationship could also be argued. Perhaps experiencing fewer symptoms, having better functional status,

and being hospitalized less often make heart failure patients more optimistic. Again, this study was not designed to evaluate this particular issue, therefore this type of relationship cannot be ruled out. However, given the large body of literature that suggests that Optimism is a stable trait over time and in a variety of situations (Matthews, et al., 2004; Schou, et al., 2005), it seems more likely that Optimism is acting in the direction hypothesized in the present investigation.

It also cannot be overlooked that when other psychosocial factors were included in the models predicting symptoms, functional status, and hospitalizations, Optimism (measured as a continuous variable) was no longer significantly predictive. While these models were likely unstable due to number of covariates and inadequate sample size, the possibility that some effects of Optimism are the manifestation of some other psychosocial factors should be explored. Optimism has been long thought by some researchers to be related to the personality construct of Neuroticism (Smith et al., 1989), although many other researchers believe that Optimism has been widely shown to be an important trait in its own right (Scheier, Carver, & Bridges, 1994). The current findings suggest Optimism is related to better overall outcomes in heart failure patients, however it may not be independent of other psychosocial factors. There is an obvious need for future research to clarify the relationship between Optimism, other psychosocial constructs, and heart failure outcomes. It seems unlike that Optimism would be completely independent of psychological constructs such as depression or positive affect and future studies should explore the relationship between these constructs instead of simply controlling for them.

Previous research suggests that psychosocial variables do in fact cluster together and looking at psychological risk factors as a set may be more beneficial than looking at each individually (Suls & Bunde, 2005). In the NHLBI-funded Women's Ischemia Syndrome Evaluation study, it was found that combining psychosocial risk markers predicted CVD events in women with suspected ischemic heart disease (Whittaker et al., 2012). One of the limitations in the WISE study was that it did not include any measures of positive psychology. The present study findings suggest that including Optimism in future research evaluating psychosocial risk factors may lead to a better understanding of how psychological constructs are operating in patients with cardiovascular disease.

The implication that Optimism maybe be beneficial for heart failure patients is an exciting one. Ultimately, Optimism could be a target for psychosocial intervention in the treatment of heart failure, designed to lessen the morbidity associated with the disease. The present study conceptualized Optimism as a trait that is stable over time however, some research has suggested that optimistic attitudes may be increased by targeted interventions (Seligman et al., 1988; Gillham & Reivich, 2004). The concept of Learned Optimism (introduced by Martin Seligman) and the research conducted by the Penn Resiliency Project suggest that, at least in adolescents, Optimism may be increased when targeted through interventions aimed at decreasing negative thought and negative environmental influences, while increasing positive thoughts, actions, and environmental situations. If Optimism can in fact be altered through targeted intervention, then Optimism may offer an exciting new path for research and a more integrative approach to the treatment of heart failure.

In addition to addressing the concerns outlined as limitations, future research should focus on identifying the mechanisms through which Optimism is operating. One mechanism not fully explored in this study is the relationship of Optimism to the stress response. It has been shown that optimists react to stressors differently (Segerstrom, 2001b). Self-regulation theory suggest that optimists persist in task longer which my increase their exposure to the physiological stress response (Carver & Scheier, 2001; Segerstrom, 2001b). Perhaps, Optimism is affecting the stress response through altering the release or response to catecholamines. Studies have shown that when optimists are faced with complex stressors they suffer decrements in cellular immunity, but when stressors are simple optimists actually seem to have improved immune function (Segerstrom, 2005). Future studies should investigate differences in catecholamine responses to stress in optimistic and pessimistic heart failure patients as a possible biological mediator of improved health outcomes.

The current study also raises the interesting question as to whether Optimism predicts changes in symptoms or functional status over time. Although not an aim of the present study, this question could easily be addressed in future investigations. Another related research inquiry would be: Does Optimism have differing effects on heart failure outcomes at different times during the disease process? Assessing Optimism in a patient population at high risk of heart failure and then following that population through the onset of the disease would yield invaluable information regarding the role of Optimism throughout various stages of the cardiovascular disease process. Understanding the role of Optimism throughout the etiology and progression of heart failure is a crucial step in the development of future psychosocial interventions. Ultimately further research is

needed to understand how and why Optimism is beneficial in relation to heart failure outcomes and health in general. This study helps to lay the groundwork for such future investigations.

Summary

In conclusion, this study yielded several key findings: (1) Optimism is related to fewer heart failure symptoms, improved functional status, and fewer heart failure hospitalizations; (2) when dichotomized into optimists and pessimists, optimistic heart failure patients had increase hospitalization-free survival and decreased number of heart-failure related hospitalizations independent of other psychosocial factors (3) Baseline levels of interleukin-6 were related to more heart failure symptoms, decreased functional status, and increased likelihood of all-cause and heart failure related hospitalizations, however Optimism was not related to levels of C-reactive protein, interleukin-6, interleukin-10, or tumor necrotic factor-α in this heart failure sample; and (4) In a heart failure sample, measuring Optimism as a bipolar construct may be useful in predicting better heart failure outcomes. The protective effects of Optimism on heart failure related outcomes such as improved symptoms, functional status, and fewer heart failure-related hospitalizations, is of great interest and also suggests potential novel intervention approaches in the treatment of cardiovascular diseases such as heart failure.

Figure 1: Research model based on Optimism as a bipolar construct
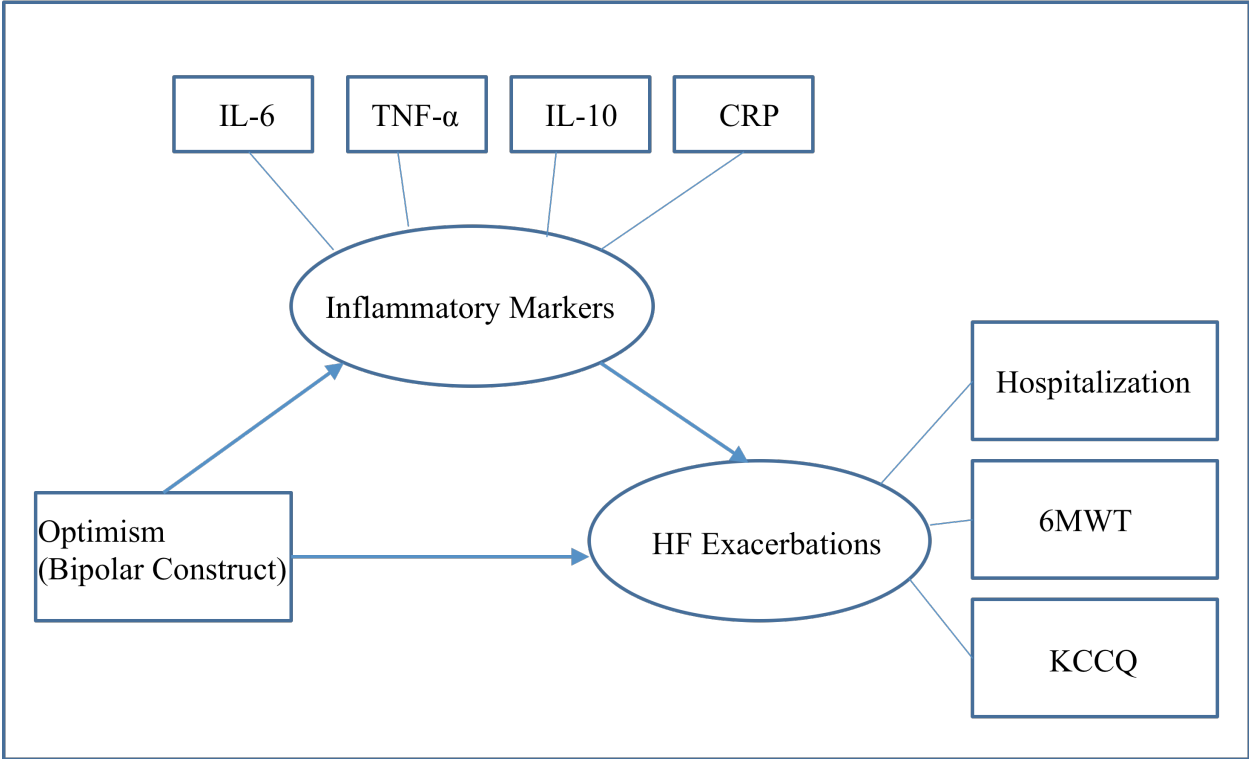
Figure 2: Research model based on Optimism as a unipolar construct
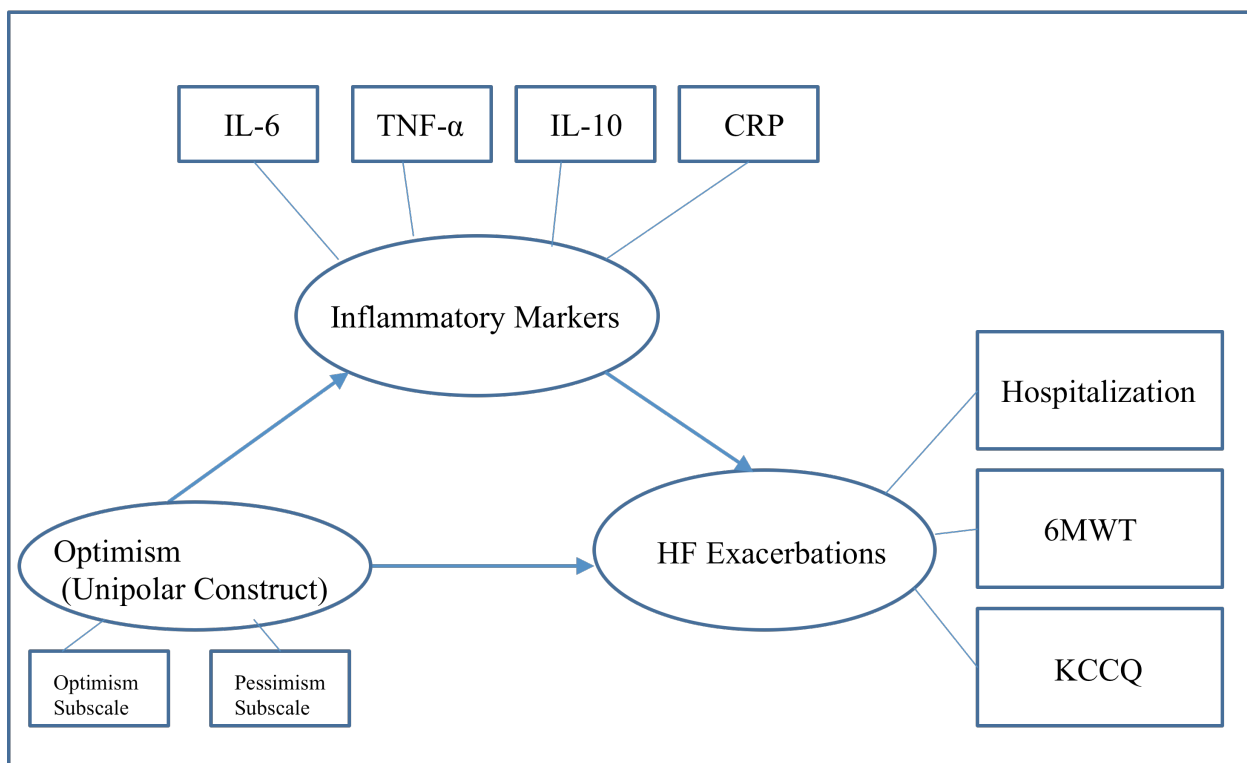
Figure 3: Kaplan-Meier Curve for Optimism and Heart Failure-Related Hospitalizations
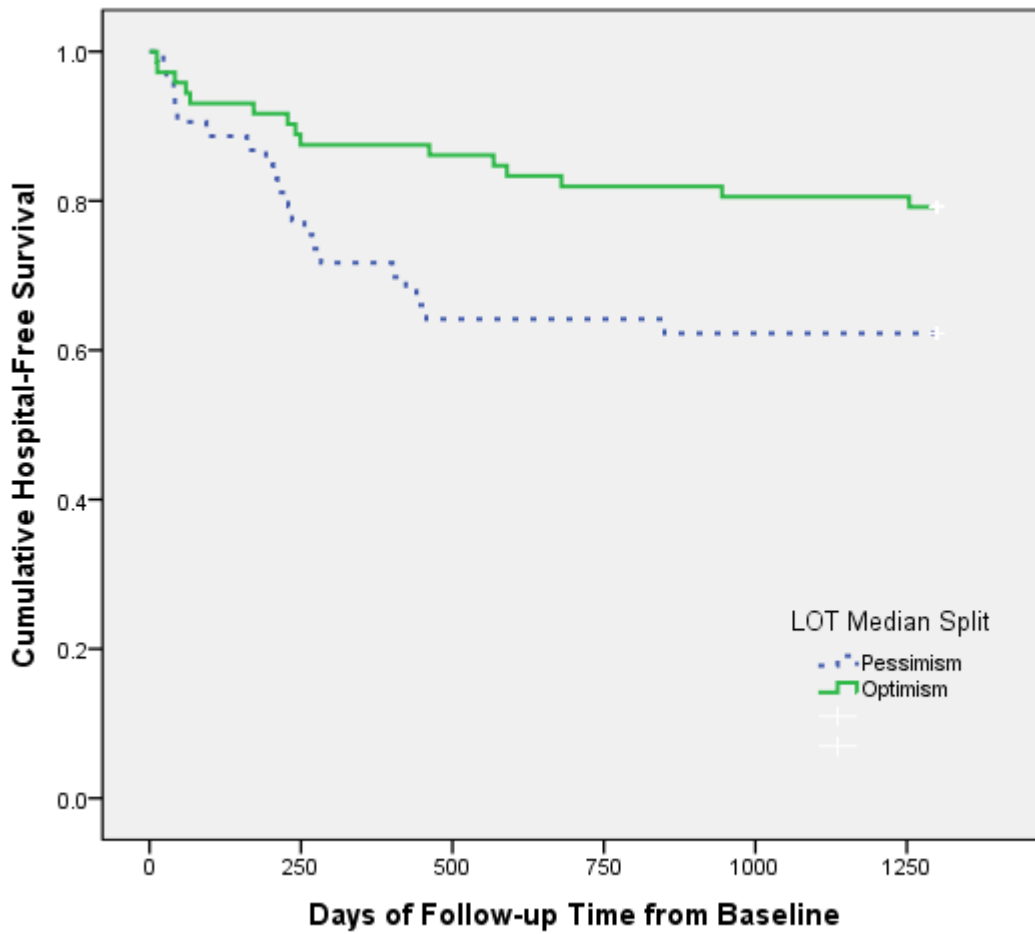
Figure 4: Kaplan-Meier Curves for Optimism and All-Cause Hospitalizations
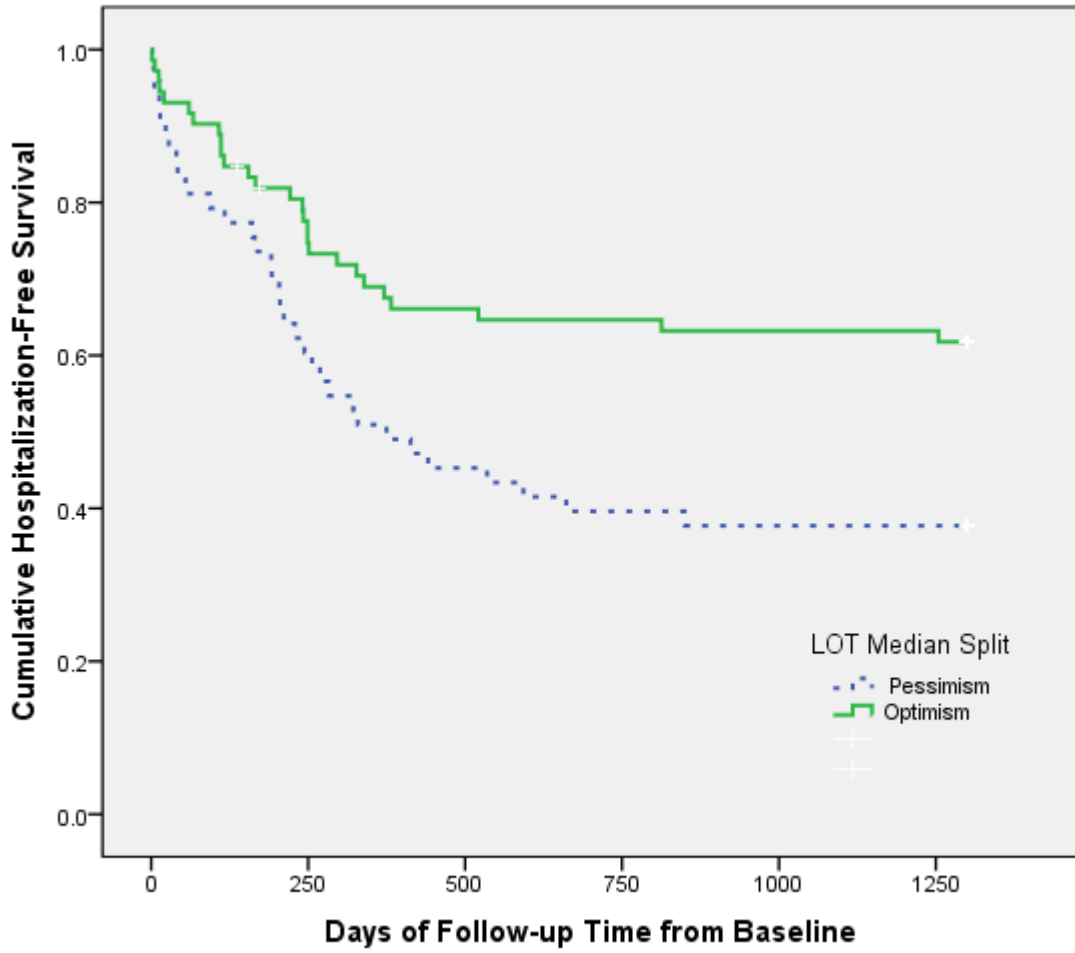
Figure 5: Summary of Significant Psychosocial and Cytokine Relationship Between Heart Failure Outcomes at Each Time Point

Symptoms

Baseline

LOT Total
BDI

Baseline IL-6
LOT Optimism
LOT Pessimism

3 month

LOT Total
LOT Pessimism

Walk Test

Baseline

Positive Affect

Baseline IL-6
LOT Total
LOT Optimism

3 month

Positive Affect

Baseline IL-6
LOT Optimism

Hospitalizations

All-Cause (Yes/No)

Median-split LOT Total
BDI
Baseline IL-6
Positive Affect
Negative Affect
Problem Focused Coping

HF-Related (Yes/No)

BDI

Baseline IL-6
Problem Focused Coping
Median-split LOT Total

Number of HF-Related

Median-split LOT Total

Baseline IL-6
LOT Total

LOT= Life Orientation Test; median-split LOT Total= total scores of the LOT dichotomized at the sample mean; LOT Optimism =LOT Optimism Subscale; LOT Pessimism = LOT Pessimism Subscale BDI= Beck Depression Inventory; Positive Affect= Positive and Negative Affect Schedule (PANAS) positive mood scale; Baseline IL-6= baseline levels of interleukin-6 (log transformed)
Measures in italics were statistically significant in covariate adjusted models (demographic and medical variables)
Measures in bold were statistically significant in full model (adjusted for covariate and psychosocial variables

Figure 6: Comparison of Different Regression Fit Lines
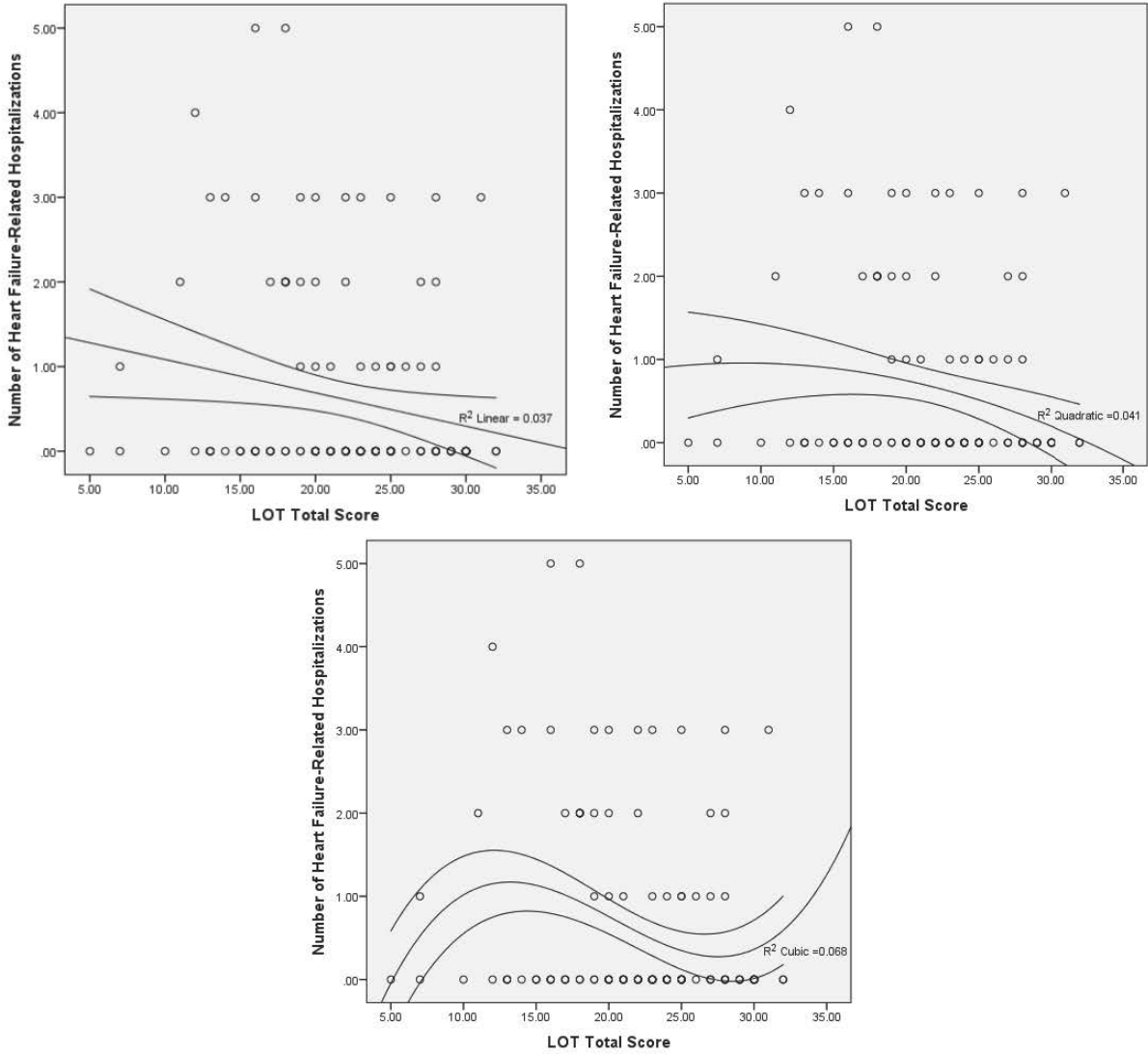
Table 1: New York Heart Association Classification of Heart Failure

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Slight limitation of physical activity. Comfortable at rest. Moderate physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Marked limitation of physical activity. Comfortable at rest. Minimal activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Inability to carry on any physical activity without discomfort. Symptoms of heart failure may be present at rest. Discomfort increased with any physical activity.

Table 2: Summary of Studies Using Optimism as a Main Independent Variable Associated with Health Outcomes

Author	N	Age at Baseline	Measure of Optimism	Outcome Measure	Main Findings
Agarwal et al., 1995	70	50.9 mean	Positive Life Orientation Scale	patient and physician rated recovery after MI	Better patient rated (r=0.039, p<0.01), better physician rated (r=0.23, p<0.05)
Boehm et al., 2011	7,942	49.5 mean	single item likert-type scale	incident CHD	HR= 0.87, (95%CI: 0.87-0.97)
Giltay et al., 2004	941	74.5 mean	SSWO Optimism Subcale	all-cause and cardiovascular mortality	All-cause(HR: 0.071, 95%CI: 0.52-0.97), cardiovascular (HR: 0.23, 95%CI: 0.10-0.55)
Giltay et al., 2007	773	71.7 mean	4-item likert-type questionnaire	physical activity, smoking status, alcohol consumption	Physically active (β=0.15, p<0.001), nonsmokers (β=5.62, p=0.02), drink more alcohol (β=0.05, p=0.01)
Giltay, Kamphuis, et al., 2006	545	71.7 mean	4-item likert-type questionnaire. Optimism broken into tertiles	cardiovascular mortality	HR: 0.57, (95%CI: 0.36-0.89)
Giltay, Zitman, & Kromhout, 2008	545	71.7 mean	4-item likert-type questionnaire	all-cause and cardiovascular mortality	All cause (HR: 1.48 95%CI:1:20-182), Cardiovascular (HR: 1.67; 95%CI: 1.25-2.24)
Kubzansky et al., 2001	1,881	60.8 years mean	MMPI PSM-R	Non-fatal MI, angina pectoris, incident CHD	Non-fatal MI=0.72 (95%CI: 0.57-0.90), angina= 0.70 (95%CI: 0.55-0.90), incident CHD= 0.75 (95%CI: 0.62-0.91)
Author	**N**	**Age at Baseline**	**Measure of Optimism**	**Outcome Measure**	**Main Findings**
Maruta et al., 2000	839	35 mean	PSM	15 year survival	RR: 0.50; (95%CI: 0.29-0.87)
Maruta et al., 2002	447	35 mean	PSM	SF-36 at 30 year follow-up	SF-36 Mental Component Summary r=-0.31, p<0.001, Physical health component summary r=-0.18, p<0.001

Matthews et al., 2004	209	47.8 mean	LOT	Mean and maximum Intima medial thickness (IMT)	mean IMT; $F = 15.4$, p<0.001; Maximum IMT $F = 5.6$, p<0.02)
Mezick et al., 2010	224	60 mean	LOT	Attenuated sleep-wake MAP Ratio from 24-hour ambulatory monitoring	MAP β=-0.08, p=0.22
Peterson, Seligman & Vaillant, 1988	99	25 mean	CAVE Analysis of Structural Interview	Physician Rated Health later in life	Better rated health at age 45 (r=.37, p<0.001), age 55 (r=.22, p<0.05), age 60 (r=.25, p<0.001)
Raikkonen & Matthews, 2008	101	14.7 mean	LOT	Daytime and nighttime systolic and diastolic blood pressure and 24 hour load from 24-hour ambulatory monitoring	LOT Total: Daytime SBP B=0.84, p=.34; Nighttime SBP B=1.90, p=.12; SBP 24-hour Load B= 1.40, p=.43 Daytime DBP B=0.69, p= .13; Nighttime DBP B=- 0.05, p= .92; DBP 24-hour Load B=1.26, p=.28 LOT Optimism Subscale: Daytime SBP B=.0.94, p=.29; Nighttime SBP B=0.06, p=.96; SBP 24-hour Load B=2.23, p=.13 Daytime DBP B=0.53, p=.23; Nighttime DBP B=0.76, p=.21; DBP 24-hour Load B=1.51, p=.14 LOT Pessimism Subscale: Daytime SBP B= 1.86, p= .04; Nighttime SBP B=2.58, p=.04; SBP 24-hour Load B=3.54, p= .02 Daytime DBP B=1.28, p= .004; Nighttime DBP B=0.36, p= .47; DBP 24-hour Load B=2.73, p=.02

Raikkonen, et al., 1999	100	36.8 mean	LOT	Systolic and diastolic blood pressure from 24-hour ambulatory monitoring	SBP=$F(1,5267)$=1.46, p=.23, DBP=$F(1,5267)$=8.33, p=0.004
Author	**N**	**Age at Baseline**	**Measure of Optimism**	**Outcome Measure**	**Main Findings**
Roy et al., 2010	5,220	62.1	LOT-R	IL-6, CRP, fibrinogen, homocysteine	LOT Optimism Subscale Percent increase in: IL-6=1.95 (95% CI: -1.52 – 5.54), p=.27; CRP= 7.67 (1.43 – 14.3), p=.02; Fibrinogen=0.44 (-0.61 – 1.51), p=.41; Homocysteine= -0.71 (-2.14 – 0.74), p= .33 LOT Pessimism Subscale Percent increase in: IL-6= 1 6.01 (2.4 – 9.75), p= .001; CRP= 10.31 (3.91 – 17.09), p=.001; Fibrinogen= 2.47 (1.4 – 3.56), p=.001; Homocysteine=1.36 (-0.1 – 2.85), p= .07
Scheier et al., 1989	51	48.5 mean	LOT	physician rated recovery after CABG, and QoL 6 months post CABG	Improved physician rated recovery ($F(1,44)$=6.25, p<0.02), better self report QoL ($F(1,43)$=34.16, p<0.0001)
Scheier et al., 1999	309	62.8 mean	LOT-R	6 month post-CABG rehospitalizations	OR = 0.53, 95% CI = 0.33 – 0.83)

Tindle et al., 2009	97,253	50-79 range	LOT-R	MI, Incident CHD, all-cause, CHD-related, and CVD-related mortality	MI (HR:0.84, 95%CI: 0.73-0.96), Incident CHD (HR:0.91, 95%CI: 0.83-0.99), All-cause mortality (HR:0.86, 95%CI: 0.79-0.93), CHD-related mortality (HR:0.70, 95%CI: 0.55-0.90), CVD-related mortality (HR:0.76, 95%CI: 0.64-0.90)
Author	**N**	**Age at Baseline**	**Measure of Optimism**	**Outcome Measure**	**Main Findings**
Tindle et al., 2012	430	65 mean	LOT-R	Response to depression treatmen, 8 month rehospitalization after CABG	LOT Total: Response to depression treatment (OR: 3.02, 95%CI:1.28-7.13) 8 month Rehospitalization (OR: 0.95, 95% CI: 0.91-0.99) LOT Optimism Subscale: Response to depression treatment (OR: 1.15, 95%CI:1.01-1.32) 8 month Rehospitalization (HR: 0.91, 95% CI: 0.83-1.00) LOT Pessimism Subscale: Response to depression treatment (OR: 0.91, 95%CI:0.82-1.01) 8 month Rehospitalization (not significant effect size close to 1.00)

Table 3: Sample Characteristics

	Full Sample	Subsample with LOT
	N=146	N=125
Gender		
male	113 (75.3%)	95 (76%)
Age	56.82 ±11.43 (SD)	56.77 ± 11.62 (SD)
BMI	30.83 ± 7.71 (SD)	31.45 ± 7.68 (SD)
Race		
African American	103 (70.5%)	85 (68.5%)
Caucasian	42 (28.8%)	38 (30.6%)
Other	1 (0.7%)	2 (0.8%)
Household Income		
< $15,000	51 (35.2%)	45 (36.6%)
$15-30,000	39 (26.9%)	32 (26.0%)
$30-70,000	43 (29.7%)	36 (29.3%)
>$70,000	12 (8.3%)	10 (8.1%)
Ejection Fraction	23.14 ± 7.48 (SD)	23.02 ± 7.52 (SD)
Baseline Creatinine Level	1.38 + 0.71	1.33 + 0.45
NYHA Class		
II	81 (55.5%)	73 (58.9%)
III	62 (42.5%)	50 (40.3%)
IV	3 (2.1%)	1 (0.8%)
History of Coronary Artery Disease	67 (44.7%)	59 (47.2%)
History of Hypertension	115 (79.3%)	96 (78%)
History of Smoking	103 (70.5%)	89 (71.8%)
History of Diabetes	60 (40.8%)	49 (39.5%)

Table 4: Means and Standard Deviations of Key Variables

Name of Measure	Mean (SD)	Minimum	Maximum
LOT Total Score	21.86 (5.63)	5	32
LOT Optimism	11.87 (3.12)	2	16
LOT Pessimism	6.02 (3.77)	0	16
KCCQ Overall Summary Baseline	71.58 (21.05)	19.38	100
KCCQ Overall Summary 3 month	78.45 (17.89)	26.3	100
6 Minute Walk Test Baseline (ft)	1063.15 (258.89)	480	1671

6 Minute Walk Test 3 month (ft)	1160.04 (273.16)	513	1730
CRP Baseline (mg/L)	6.68 (7.99)	0.35	40.1
CRP 3 month (mg/L)	6.39 (6.84)	0.33	39.1
IL-6 Baseline (pg/ml)	6.38 (8.47)	0.95	62.03
IL-6 3 month (pg/ml)	5.36 (5.55)	1.12	26.73
IL-10 Baseline (pg/ml)	1.66 (1.07)	0.32	7.25
IL-10 3 Month (pg/ml)	1.93 (2.86)	0.54	30.66
TNF-α baseline (pg/ml)	5.79 (4.01)	0	32.74
TNF-α 3 month (pg/ml)	5.48 (3.04)	0	15.83

Table 5a: Correlations Among Psychological Variables

	LOT Optimism Subscale	LOT Pessimism Subscale	PANAS Negative Mood	PANAS Positive Mood	Problem Focused Coping	Emotion Focused Coping	BDI
LOT Total Score	0.78**	-0.85**	-0.35**	0.31**	0.34**	-0.18*	-0.47*
LOT Optimism Subscale		-0.33**	-0.19*	0.36**	-0.39**	0.05	0.32**
LOT Pessimism Subscale			0.36**	-0.16	-0.19*	0.31**	0.43**
PANAS Negative Mood				-0.44**	0.01	0.28**	0.57**
PANAS Positive Mood					0.25**	0.02	-0.48**
Problem Focused Coping						0.37**	-0.28**
Emotion Focused Coping							0.31**

* p<0.05; ** p<0.001

Table 5b: Correlations Among Psychological Variables and Heart Failure Outcomes

	KCCQ Overall Summary Score Baseline	KCCQ Overall Summary Score 3 Month	6 Miunte Walk Test Baseline	6 Miunte Walk Test 3 month	Total Number of Hospitalizations	Total Number of HF Hospitalizations

LOT Total Score	0.43**	0.26**	0.13	0.14	-0.15	-0.19*
LOT Optimism Subscale	0.34**	0.16	0.12	0.11	-0.21*	-0.15
LOT Pessimism Subscale	-0.37**	-0.26**	-0.09	-0.11	0.06	0.17
PANAS Negative Mood	-0.46**	-0.30**	-0.09	-0.06	-0.03	0.13
PANAS Postive Mood	0.47**	0.27**	0.25**	0.24*	-0.01	-0.14
Problem Focused Coping	0.26**	0.19*	0.29**	0.25**	-0.10	-0.03
Emotion Focused Coping	-0.19*	-0.26**	0.03	0.04	-0.07	0.12
BDI	-0.61**	-0.54**	-0.13	-0.12	0.08	0.18*

* $p<0.05$; ** $p<0.001$

Table 5c: Correlations Among Heart Failure Outcomes

	KCCQ Overall Summary Score 3 Month	6 Minute Walk Test Baseline	6 Minute Walk Test 3 month	Total Number of Hospitalizations	Total Number of HF Hospitalizations	Any Hospitalization	Any HF Hospitalization
KCCQ Overall Summary Score Baseline	0.65**	0.28**	0.15	-0.14	-0.18*	-0.12	-0.14

KCCQ Overall Summary Score 3 Month		0.17	0.17	-0.11	-0.23*	-0.17	-0.13
6 Minute Walk Test Baseline			.80**	0.001	-0.14	0.02	-0.19*
6 Minute Walk Test 3 month				0.03	-0.07	-0.01	-0.12
Total Number of					0.30**	0.16	0.29**
Total Number of HF Hospitalizations						0.64**	0.41**
All-cause Hospitalization							0.62**

* p<0.05; ** p<0.001

Table 5d: Correlations Among Heart Failure Outcomes and Baseline and 3 Month Cytokine Levels

	CRP Baseline	IL-6 Baseline	IL-10 Baseline	TNF-α Baseline	TNF-α/IL-10 ratio Baseline	CRP 3 Months	IL-6 3 month	IL-10 3 month	TNF-α 3 Month	TNF-α/IL-10 ratio 3 month
KCCQ Overall Summary Score Baseline	-0.06	-0.27**	-0.17	0.05	0.19*	-0.07	-0.17	0.09	-0.07	-0.18
KCCQ Overall Summary Score 3 Month	0.03	-0.10	-0.09	0.1	0.17	-0.06	-0.08	-0.01	-0.01	-0.01
6 Minute Walk Test Baseline	-0.11	-0.38**	-0.33**	-0.35**	-0.07	-0.19*	-0.41**	-0.17	-0.35**	-0.18
6 Minute Walk Test 3 month	-0.04	-0.31**	-0.14	-0.24*	-0.12	-0.10	-0.43	-0.06	-0.24*	-0.2*
Total Number of Hospitalizations	-0.15	-0.04	-0.18*	-0.04	0.12	-0.02	-0.08	-0.09	-0.02	0.08

Total Number of HF Hospitalizations	0.1	0.13	0.03	0.08	0.07	0.14	0.16	0.04	0.16	0.13
All-Cause Hospitalization	-0.05	0.16	-0.01	0.19*	0.21*	-0.02	0.06	0.05	0.05	0.03
Any HF Hospitalization	0.11	0.20*	0.03	0.21*	0.20*	0.19*	0.18*	0.1	0.30**	0.20*
CRP Baseline		0.56**	0.17	0.06	-0.09	0.68**	0.43**	0.08	0.22*	0.11
IL-6 Baseline			0.37**	0.33**	0.01	0.26**	0.71**	0.25**	0.33**	0.05
IL-10 Baseline				0.43**	-0.42**	-0.02	0.39**	0.58**	0.40**	-0.22*
TNF-α Baseline					0.64**	0.1	0.35**	0.42**	0.54**	0.08
TNF-α/IL-10 ratio Baseline						0.12	0.01	-0.09	0.16	0.26**

* $p < 0.05$; ** $p < 0.001$

Table 6: Relationship Among Psychological Variables and Symptoms and Functional Status in Linear Regression Models

		KCCQ-OS* Baseline			KCCQ-OS* 3 Month			6 Minute Walk Test Baseline			6 Minute Walk Test 3 Month		
		β	t	p-value	β	T	p-value	β	t	p-value	β	t	p-value
BDI*	Model 2	**-0.36**	**-3.38**	**0.001**	**-0.59**	**-4.94**	**0.001**	0.06	0.49	0.63	-0.05	-0.41	0.69
	Model 3	**-0.34**	**-3.18**	**0.002**	**-0.59**	**-4.80**	**0.001**	0.08	0.60	0.55	-0.04	-0.32	0.75
PANAS Positive Mood*	Model 2	**0.16**	**1.73**	**0.09**	-0.02	-0.24	0.81	**0.22**	**2.17**	**0.03**	**0.24**	**2.28**	**0.03**
	Model 3	0.15	1.63	0.11	-0.03	-0.25	0.80	**0.22**	**2.17**	**0.03**	**0.24**	**2.27**	**0.03**
PANAS Negative Mood*	Model 2	-0.16	-1.61	0.11	0.12	1.06	0.29	-0.08	-0.76	0.45	0.09	0.85	0.40
	Model 3	-0.13	-1.37	0.17	0.12	1.07	0.29	-0.08	-0.68	0.50	0.10	0.87	0.39
Problem Focused Coping	Model 2	0.13	1.38	0.17	-0.02	-0.23	0.82	**0.24**	**2.22**	**0.03**	0.18	1.62	0.11
	Model 3	0.06	0.56	0.58	-0.03	-0.30	0.77	**0.22**	**1.81**	**0.07**	0.17	1.36	0.18
Emotion Focused Coping	Model 2	-0.11	-1.18	0.24	-0.09	-0.84	0.40	-0.02	-0.15	0.88	0.01	0.07	0.94
	Model 3	-0.06	-0.63	0.53	-0.08	-0.75	0.46	0.002	.013	0.99	0.02	0.16	0.87
LOT Total Score*	Model 2	**0.45**	**5.31**	**0.001**	**0.26**	**2.85**	**0.01**	**0.20**	**2.16**	**0.03**	**0.15**	**1.70**	**0.09**
	Model 3	**0.18**	**1.99**	**.049**	0.02	0.22	0.83	0.07	0.63	0.53	0.04	0.37	0.71
LOT Median-Split	Model 2	**0.40**	**4.43**	**0.001**	**0.26**	**2.75**	**0.01**	0.12	0.13	0.20	0.07	0.70	0.48
	Model 3	**0.20**	**2.35**	**0.02**	0.10	1.03	0.30	0.02	0.19	0.85	-0.01	-0.09	0.93

*Kansas City Cardiomyopathy Questionnaire Overall Summary; Beck Depression Inventory; Positive and Negative Affect Scale, Life Orientation Test
Model 2 is adjusted for the following demographic and medical covariates: age, gender, baseline creatinine levels, baseline ejection fraction, hypertension and income
Model 3 represents the final step of the full model, the first step contains the demographic and medical covariates, the second step contains the psychological covariates: BDI, negative affect, positive affect, Problem Focused Coping, and Emotion Focused Coping.

Table 7: Relationship Among Psychological Variables and Hospitalizations

		All-Cause Hospitalization (yes/no)			Heart Failure Hospitalization (yes/no)			Heart Failure Hospitalization and Death			Total Number of Heart Failure Hospitalizations		
		EXP(β)	(95% CI)	p-value	EXP(β)	95% CI	p-value	EXP(β)	95% CI	p-value	β	t	p-value
BDI	Model 2	1.02	(0.98 - 1.03)	0.93	0.99	(0.96 - 1.02)	0.57	1.01	(0.98-1.04)	0.59	-0.16	-1.27	0.21
	Model 3	**0.95**	**(0.91 - 1.00)**	**0.05**	**0.92**	**(0.86 - 0.98)**	**0.01**	**0.95**	**(0.90-1.00)**	**0.05**	-0.19	-1.43	0.16
PANAS													
Positive	Model 2	1.00	(0.97 - 1.03)	0.98	0.99	(0.95 - 1.03)	0.99	0.98	(0.95-1.02)	0.35	-0.17	-1.53	0.13
Mood	Model 3	1.01	(0.97 - 1.05)	0.69	0.98	(0.93 - 1.04)	0.50	0.97	(0.93-1.01)	0.17	-0.16	-1.44	0.15
PANAS													
Negative	Model 2	1.02	(0.99 - 1.05)	0.33	1.01	(0.97 - 1.05)	0.67	1.02	(0.98-1.06)	0.29	0.02	0.15	0.88
Mood	Model 3	1.04	(1.00 - 1.10)	0.07	1.05	(0.98 - 1.12)	0.16	1.02	(0.96-1.08)	0.49	0.00	-0.03	0.97
Problem													
Focused	Model 2	0.94	(0.87 - 1.02)	0.13	0.94	(0.83-1.05)	0.26	0.95	(0.87-1.05)	0.33	-0.20	-1.79	0.08
Coping	Model 3	0.91	(0.81 - 1.03)	0.13	0.86	(0.72-1.02)	0.08	0.92	(0.79-1.07)	0.29	-0.14	-1.14	0.26
Emotion													
Focused	Model 2	0.99	(0.92 - 1.07)	0.86	1.03	(0.93-1.14)	0.57	1.04	(0.95-1.14)	0.43	0.18	1.56	0.12
Coping	Model 3	1.01	(0.91 - 1.13)	0.81	1.10	(0.95-1.27)	0.20	1.06	(0.93-1.21)	0.36	0.13	1.14	0.26
LOT Total	Model 2	0.96	(0.92 - 1.01)	0.09	0.95	(0.89 - 1.00)	0.07	**0.94**	**(0.89-0.99)**	**0.03**	**-0.20**	**-2.29**	**0.02**
Score	Model 3	0.96	(0.91 - 1.02)	0.24	0.95	(0.88-1.02)	0.16	0.94	(0.88-1.01)	0.09	-0.16	-1.46	0.15
LOT	Model 2	**0.50**	**(0.29 - 0.85)**	**0.01**	**0.47**	**(0.23 - 0.96)**	**0.04**	0.56	(0.30-1.06)	.070	**-0.21**	**-2.42**	**0.02**
Mean Split	Model 3	**0.51**	**(0.28 - 0.92)**	**0.03**	0.50	(0.23 - 1.09)	0.08	0.59	(0.29-1.17)	0.59	**-0.20**	**-1.97**	**0.05**

Model 2 is adjusted for: age, gender, baseline creatinine levels, baseline ejection fraction, hypertension, income, and follow-up time for number of HF Hospitalizations
Model 3 adjusted for Model 2 covariates and psychological covariates: BDI, negative affect, positive affect, Problem Focused Coping, and Emotion Focused Coping.
All-Cause, HF, and HF/Death Combined hospitalization represent Cox regression models; Number of HF-hospitalization represents linear regression model

Table 8: Regression Results for Optimism and Pessimism Subscales

| | LOT Optimism Subscale | | | | LOT Pessimism Subscale | | | |
| | Univariate | | Multivariate | | Univariate | | Multivariate | |
	Model R^2	β	Model R^2	β	Model R^2	β	Model R^2	β
KCCQ-OS								
Baseline	0.11**	0.34**	0.19**	0.37**	0.14**	-0.38**	0.18*	-0.37**
3 month	0.02	0.16	0.05	0.18*	0.07**	-0.26**	0.07*	0.24*
6MWT								
Baseline	0.02	0.12	0.26**	0.23*	0.01	-0.09	0.22*	-0.09
3 month	0.010	0.11	0.31**	0.21*	0.01	-0.11	0.27**	-0.05
Number of HF-Hospitalization	0.02	-0.15	0.17	-0.16	0.03	0.17	0.17	0.17
	Exp(β)	(95% CI)	Exp(β)	(95% CI)	Exp(β)	(95% CI)	Exp(β)	(95% CI)
HR-Hospitalization†	0.93	(0.82-1.05)	0.91	(0.79-1.04)	1.08	(0.98-1.20)	1.11	(0.98-1.04)
All-Cause Hospitalization†	0.97	(0.86-1.08)	0.95	(0.84-1.08)	1.10	(0.996-1.21)	1.11	(0.998-1.24)
HF Hospitalization and Death†	0.92	(0.84-1.07)	0.89*	(0.81-0.98)	1.04	(0.97-1.13)	1.05	(0.97-1.14)

Multivariate Model adjusted for: age, gender, baseline creatinine levels, baseline ejection fraction, hypertension, and income (and in for follow-up time in the number of HF hospitalizations)

† Cox regression model

* P<0.05, **p<0.001

Table 9: Linear Regression Models for Cytokines and Symptoms and Functional Status

	KCCQ-OS Baseline		KCCQ-OS 3 month		6MWT Baseline		6MWT 3 Month	
	Model R^2	β	Model R^2	B	Model R^2	β	Model R^2	β
logCRP								
Baseline	0.05	-0.08	0.08	-0.04	0.20	-0.19	0.29	-0.15
3 month	-	-	0.08	-0.10	-	-	0.28	-0.12
logIL-6								
Baseline	0.11	-0.28*	0.08	-0.11	0.28	-0.36**	0.35	-0.29**
3 month	-	-	0.07	-0.07	-	-	0.32	-0.33**
logIL-10								
Baseline	0.07	-0.17	0.08	-0.12	0.21	-0.24*	0.28	-0.04
3 month	-	-	0.07	-0.01	-	-	0.24	0.03
logTNF-α								
Baseline	0.040	-0.03	0.07	0.07	0.20	-0.26*	0.28	-0.41
3 month	-	-	0.07	-0.06	-	-	0.22	-0.15
logTNF-α to logIL-10 ratio								
Baseline	0.05	0.12	0.09	0.15	0.15	-0.02	0.28	0.01
3 month	-	-	0.07	-0.03	-	-	0.23	-0.17

Models adjusted for: age, gender, baseline creatinine levels, baseline ejection fraction, hypertension, and income
* P<0.05, **p<0.001

Table 10: Logistic and Linear Regression Models for Cytokines and Hospitalizations

	All-Cause Hospitalization		HF Hospitalization		Number of HF Hospitalizations	
	Exp(β)	(95% CI)	Exp(β)	(95% CI)	Model R^2	β
logCRP						
Baseline	0.52	(0.35-1.70)	1.74	(0.73-4.12)	0.13	0.08
3 month	0.66	(0.27-1.61)	1.87	(0.74-4.75)	0.17	0.09
logIL-6						
Baseline	3.57*	(1.28-10.01)	4.04*	(1.40-11.69)	0.13	0.18*
3 month	1.33	(0.32-5.48)	2.10	(0.49-9.01)	0.18	0.06
logIL-10						
Baseline	2.70	(0.47-15.56)	1.93	(0.28-13.39)	0.11	0.05
3 month	2.01	(0.31-13.29)	2.83	(0.39-20.65)	0.17	0.02
logTNF-α						
Baseline	14.13*	(2.40-83.32)	6.95	(0.93-51.69)	0.12	0.13
3 month	0.78	(0.10-6.25)	11.33*	(1.01-126.95)	0.18	0.11
logTNF-α to logIL-10 ratio						
Baseline	5.64*	(1.10-28.96)	3.37	(0.53-21.45)	0.11	0.74
3 month	0.57	(0.09-3.74)	3.24	(0.36-28.81)	0.17	0.08

Models adjusted for: age, gender, baseline creatinine levels, baseline ejection fraction, hypertension, income, and follow-up time
* P<0.05, **p<0.001

Table 11: Linear Regression Results for LOT Total Scores and Cytokines

	Univariate		Multivariate†	
	Model R^2	B	Model R^2	B
logCRP				
Baseline	0.00	0.00	0.10	-0.05
3 month	0.00	-0.01	0.10	-0.08
logIL-6				
Baseline	0.002	-0.04	0.08	-0.11
3 month	0.00	-0.02	0.20	-0.08
logIL-10				
Baseline	0.01	0.09	0.22	0.01
3 month	0.002	0.05	0.16	-0.05
logTNF-α				
Baseline	0.01	0.11	0.32	0.06
3 month	0.01	0.12	0.26	0.10
logTNF-α to logIL-10 ratio				
Baseline	0.002	0.04	0.14	0.05
3 month	0.001	0.03	0.07	0.13

*p<0.05; ** p<0.001
† adjusted for age, gender, baseline creatinine levels, baseline ejection fraction, hypertension, and income

Table 12: Linear Regression Results for LOT Optimism and Pessimism Subscale Scores and Cytokines

| | Optimism Subscale | | | | Pessimism Subscale | | | |
| | Univariate | | Multivariate[†] | | Univariate | | Multivariate[†] | |
	Model R^2	β	Model R^2	B	Model R^2	β	Model R^2	β
logCRP								
Baseline	0.00	0.02	0.10	0.01	0.00	0.01	0.10	0.09
3 month	0.00	0.00	0.10	-0.04	0.00	0.01	0.10	0.08
logIL-6								
Baseline	0.01	-0.08	0.09	-0.14	0.00	-0.002	0.07	0.05
3 month	0.001	-0.02	0.20	-0.11	0.00	0.01	0.19	0.02
logIL-10								
Baseline	0.01	0.12	0.22	0.02	0.001	-0.03	0.22	-0.01
3 month	0.004	0.06	0.16	-0.02	0.00	-0.02	0.16	0.06
logTNF-α								
Baseline	0.03	0.161[†]	0.33	0.09	0.001	-0.04	0.32	-0.02
3 month	0.021	0.15	0.27	0.14	0.003	-0.06	0.25	-0.04
logTNF-α to logIL-10 ratio								
Baseline	0.004	0.06	0.14	0.07	0.00	-0.01	0.14	-0.02
3 month	0.002	0.04	0.07	0.12	0.00	-0.01	0.06	-0.09

*p<0.05; **p<0.10

† adjusted for age, gender, baseline creatinine levels, baseline ejection fraction, hypertension, and income

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