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I. Introduction

Over 85 million U.S. adults (> 1 in 3) have one or more types of cardiovascular disease (CVD), including hypertension, angina pectoris, myocardial infarction (MI), heart failure (HF), and stroke (American Heart Association [AHA], 2015). Despite increased awareness of risk factors and advances in treatment, overall rates of CVD are projected to increase (Heidenreich et al., 2013; AHA, 2015).

CVD is associated with high hospitalization rates and mortality. In 2010, CVD was the most common hospital discharge diagnosis (AHA, 2015). Further, CVD has been the leading cause of death in the U.S. every year since 1900 except for 1918, representing more deaths than cancer and chronic lower respiratory disease combined (AHA, 2015). In 2011, approximately 1 in 3 U.S. deaths were attributed to CVD (AHA, 2015). Globally, similar patterns exist. CVD remains the worldwide leading cause of death, with CVD mortality projected to increase to >23.6 million per year by 2030 (World Health Organization (WHO), 2011; AHA, 2015). Although the expanded use of improved medical therapies such as statins and beta-blockers, as well as population-level lifestyle and environmental changes have contributed to some improvement in survival (Ford et al., 2007), poor self-management often prevents the realization of the full benefits of medical interventions.

1.1. Depression in Cardiovascular Disease

Prevalence of depression in CVD. Depressive symptoms or clinical depression is common in CVD, and depression plays a role in reduced self-management as well as poor outcomes. Approximately 20-45% of patients with CVD experience symptoms of a depressive
disorder during the course of their illness (Child, Sanders, Sigel, & Hunter, 2010; Lespérance & Frasure-Smith, 2000; Wenger, 2008). Further, rates of depression in both inpatient and outpatient CVD samples appear to match or exceed those in community samples without CVD or other comorbid illness (Egede, 2007; Rutledge, Reis, Linke., Greenberg, & Mills, 2006).

The development and course of depressive symptoms is highly variable across individuals with CVD. Some individuals who have experienced depression prior to CVD diagnosis may experience a recurrence in response to the physiological and psychological stress of the illness. Alternatively, individuals without history of clinically significant depressive symptoms may experience difficulty with psychological adjustment to illness or neuropsychiatric consequence of vascular disease. A population-based survey of 224 individuals with CVD and depression revealed that approximately 80% of individuals with some form of CVD reported experiencing depression prior to the onset of CVD and approximately 20% reported onset of depression at or around the onset of CVD (O’Neil, Williams, Stevenson, Oldenburg, & Sanderson, 2012). Further, many patients experience remission of depressive symptoms, whereas as high as 30% experience persistent depressive symptoms (Diez-Quevedo et al., 2013; Kronish et al., 2006).

**Depression and prognosis in CVD.** Depression is not only prevalent in CVD patients, but also is associated with negative health outcomes such as more ambulatory care visits, emergency room visits, and functional disability (Egede, 2007). Beyond the extra burden of additional healthcare usage, depression is a demonstrated risk factor for mortality in patients with CVD (Barth, Schumacher, & Herrmann-Lingen, 2004; Blumenthal et al., 2003; Carney et al., 2004). In an influential study, Frasure-Smith, Lespérance, and Talajic (1993) first reported a 3.5-fold increased risk of mortality 6 months following acute MI in patients who met criteria for
major depression based on a modified version of the Diagnostic Interview Schedule. Further, later evidence suggested a dose-response relationship between depressive symptoms and 5-year mortality post-MI (Lespérance, Frasure-Smith, Talajic, & Bourassa, 2002). Meta-analyses have also demonstrated the increased risk of mortality in depressed CVD patients (Barth et al., 2004; Meijer et al., 2011; van Melle et al., 2004), consistently reporting that mortality risk in depressed CVD patients is approximately 2 times higher than mortality risk in non-depressed CVD patients (Barth et al, 2004; Meijer et al., 2011; van Melle et al., 2004).

**Possible mechanisms of the association between depression and mortality risk.** Both pathophysiological and behavioral factors have been implicated in the relationship between depression and mortality in CVD. Depression and CVD share several underlying physiological changes, including altered autonomic functioning, increased hypothalamic pituitary axis activity, platelet activation, increased catecholamine levels, and inflammation (Whooley, 2006; Kent & Shapiro, 2009; Fiedorowicz, 2014). For example, growing evidence indicates that increased inflammation present in CVD may also play a role in depression. Excess levels of inflammatory cytokines have been reported in both medically ill and healthy patients with depression and have also been related to depression severity (Raison, Capuron, & Miller, 2006; Miller, Maletic, & Raison, 2009). Inflammation has also been suggested as a mechanism of increased morbidity and mortality in depressed individuals without medical illness (Kiecolt-Glaser & Glaser, 2002). Chronic physiological changes such as increased inflammation lead to further decompensation of cardiovascular health over time, which may negatively impact prognosis.

In addition to pathophysiological contributions, behavioral factors may also influence the relationship between depression and mortality. Depression is negatively linked to multiple health behaviors including to lower medication adherence, poor diet, physical inactivity, and smoking
(Bonnet et al., 2005; DiMatteo, Lepper, & Croghan, 2000; Kronish et al., 2006). Although these examples represent different aspects of health and disease management, many of these factors covary. For example, medication non-adherence is often considered a marker of several unhealthy lifestyle behaviors associated with increased risk of cardiac events and poor outcomes (Bonnet et al., 2005; Whooley, 2006; Simpson et al., 2006), and the effects of unhealthy behaviors may be magnified in depressed patients at risk for inadequate adherence. Adherence to health behaviors and medication regimens is essential for slowing disease progression and reducing mortality risk. As such, depressed individuals who do not practice the recommended health behaviors (i.e., medication adherence, abstinence from smoking, following a low sodium diet) appear to be at increased risk for poorer prognosis.

1.2. Heart Failure

Individuals with severely decompensated CVD, such as HF, are likely to experience even more complications when co-occurring depression is present. Given the aging population and improved treatment and survival rates following cardiac events such as MI, the prevalence of more severe forms of CVD such as HF is increasing. Within the United States, 5.7 million persons ≥ 20 years of age have HF and 870,000 new HF cases are diagnosed each year (AHA, 2015). Estimates indicate that the prevalence of HF will increase 46% by 2030, such that > 8 million U.S. adults ≥ 18 years of age will have HF (AHA, 2015; Heidenreich et al, 2013). Given the high morbidity, HF carries significant economic and social burdens. For example, HF costs are expected reach 69.7 billion U.S. dollars by 2030 (AHA, 2015; Heinderech et al., 2013).

Many individuals with CVD develop ischemic HF as a result of ongoing physiological changes resulting from structural and functional damage to the cardiovascular system that lead to impairment in the heart’s ability to efficiently pump blood throughout the body (Francis,
Sonnenblick, Wilson Tang, & Poole-Wilson, 2008). However, HF is not solely caused by disease progression. Other individuals may develop HF of a non-ischemic origin. Although the precise etiologies of non-ischemic HF are poorly understood, a history of hypertension, diabetes, hypothyroidism, myocarditis, malnutrition, and excessive alcohol use are commonly identified as precursors (Follath, 1999; Follath, 2001).

In both ischemic and non-ischemic HF, the heart’s ability to deliver adequate blood and oxygen supply to the body is restricted. Multisystem compensatory changes occur to counteract the effects of the myocardial damage and ventricular dysfunction. For example, HF is characterized by many peripheral changes in the skeletal muscle including reduced muscle mass partially resulting from reduced blood flow, alterations in muscle structure, metabolism, and normal function (Jackson, Gibbs, Davies, & Lip, 2000). Other changes include decreased stroke volume, renal function abnormalities, arterial changes such as vasoconstriction, autonomic nervous system dysregulation, and a cascade of neurohormonal changes (Jackson et al., 2000). Initially, many of these changes are adaptive, short-term responses to increase blood pressure and maintain adequate blood supply to the body; however, over time these mechanisms lead to further damage and dysfunction in the cardiovascular system.

Externally, these physiological changes lead patients with HF to experience an array of physical symptoms including fatigue, shortness of breath, and edema (AHA, 2013). HF symptoms require regular monitoring and self-management encompassing lifestyle modification including complex medication regimens, dietary sodium restrictions, and appropriate responses to changes in health. Patients and their caregivers experience significant distress related to functional limitation and the burden of managing HF (Pattenden, Roberts, & Lewis, 2007). Given the complexity of disease management, as well as psychological factors such as
depression that further impede adherence to treatment recommendations, self-management is often poor.

Despite efforts to improve outcomes through medical therapies and interventions to promote self-management, mortality in HF remains high. The 1-year mortality rate for Medicare beneficiaries with HF from 1998 to 2008 was 29.6% (Chen, Normand, Wang, Y, & Krumholz, 2011) and approximately fifty percent of HF patients die within five years of diagnosis (Levy et al., 2002; Roger et al., 2004; Murphy, Xu, & Kochanek, 2013). Demographic and medical predictors of mortality in HF include older age (> 60 years), comorbid diabetes, lower ejection fraction, higher NYHA class, cardiomegaly, prior HF hospitalization, lower body mass index, and lower diastolic blood pressure (Pocock et al., 2006). Psychological factors, depression in particular, carry increased mortality risk in HF over and above these medical factors alone, potentially through the negative impact on disease management and self-care.

1.3. Depression in Heart Failure

Epidemiology of depression in HF. Approximately 21.5% of HF patients experience depression or depressive symptoms during the course of their illness and the prevalence of depression increases alongside disease severity (Havranek, Spertus, Masoudi, Jones, & Rumsfeld, 2004; Rutledge et al., 2006; Faller et al., 2007). HF patients diagnosed as higher NYHA class, indicating more severe functional limitation, report higher rates of depressive symptoms, with nearly a 4-fold increase in prevalence of depression between class I and class IV HF patients (Rutledge et al., 2006). This increase is likely due to the greater symptom burden and impact on quality of life associated with more severe HF (i.e., NYHA class III and IV). Depression also occurs more often in HF patients with common comorbidities such as chronic
obstructive pulmonary disease, anemia, insulin-dependent diabetes mellitus, and hyperlipidemia (Albert et al., 2009).

In addition to disease severity and presence of comorbidities, age and gender are also associated with depressive symptoms in HF patients. Younger patients HF report higher rates of depression (Gottlieb et al., 2004; Jiang et al., 2007; Rohyans and Pressler, 2009), as well as worse quality of life, bodily pain, and general functioning (Gottlieb et al., 2004). Younger patients may experience more interference with employment and daily functioning, and therefore, be at greater risk to feel limited or depressed as a result of illness. In terms of gender, both individual reports and aggregated estimates indicate that women with HF demonstrate higher rates of depression compared with men with HF (32.7% versus 26.1%; Albert et al., 2009; Eastwood et al., 2012; Gottlieb et al., 2004; Hsich et al., 2012; van den Broek, Christenson, Seliger, Gottdiener, & Kop, 2011; Rutledge et al., 2006). However, the predictors of depressive symptoms may differ between genders. Among men, unemployment, lower ejection fraction, and low quality of life are associated with depressive symptoms, whereas in women, uncertainty related to illness appears to be linked to depressive symptoms (Kao et al., 2013). In both men and women with HF, depressive symptoms are associated with worse quality of life (Kao et al., 2013).

**Depression and healthcare usage in HF.** In HF, depressive symptomology is not only detrimental to quality of life, but is also associated with increased healthcare usage and associated costs. For example, depressed HF patients have a 2-fold risk of emergency room visits (Himelhoch, Weller, Wu, Anderson, & Cooper, 2004), markedly higher hospital readmission rates (Rutledge et al., 2006), and longer hospital stays (Freedland et al., 1991). Increased healthcare usage leads to increased economic and financial burden. In a 3-year, retrospective
analysis of health care utilization in 10,980 HF patients, Sullivan, Simon, Spertus, and Russo (2002) reported that annual healthcare costs for HF patients with a diagnosis of depression and who were prescribed antidepressants were 29% higher than for patients with no evidence of depression. The increase in cost is not attributable to mental health-related costs alone, but primarily stems from increased inpatient and outpatient medical visits (Sullivan et al., 2002).

**Depression and Prognosis in HF.** Beyond the impact on the healthcare system, depression is also a predictor of reduced survival in HF patients. Freedland and colleagues (1991) first reported a trend towards increased length of hospitalization and 1-year mortality in depressed 60 hospitalized HF patients. Although there was no difference in discharge vital status or 3-month readmission between patients with and without major depression, 50% of patients who met criteria for major depression at the time of index hospitalization died by 1 year follow-up compared to 29% of non-depressed patients.

Following Freedland et al.’s investigation, additional studies have confirmed that reduced survival in depressed HF patients using larger samples. Diez-Quevedo and colleagues (2013) followed 1,017 HF outpatients for a median of 5.4 years to explore the impact of depression, assessed using an abbreviated version of the Geriatric Depression Scale, on mortality. After adjustment for sex, age, duration of HF, ischemic etiology, NYHA class, ejection fraction, diabetes, chronic obstructive pulmonary disease, peripheral vasculopathy, body mass index, ACE or ARB use, and beta-blocker use, depression was associated with increased all-cause (HR = 1.39, 95% CI: 1.15 – 1.68), but not cardiovascular, mortality. Further, participants who reported improvement in depressive symptoms during the first year of follow-up also demonstrated reduced cardiovascular and all-cause mortality risk (Diez-Quevedo et al., 2013).
Additionally, one of the largest studies conducted to date utilized a hospital-based registry to determine risk factors for 60- and 90-day mortality post-discharge from HF hospitalization (O’Connor et al., 2008). A step-wise analysis was used to develop a comprehensive risk prediction model based on 19 predetermined demographic and clinical variables. History of depression, as noted in medical records, was one of the strongest predictors of increased mortality risk (HR = 1.48, 95% CI: 1.14 – 1.93), only surpassed by comorbid liver disease (HR = 1.98, 95% CI: 1.20 – 3.26) and reactive airway disease (HR = 1.58, 95% CI: 1.17 – 2.14; O’Connor et al., 2008).

Meta-analyses have confirmed individual reports. An initial meta-analysis reported over a 2-fold increased risk of death and associated cardiac events (e.g., heart transplantation, new cardiac events) for HF patients with elevated depressive symptoms or a diagnosis of a depressive disorder (Rutledge et al., 2006; relative risk: 2.1, 95% CI: 1.7 – 2.6). Rutledge and colleagues also reported that the association between depression and HF outcomes (mortality and clinical events) did not differ by study duration. However, Rutledge et al. noted that the studies included were limited by small sample sizes and likely underpowered to detect short-term differences in mortality and clinical events between depressed and non-depressed individuals. However, this was a small portion of a larger meta-analysis and only included eight studies. Furthermore, the authors did not examine mortality alone, likely due to an insufficient number of studies solely estimating mortality risk (Rutledge et al., 2006).

A more recent meta-analysis of thirteen studies that examined mortality alone demonstrated similar results (Gathright & Hughes, in preparation). Results indicated that depressive symptoms increased all-cause (HR = 1.48; 95% CI: 1.28 – 1.71) and cardiovascular (HR = 1.64; 95% CI: 0.88 – 3.06) mortality risk in HF patients compared to non-depressed HF
patients. Subgroup analyses indicated that depressed participants recruited from inpatient (HR = 1.31; 95% CI: 1.10 – 1.56), but not outpatient, settings demonstrated a significant increased risk of mortality. Participants recruited from inpatient settings may represent patients with more severe illness or poorer disease self-management, and may also be at increased risk for mortality. Mean age of the sample, gender, and length of follow-up did not impact the relationship between depression and mortality (Gathright & Hughes, in preparation).

Given the increased mortality risk conferred by co-morbid depressive symptoms, greater understanding of the factors that contribute to increased mortality in depressed HF patients is needed to guide intervention efforts. A potential mechanism of action relates to disease self-management. In both healthy and patient samples, depression is associated with inadequate engagement in health behaviors and adherence to treatment recommendations. Symptoms such as low motivation, increased fatigue, reduced attention and concentration, and a sense of helplessness or hopelessness may interfere with compliance with treatment recommendations. As such, depression may lead to increased mortality through its negative effects on self-management behaviors such as medication adherence (see Figure 1).
1.4. Medication Non-adherence

Approximately half of all medical patients in the United States do not adequately follow medication regimens prescribed for the prevention or treatment of acute or chronic conditions, with most estimates of non-adherence ranging from 20%-80% (DiMatteo, 2004; DiMatteo, 1994; Dunbar-Jacob, J., & Schlenk, 2001; Haynes, Ackloo, Sahota, McDonald, & Yao, 2008; Haynes, McDonald, Garg, & Montague, 2002). Adherence for chronical medical conditions tends to be worse than for acute illnesses (Gilberg, Laouri, Wade, & Isonaka, 2003). For many chronic illnesses, proper medication adherence requires multiple steps such as refilling prescriptions appropriately, as well as following home regimens encompassing correct dosage, timing, and frequency. The complexity of medication regimens often vary based on the individual and medical condition(s).
Medication adherence in HF. In diseases requiring complicated disease-management regimens and lifestyle modifications, such as HF, managing multi-step medication adherence can be difficult. HF patients are recommended to follow complex regimens composed of one or more medications from different drug subclasses including diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and β-blockers (Hunt et al., 2001; Remme & Swedberg, 2001; Nohria, Lewis, & Stevenson, 2002). Across medications, adherence estimates in HF range from approximately 40-60% (Wu Moser, Chung, & Lennie, 2008; Wu et al., 2009), although one report has suggested that at least 88% adherence may be necessary to achieve improved outcomes (Wu et al., 2009).

Medication adherence and prognosis in HF. Adherence to medications is critical for reducing risk factors related to cardiac events and worsening CVD, such as reducing high blood glucose levels and improving lipid profiles. Indeed, better adherence is associated with lower rates of emergency room visits, fewer cardiac events and readmissions, and shorter hospital stays (Ansell, 2008; Annema, Luttik, & Jaarsma, 2009; Esposito, Bagchi, Verdier, Bencio, & Kim., 2009; Gehi, Ali, Na, & Whooley, 2007). A survey of patients, caregivers, cardiologists, and HF nurses indicate that 13% - 26% of participants identified non-adherence as a contributor to rehospitalization and respondents reported adherence to be one of the most important means of preventing additional rehospitalization (Annema et al., 2009). Increased healthcare usage stemming from poor adherence also leads to higher healthcare-related costs (Sokol, McGuigan, Verbrugge, & Epstein, 2005; Esposito et al., 2009; Roebuck, Liberman, Gemmill-Toyama, & Brennan, 2011). For example, an examination of Medicaid beneficiaries reported that total healthcare costs, including drug costs, were 23% ($5910) lower for adherent adults with HF (Esposito et al., 2009). Better medication adherence is also linked to reduced mortality risk in
HF (Fitzgerald et al., 2011; Granger et al., 2005; Miura et al., 2001; Wu et al., 2008a). In a retrospective analysis of 3-month pharmacy refill adherence and 1-year mortality in 577 HF patients, < 80% adherence was associated with increased all-cause mortality (HR = 2.99, 95% CI: 2.09 – 4.29; Fitzgerald et al., 2011)

**Predictors of poor adherence.** Common sociodemographic and medical predictors of non-adherence include low social support (Wu et al., 2008b), lower financial status (Wu et al., 2008b), ethnic minority status (Wu et al., 2008b), and cognitive dysfunction (Hawkins et al., 2012). Research of gender differences appears mixed, with some studies reporting greater rates of non-adherence in women with HF compared to men with HF (Lewey et al., 2013) and others reporting poorer adherence rates in men with HF (Monane, Bohn, Gurwitz, Glynn, & Avorn, 1994). Although some individual reports suggest that adherence worsens with age (Jin et al., 2014), a recent meta-analysis indicates that age does not appear to be related to adherence in HF patients (Krueger et al., 2015).

Factors related to the regimen itself can also interfere with adherence, such as high medication costs (Dunlay, Eveleth, Shah, McNallan, & Roger, 2011) and the complexity of the medication regimen (Libby et al., 2013). A meta-analysis of adherence in CVD revealed that that taking one medication per day as compared to two doses per day reduces medication non-adherence by 50% (Caldeira, Vaz-Carneiro, & Costa, 2014). Patient reports support these findings. According to one study, approximately one-third of primary care patients with elevated CVD risk reported having too much medication to take as a significant barrier to their adherence to hypertension and/or hyperlipidemia medications (Zullig et al., 2015). Additionally, nearly one-fourth of the sample reported that difficulty remembering whether their medication was taken at the appropriate time (Zullig et al., 2015). Surprisingly, participants did not frequently
cite delaying medications due to negative side effects, confusion over how much medication of each type they are supposed to take, difficulty remember what the medication was for, and not understanding medication instructions as additional reasons for poor adherence (Zullig et al., 2015).

HF patients commonly attribute poor adherence to forgetfulness (50%), with a significant portion of patients also reporting that having multiple prescribed medications (20%), and the absence of symptoms (20%) as negatively impacting medication adherence (Aggarwal, Aggarwal, Pender, Mosca, & Mochari-Greenberger, 2015). Unfortunately, hospitalizations due to worsening HF do not necessarily lead to improvements in medication-taking behavior to prevent future exacerbations. Following hospitalization, adherence to HF medications steadily declines (Sueta et al., 2014). Declines in adherence may be attributed to lapses in attention, excessive daytime sleepiness, and having ≥ 2 medication prescribed doses per day (Riegel et al., 2012).

In addition to regimen-related factors, patient beliefs and perceptions about their disease and the efficacy of treatment may also impact medication-taking behavior. For example, patients who view their disease as fatal with little hope for longevity or improvement may be less prone to adhere to medication protocols (Rashid, Edwards, Walter, & Mant, 2014). As depression is associated with maladaptive thinking styles including hopelessness and negative views of the future, depressed patients may also hold negative beliefs about the efficacy of their treatment regimens.

Medication adherence and depression. Medication adherence appears more difficult for patients experiencing co-morbid depressive symptomology. Estimates in general medical populations suggest that depressed patients are 1.76 to 3.03 more likely to be non-adherent than
non-depressed patients (DiMatteo, Lepper, & Croghan, 2000; Grenard et al., 2011). Depression has also been linked to non-adherence CVD populations (Gehi, Haas, Pipkin, Whooley, 2005; Bane, Hughes, & McElnay, 2006), as well as patient-reported difficulty taking medications in HF (Morgan et al., 2006). For example, a cross-sectional analysis from the Heart and Soul study revealed that depressed HF patients were more likely to incorrectly take their medication and to skip their medications; no statistically significant difference emerged between depressed and non-depressed patients reported rates of forgetting to take their medications after adjustment for covariates (Gehi et al., 2005).

In addition to the link between depression and poor adherence, treatment of depressive symptoms may improve adherence. For example, adherence improves alongside remission of depressive and anxiety symptoms post-hospitalization in patients with acute coronary syndrome (Rieckmann et al., 2006; Bauer et al., 2012). Conversely, persistent depressive symptoms are associated with continued rates of poorer adherence (Kronish et al., 2006). As a result, poor medication adherence likely reduces the effectiveness of treatment.

**Depression, medication adherence, and prognosis in CVD.** Very limited research has examined the combined impact of depressive symptoms and poor medication adherence on outcomes such as mortality in CVD populations. Only two studies to date have reported related findings.

First, in a prospective cohort study of 1017 patients with coronary heart disease, Whooley and colleagues (2008) explored how medical, biological, and behavioral factors impacted the association between depressive symptoms and later cardiac events (e.g., HF, MI, stroke, transient ischemic attack, or death) after an average of 4.8 years of follow-up. Patients who reported depressive symptoms at baseline experienced 50% more cardiac events compared with non-
depressed individuals. Results indicated that behavioral mediators, rather than biological factors, primarily explained the relationship between depressive symptoms and subsequent cardiac events. The association between depressive symptoms and subsequent cardiac events was unchanged after adjustment for selective serotonin reuptake inhibitor or tricyclic antidepressant use, heart rate variability, levels of serotonin and omega-3 fatty acids, or norepinephrine and cortisol. However, comorbidity, smoking status, medication adherence, physical activity, left ventricular function, and C-reactive protein level attenuated the relationship between depressive symptoms and cardiac events. Though self-reported physical activity accounted for the largest proportion of variance (31%), medication adherence was only assessed through a single, self-reported response to the question, “In the past month, how often did you take your medications as the doctors prescribed?: all of the time (100%), nearly all of the time (90%), most of the time (75%), about half the time (50%), or less than half the time (< 50%).” Medication adherence reported to be 75% of the time or less was classified as non-adherent (Whooley et al., 2008). However, self-reported medication adherence may not fully capture the relationship between medication-taking behavior and outcomes. Prior research has indicated that significant discrepancy can exist between self-report and objective measurement in patients with complex diseases and medication regimens, such as CVD (Nieuwenhuis, Jaarsma, van Veldhuisen, and van der Wal, 2012). For example, Wu, Moser, Chung, and Lennie (2008a) found that objectively measured, but not self-reported, medication adherence predicted cardiac event-free survival in HF patients and some reports suggest a relationship between depressive symptoms and over-reporting of poor adherence (Kronish et al., 2006; DiMatteo et al., 2000; Tang et al., 2014). Objective medication monitoring is needed to better understand these findings.
Second, Wu, Lennie, Dekker, Biddle, & Moser, (2013) conducted a secondary analysis of two prospective studies, including a randomized control trial, and sought to explore the combined impact of depressive symptoms and medication adherence on cardiac event-free survival (e.g., cardiac-related emergency room visit, hospitalization, or death) in 216 HF patients. This study had several strengths, including the use of objective medication monitoring using Medication Event Monitoring System (MEMS) of 1 HF medication for 1 to 3 months and follow-up of up to 3.5 years. Participants who reported depressive symptoms, assessed using the Patient Health Questionnaire—9, were more likely to be classified as non-adherent (e.g., < 88% days taking correct dose). Both depressive symptoms and medication non-adherence were associated with reduced cardiac event-free survival after adjustment for covariates including study and group assignment, age, NYHA class, ace inhibitor use, and anxiety. HF patients with worse medication adherence who also reported elevated depressive symptoms had 5 times greater risk of cardiac events than adherent, non-depressed patients at 3.5 year follow-up (Wu et al., 2013). Although many have speculated about the importance of medication adherence in the relationship between depression and mortality in HF, no studies to date have examined these relationships.

1.5. The Present Study

The association between depression and increased mortality risk in HF is well-documented. Further, depression is known to negatively impact medication adherence in healthy and disease samples, and inadequate medication adherence is associated with poorer outcomes. However, relationships among depressive symptoms, medication adherence, and mortality have not been examined in a sample of HF patients. Given the vulnerability of HF patients, it is essential to understand how these factors are related in HF to the end of targeting the underlying
contributors to increased healthcare usage, costs, and mortality rather than focusing on symptom-reduction alone. As individuals with HF represent a clinically compromised population with complicated self-management regimens, it appears likely that depression would negatively impact medication adherence in such a population, which is known to worsen prognosis.

The objective of the present study is to evaluate whether medication non-adherence contributes to the link between depression and mortality in HF. The following hypotheses were tested:

1. Approximately 20% of the current sample of HF patients would report depressive symptoms.
2. Depressive symptoms would be positively related to mortality risk, such that individuals reporting higher levels of depressive symptoms would demonstrate increased all-cause and cardiovascular mortality risk.
3. Depressive symptoms would be negatively associated with medication adherence, such that patients with higher depressive symptoms would demonstrate poorer medication adherence.
4. Medication adherence would be negatively related to mortality risk, such that individuals with lower medication adherence would demonstrate increased all-cause and cardiovascular mortality risk.

Medication adherence would mediate the relationship between depression and mortality risk. Controlling for social support, anxiety, global cognitive function, functional status, and disease severity, medication adherence would attenuate the relationship between depressive symptoms and mortality.
II. METHOD

2.1. Participants

The current study consisted of 303 older adults with HF enrolled in the Heart Adherence, Behavior, and Cognition (HeartABC) study. HeartABC is a longitudinal, observational study of the impact of psychosocial and cognitive factors on self-care behaviors in older adults with HF. Participants were recruited between August 2010 through October 2013 from inpatient and outpatient cardiology services at Summa Health System's Akron City Hospital (Akron, OH) and University Hospitals (Cleveland, OH). Potential participants were eligible for inclusion if they were aged 50-85 years at enrollment, had documented systolic HF (i.e., HF diagnosis was verified within 36 months prior to study enrollment), and classified as New York Heart Association class II or III by their physician. Potential participants were ineligible if they underwent cardiac surgery within 3 months of enrollment or had history of neurological disorder or injury (e.g., Alzheimer’s disease, dementia, stroke, seizures), moderate or severe head injury, past or current significant psychiatric disorders (e.g., psychotic disorders, bipolar disorder, learning disorder, developmental disability), renal failure requiring dialysis, or untreated sleep apnea, current substance abuse or within the past 5 years. Potential participants were also ineligible if they were currently utilizing a home tele-health monitoring program for HF. Participants with complete data on measures of depressive symptoms and medication adherence were included in the present analysis.
2.2. Measures

**Depressive Symptoms.** The Patient Health Questionnaire—9 (PHQ-9) was used to assess depressive symptoms (Kroenke, Spitzer, & Williams, 2001). The PHQ-9 is a 9-item questionnaire, with scores ranging from 0 to 27. Higher scores represent greater depressive symptomology. Total scores are categorized as representing none to minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe depression (20-27) (Kroenke, Spitzer, & Williams, 2001). The PHQ-9 was administered by a trained research assistant at the baseline and third study visits. The two scores were averaged to create a more reliable measure of each participant’s level of depression over the course of the study. In the current analysis, a mean PHQ-9 score of $\geq$ 5 indicated presence of depressive symptoms.

**Medication Adherence.** Participants completed 28 days of objective medication monitoring using an electronic Medsignals pillbox (VitalSignals, LLC, Lexington, KY). The initial 7 days of monitoring were designed to serve as a “run-in” period to allow participants to adjust to using the electronic pillbox as a part of their self-management routine. A research assistant returned to the participants’ home following the run-in to ensure that participants understood instructions for use. If necessary, such as in the event of a prescribed change in the medication regimen, adjustments were made in the pills selected for monitoring. Only the final 21 days of medication monitoring were included in analysis.

The Medsignals pillbox transferred daily adherence data to an electronic server through the participants’ home telephone lines. The pillbox contains four individual bins so that up to four common HF medications (e.g., beta-blockers, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, diuretics, aspirin, aldosterone antagonists, Plavix, and statins) were tracked throughout the monitoring period. Medications chosen for each participant were
based on a predetermined priority list created for the current study (Table 1). Participants were instructed to take their medications as prescribed by their physicians.

Table 1. Medication Selection.

<table>
<thead>
<tr>
<th>Bin 1</th>
<th>Bin 2</th>
<th>Bin 3</th>
<th>Bin 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choice A</td>
<td>Beta Blocker</td>
<td>ACE</td>
<td>Diuretic</td>
</tr>
<tr>
<td>Choice B</td>
<td>Aldosterone Antagonist</td>
<td>ARB</td>
<td>Plavix</td>
</tr>
<tr>
<td>Choice C</td>
<td>Statin</td>
<td>Digoxin</td>
<td>Statin</td>
</tr>
</tbody>
</table>

Medication adherence was calculated as a ratio of the percent of days that the patient was compliant with their medication regimen divided by the number of total days monitored. Patients were considered compliant (0 = non-compliant, 1 = compliant) with their medication regimen when the bin was opened the prescribed number of times each day (i.e., no overdose or underdose). The percent compliance for each of the four bins was averaged to create a total score. Trained research assistants interviewed patients to determine days the participant did not use the box for a specific reason, such as travel or reshospitalization, and these days were excluded from analysis. Medication adherence was entered as a continuous variable in primary analyses.
Global Cognitive Function. The Modified Mini-Mental Status Examination (3MS; Teng & Chui, 1987) was used to assess global cognitive performance. The 3MS is a brief screening tool commonly used to screen for cognitive impairment. The 3MS represents an expansion to the Mini-Mental Status Examination (Folstein, Folstein, & McHugh, 1975) and includes assessment of orientation, aspects of executive function, learning and memory, language, and visuospatial abilities. Scores range from 0 to 100, with higher scores indicating better cognitive function. 3MS was entered as a continuous variable.

Social Support. The Multidimensional Scale of Perceived Social Support (MSPSS; Zimet, Dahlem, Zimet, & Farley, 1988) was used to assess social support. The MSPSS consists of 12 total items divided into subscales of perceived support derived from family, friends, and significant other. A total score is created by summing responses to all items. The MSPSS subscales and total score demonstrate strong psychometric properties (i.e., Cronbach’s α ranges from 0.84 to 0.92 for the total score) (Zimet et al., 1990). The MSPSS total score was included as a continuous variable in analyses.

Anxiety. Participants completed a short-form scale from the Patient-reported Outcomes Measurement Information System (PROMIS) to provide an assessment of anxiety (Pikonis et al., 2011). The PROMIS scale consists of 7 items rated on a Likert scale (1=never to 5=always). Total scores range from 7 to 35, with higher scores reflecting higher reported anxiety in the past seven days. The PROMIS total score was entered as a continuous variable.

Co-morbidity. The Charlson Comorbidity Index (Charlson, Szatrowski, Peterson, & Gold, 1994) was used to provide an age-corrected numerical estimate of the impact of comorbid conditions on the relative risk of death. Medical diagnoses from a predetermined list are assigned a value from 1 to 4 based on the severity of the condition, with more severe conditions receiving
higher values. A total score is calculated such that higher scores correspond to increased mortality risk due to the presence of comorbid conditions. Participants’ self-reported list of medical conditions was validated by medical chart review conducted by a trained research assistant.

**Disease Severity.** HF severity was assessed using physician-documented New York Heart Association (NYHA) class, which classified patients as Class I (no symptoms), Class II (Mild), Class III (Moderate), or Class IV (Severe). Although NYHA class was documented by physicians prior to enrollment, a trained research assistant assessed self-reported HF symptoms and limitations to confirmed NYHA classification at the time of study participation. In the primary analysis, classes I and II were combined into one group and classes III and IV were combined into a second group representing more severe HF.

**Mortality.** All-cause and cardiovascular mortality were determined using data obtained from the Centers for Disease Control and Prevention’s National Death Index (NDI; http://www.cdc.gov/nchs/ndi.htm). The NDI is a centralized database that allows researchers to obtain vital status and cause of death information of study participants. The NDI compares study participants with death records from state vital statistics offices based on demographic variables obtained as part of the initial data collection. For the current sample, first and last name, month, day, and year of birth, race, sex, and state of residence were provided to link participants with relevant death records.

The NDI is updated annually, with death records added approximately 12 months after the end of each calendar year. For the current study, deaths recorded through December 2014 were obtained. A death was classified as a cardiovascular death if the first cause of death according to ICD-10 codes listed was acute rheumatic fever/chronic rheumatic heart diseases
(I00-I09), hypertensive heart disease (I11), hypertensive heart and renal disease (I13), coronary heart disease (I20-I25), other heart diseases (I26-I51), essential hypertension and hypertensive renal disease (I10, I12, I15), or cerebrovascular diseases (I60-169) (WHO, 2004). In the proposed analyses, time-to-event (i.e., days from the end of the observation period until death or end of follow-up) will be entered as a continuous variable.

2.3. Procedure

The original study protocol was approved by the institutional review boards of Kent State University, Summa Health System, University Hospitals of Cleveland, and Case Western Research University. The institutional review boards of Summa Health System and University Hospitals of Cleveland approved the request to obtain mortality data from the NDI.

Following informed consent, participants completed four study visits over the course of 1-2 months, as well as 28 days of medication monitoring using the electronic pillbox. At the baseline study visit, demographic, psychosocial, and medical history was collected using self-report questionnaires. Approximately 2 weeks later, a trained research assistant conducted the second study visit at the participant’s home. This visit included installation of the electronic pillbox and instructions for use, as well as administration of neuropsychological testing. The third study visit occurred approximately 1 week later and consisted of additional brief, cognitive testing, as well as a check of the electronic pillbox. The final study visit occurred 3 weeks later and included additional neuropsychological testing and collection of the electronic pillbox.

The request for data from the NDI was initiated in June 2014. Following NDI approval of the request, participant demographic information (i.e., first and last name, date of birth, race) were provided on a password-encrypted disk to the NDI. The data linking individuals in the NDI database to study participants were received in January 2016. A trained research assistant cross-
referenced each potential NDI match with self-reported demographic data to ensure true matches were included in the analysis.

2.4. Analytic Plan

**Preliminary Analyses.** Descriptive statistics (means, SDs, frequencies, percentages) were used to characterize the sample. Bivariate correlations were calculated to assess relationships among the predictor variable (depressive symptoms), mediator (medication adherence), dependent variable (mortality), and covariates. Pearson chi-square tests and *t*-tests were used to examine differences between depressed and non-depressed participants.

Several of the basic assumptions of survival analysis were met based on the study design, including statistically independent events, change from one of two mutually exclusive and collectively exhaustive states (e.g., life to death), the assumption that all study participants will be event free upon study entry, and independent censoring. (Kalbfleisch & Prentice, 1980; Grimm & Yarnold, 2000).

Prior to testing study hypotheses, the data was examined for violations of the assumptions of hierarchical multiple linear regression and cox proportional hazards modelling. To examine potential violations of univariate normality, skewness and kurtosis statistics were calculated. Bivariate correlations were examined to assess for the presence of multicollinearity. The Schonfield residuals were used to test the proportionality of hazards assumption for continuous data. Examination of plots was used to test the assumption for categorical variables. No violations of assumptions were evident. The criterion for statistical significance was set at *p* < .05 for correlation and linear regression analyses. For the Cox proportional hazards ratios, 95% CI were used to determine statistical significance of HRs. In addition, a reduction of ≥ 3% in the HR following adjustment for a potential mediator was deemed to signify significant mediation.
**Primary and Secondary Analyses.** Given the presence of censored data (i.e., not all participants experienced the primary outcome prior to the end of the observation period) and the use of multivariable analysis, Cox proportional hazards regression (Cox, 1972; Cox & Oakes, 1984) was used to assess the relationship between depressive symptoms and mortality, with and without adjustment confounding variables. For both outcomes (i.e., all-cause and cardiovascular mortality), three separate Cox proportional hazards regression models was performed. First, a model included covariates determined a priori based on known associations with medication adherence and mortality in HF. The following covariates were included: age, sex, global cognitive function, anxiety, social support, co-morbidity, and disease severity. Next, Model 2 included covariates included in Model 1 as well as depressive symptoms (PHQ-9 ≥ 5). Finally, Model 3 included medication adherence to assesses whether medication adherence attenuated the hypothesized relationship between depressive symptoms and mortality. A secondary series of Cox proportional hazards models were performed treating PHQ-9 scores as a continuous variable. For each series of analyses, the percentage change in the log HR was calculated to determine the impact of the contribution of medication adherence to the relationship between depression and mortality in adjusted analyses. A percentage change ≥ 5% was considered to be a meaningful contribution to the relationship.

**Sensitivity Analyses.** A series of Cox proportional hazards models were conducted with different PHQ-9 and medication adherence cutoffs to determine at what point an elevated score was associated with increased mortality risk. For PHQ-9 scores, participants were classified as either non-depressed (coded as “0”) or depressed (coded as “1”) using cutoffs that increased incrementally for each additional depressive symptom reported. For medication adherence, participants were classified as either non-adherence (coded as “0”) or adherent (coded as “1”).
Similar to PHQ-9 scores, one-point incremental cutoffs were created representing each 1 percent increase in adherence. Covariates included age, sex, NYHA class, comorbidity, and PHQ-9 scores (medication adherence analysis only).

**Power Analysis.** Power analyses were conducted using PASS 13 Power Analysis and Sample Size Software (Kaysville, Utah) to provide a justification of sample size. With the mortality rate in the current study, analysis indicated a power of .73 given the sample size of 303 and adjustment for covariates when presence of depression was defined as PHQ-9 ≥ 5. This suggests that the analysis may be underpowered. When PHQ-9 scores were treated as a continuous variable, analysis revealed a power of .93, which indicates adequate power.
III. Results

3.1. Sample Characteristics

The sample included 303 patients with HF with an average age of 68.5 years (SD = 9.64). Participants primarily included Caucasian (n = 223, 73.6%) males (n = 183, 60.4%). Most had class III HF (n = 184, 60.7%) and a mean Charlson Comorbidity Index Score of 3.30 (SD = 1.74). Average medication adherence was 73.05% (SD = 25.42). Complete demographic and clinical characteristics stratified by presence of depression (PHQ-9 score ≥ 5) are presented in Table 2. Bivariate correlations among study variables are presented in Table 3.

Participants averaged 996.08 ± 334.03 days of follow-up (median = 1048; range = 41 – 1801). This corresponds to an average of 2.73 ± .91 years (median = 2.87; range = .11 – 4.93). During follow-up, 51 deaths (16.8%) from any cause occurred. Forty-three percent (n = 22) of deaths were classified as occurring due to a cardiovascular-related cause. Of the sample, 104 patients (34.3%) were classified as depressed (PHQ-9 ≥ 5), indicating at least mild depressive symptomology. Of the depressed individuals, 22 (21.2%) experienced the primary outcome (i.e., mortality) by the end of the follow-up period. Eight participants who were classified as depressed died from a cardiovascular cause.
Table 2. Demographic and Clinical Characteristics of Participants at Baseline ($n = 303$).

<table>
<thead>
<tr>
<th></th>
<th>Total Sample</th>
<th>Depressive Symptoms</th>
<th>PHQ-9 ≥ 5</th>
<th>PHQ-9 &lt; 5</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size (n)</td>
<td>303</td>
<td>104</td>
<td>199</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>68.50 (9.64)</td>
<td>66.49 (10.23)</td>
<td>69.56 (9.16)</td>
<td>.011</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>183 (60.4)</td>
<td>52 (50.0)</td>
<td>131 (65.8%)</td>
<td>.007</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>223 (73.6)</td>
<td>67 (64.4)</td>
<td>156 (78.4)</td>
<td>.009</td>
<td></td>
</tr>
<tr>
<td>Highest Education Level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8th grade or less</td>
<td>4 (1.3)</td>
<td>0 (0)</td>
<td>4 (3.8)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>9th – 11th grade</td>
<td>28 (9.2)</td>
<td>14 (13.5)</td>
<td>14 (7.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High School</td>
<td>87 (28.7)</td>
<td>35 (33.7)</td>
<td>52 (26.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Technical/trade school</td>
<td>30 (9.9)</td>
<td>10 (9.6)</td>
<td>20 (10.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>84 (27.7)</td>
<td>29 (27.9)</td>
<td>55 (27.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>41 (13.5)</td>
<td>3 (2.9)</td>
<td>38 (19.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Master’s degree</td>
<td>29 (9.6)</td>
<td>9 (8.7)</td>
<td>20 (10.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>182 (60.1)</td>
<td>53 (51.0)</td>
<td>129 (64.8)</td>
<td>.013</td>
<td></td>
</tr>
<tr>
<td>Charlson</td>
<td>3.30 (1.74)</td>
<td>3.31 (1.71)</td>
<td>3.29 (1.76)</td>
<td>.939</td>
<td></td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I/II</td>
<td>104 (34.3)</td>
<td>15 (14.4)</td>
<td>89 (44.7)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Class III/IV</td>
<td>199 (65.7)</td>
<td>89 (85.6)</td>
<td>110 (55.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROMIS</td>
<td>12.97 (5.30)</td>
<td>17.12 (5.43)</td>
<td>10.80 (3.72)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>MPSS</td>
<td>69.17 (14.57)</td>
<td>64.65 (15.17)</td>
<td>71.52 (13.70)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>3MS</td>
<td>92.03 (6.44)</td>
<td>91.22 (6.37)</td>
<td>92.46 (6.46)</td>
<td>.113</td>
<td></td>
</tr>
<tr>
<td>Medication Adherence</td>
<td>73.05 (25.42)</td>
<td>65.25 (27.77)</td>
<td>77.12 (23.14)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* Means and standard deviations presented for continuous variables. Frequencies and percentages presented for categorical variables. Pearson $\chi^2$ tests (categorical variables) or $t$-tests (continuous variables) were used to calculate $p$ values.

*Abbreviations:* Charlson = Charlson Comorbidity Index; NYHA = New York Heart Association; PHQ-9 = Patient Health Questionnaire—9; PROMIS = Patient-reported Outcomes Measurement Information System (short-form anxiety scale); MPSS = Multidimensional Scale of Perceived Social Support; 3MS = Modified Mini-Mental Status Examination.
Table 3. Pearson correlations between continuous demographic and clinical variables.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>NYHA</th>
<th>Comorbidity</th>
<th>3MS</th>
<th>MPSS</th>
<th>PROMIS</th>
<th>Medication Adherence</th>
<th>PHQ-9 (continuous)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>-</td>
<td>.07</td>
<td>-</td>
<td>.14*</td>
<td>-.14*</td>
<td>.11</td>
<td>-.13*</td>
<td></td>
</tr>
<tr>
<td><strong>NYHA</strong></td>
<td>-</td>
<td>.07</td>
<td>-</td>
<td>.08</td>
<td>-.13*</td>
<td>.18**</td>
<td>-.11</td>
<td>.34***</td>
</tr>
<tr>
<td><strong>Comorbidity</strong></td>
<td>-</td>
<td>.09</td>
<td>.01</td>
<td>-.04</td>
<td>-.05</td>
<td>.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3MS</strong></td>
<td>-</td>
<td>-</td>
<td>-.13*</td>
<td>-.13*</td>
<td>.07</td>
<td>-.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MPSS</strong></td>
<td>-</td>
<td>-</td>
<td>-.29***</td>
<td>.20***</td>
<td>.31***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PROMIS</strong></td>
<td>-</td>
<td>-</td>
<td>-.11*</td>
<td>.65***</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medication Adherence</strong></td>
<td>-</td>
<td>-</td>
<td>-.22***</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p < .05, ** p < .01, *** p < .001. Note. PHQ-9 (categorical): 0 = not depressed; 1 = depressed. Abbreviations: Charlson = Charlson Comorbidity Index; NYHA = New York Heart Association; PHQ-9 = Patient Health Questionnaire—9; PROMIS = Patient-reported Outcomes Measurement Information System (short-form anxiety scale); MPSS = Multidimensional Scale of Perceived Social Support; 3MS = Modified Mini-Mental Status Examination.
3.2. *Primary Analyses*

**Depressive symptoms and medication adherence.** A hierarchical multiple linear regression analysis was performed to examine the relationship between depressive symptoms (PHQ-9 ≥ 5) and medication adherence. In the first block, the linear combination of demographic and clinical covariates explained 6.7% of the variability in medication adherence, $F(7, 295) = 3.03, p < .01$. Specifically, higher perceived social support ($\beta = .17, p < .01$) was associated with higher medication adherence. In the second block, the addition of depression significantly improved model fit, $\Delta R^2 = .02, \Delta F(1, 294) = 7.27, p < .01$. Depressive symptoms were negatively related to medication adherence, ($\beta = -.19, p < .01$).

**Depressive symptoms, medication adherence, and all-cause mortality.** A series of Cox proportional hazards regression analyses were conducted to assess the relationships between depression, medication adherence, and all-cause mortality before and after adjustment for covariates. Univariate analysis indicated no relationship between depression and all-cause mortality (HR = 1.52; 95% CI: .88 – 2.65). Following adjustment for covariates, an association emerged between depression and all-cause mortality (HR = 2.07; 95% CI: (1.02 – 4.17). See Figure 2.
Next, medication adherence was added to the model to examine the relationship between medication adherence and all-cause mortality. Higher medication adherence was associated with decreased mortality risk in univariate (HR = .99; 95% CI: .98 – .99) analysis. In the fully adjusted model, higher medication adherence remained associated with all-cause mortality (HR = .99; 95% CI: .98 - .997). Following adjustment for medication adherence, depression was no longer a significant predictor (HR = 1.66; CI: .80 – 3.43). This represents a 19.83% decrease in the log HR.
Depressive symptoms, medication adherence, and cardiovascular mortality. A second series of Cox proportional hazards regression analyses were performed to examine the relationships between depressive symptoms, medication adherence, and cardiovascular mortality before and after adjustment for covariates. Depression was not associated with cardiovascular mortality in univariate analysis (HR = 1.70; 95% CI: .74 – 3.95). Depression was associated with increased cardiovascular mortality risk following adjustment for covariates (HR = 2.93; 95% CI: 1.03 – 8.38). See Figure 3.

*Figure 3.* Cumulative survival curve for presence or absence of depressive symptoms and cardiovascular mortality in 303 patients with heart failure.
In the final model, medication adherence was added to assess the relationship between medication adherence and cardiovascular mortality. A trend emerged suggesting that higher medication adherence was associated with decreased cardiovascular mortality risk in univariate (HR = .99; 95% CI: .97 – 1.00). Medication adherence was not associated with cardiovascular mortality in multivariate analyses (HR = .99; 95% CI: .97 – 1.00). Furthermore, following adjustment for medication adherence, depression was no longer a significant predictor (HR = 2.36; 95% CI: .80 – 7.01). This represents a 20.12% decrease in the effect. See Table 4 for a full summary of univariate Cox proportional hazards models. Multivariate analyses for all-cause and cardiovascular mortality are presented in Tables 5 and 6.

<table>
<thead>
<tr>
<th></th>
<th>All-Cause Mortality</th>
<th>Cardiovascular Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age</td>
<td>1.04 (1.01 – 1.08)</td>
<td>.006</td>
</tr>
<tr>
<td>Sex</td>
<td>.43 (.22 – .84)</td>
<td>.013</td>
</tr>
<tr>
<td>NYHA</td>
<td>1.21 (.67 – 2.22)</td>
<td>.528</td>
</tr>
<tr>
<td>Charlson</td>
<td>1.10 (.95 – 1.26)</td>
<td>.216</td>
</tr>
<tr>
<td>PROMIS</td>
<td>1.0 (.947 – 1.05)</td>
<td>.931</td>
</tr>
<tr>
<td>MSPSS</td>
<td>.99 (.97 – 1.01)</td>
<td>.297</td>
</tr>
<tr>
<td>3MS</td>
<td>.95 (.91 – .98)</td>
<td>.003</td>
</tr>
<tr>
<td>PHQ-9 (categorical)</td>
<td>1.52 (.88 – 2.65)</td>
<td>.137</td>
</tr>
<tr>
<td>PHQ-9 (continuous)</td>
<td>1.04 (.99 – 1.10)</td>
<td>.136</td>
</tr>
<tr>
<td>Medication Adherence</td>
<td>.99 (.98 – .99)</td>
<td>.004</td>
</tr>
</tbody>
</table>

*Note.* PHQ-9 (categorical): 0 = not depressed; 1 = depressed. *Abbreviations:* NYHA = New York Heart Association; Charlson = Charlson Comorbidity Index; PROMIS = Patient-reported Outcomes Measurement Information System (short-form anxiety scale); MPSS = Multidimensional Scale of Perceived Social Support; 3MS = Modified Mini-Mental Status Examination; PHQ-9 = Patient Health Questionnaire—9.
<table>
<thead>
<tr>
<th>Block 1</th>
<th>All-Cause Mortality</th>
<th></th>
<th>Cardiovascular Mortality</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age</td>
<td>1.04 (1.01 – 1.07)</td>
<td>.023</td>
<td>1.08 (1.02 – 1.14)</td>
<td>.005</td>
</tr>
<tr>
<td>Sex</td>
<td>.47 (.24 – .92)</td>
<td>.028</td>
<td>.36 (.12 – 1.08)</td>
<td>.068</td>
</tr>
<tr>
<td>NYHA</td>
<td>1.35 (.73 – .92)</td>
<td>.335</td>
<td>1.02 (.42 – 2.47)</td>
<td>.965</td>
</tr>
<tr>
<td>Charlson</td>
<td>1.06 (.92 – 1.22)</td>
<td>.442</td>
<td>.97 (.78 – 1.22)</td>
<td>.812</td>
</tr>
<tr>
<td>PROMIS</td>
<td>1.0 (.95 – 1.06)</td>
<td>.985</td>
<td>1.02 (.93 – 1.11)</td>
<td>.706</td>
</tr>
<tr>
<td>MSPSS</td>
<td>.99 (.97 – 1.01)</td>
<td>.294</td>
<td>1.0 (.97 – 1.03)</td>
<td>.886</td>
</tr>
<tr>
<td>3MS</td>
<td>.96 (.92 – .99)</td>
<td>.034</td>
<td>.97 (.91 – 1.02)</td>
<td>.247</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Block 2</th>
<th>All-Cause Mortality</th>
<th></th>
<th>Cardiovascular Mortality</th>
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<td>P value</td>
<td>HR (95% CI)</td>
<td>P value</td>
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<tr>
<td>Age</td>
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<td>.020</td>
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</tr>
<tr>
<td>Sex</td>
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<tr>
<td>NYHA</td>
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<td>.642</td>
<td>.82 (.33 – 2.03)</td>
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<tr>
<td>Charlson</td>
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<td>.580</td>
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<tr>
<td>3MS</td>
<td>.96 (.92 – .99)</td>
<td>.049</td>
<td>.97 (.92 – 1.03)</td>
<td>.349</td>
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<tr>
<td>PHQ-9 (categorical)</td>
<td>2.07 (1.02 – 4.71)</td>
<td>.043</td>
<td>2.93 (1.03 – 8.38)</td>
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<table>
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<tr>
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<td>HR (95% CI)</td>
<td>P value</td>
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<td>NYHA</td>
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<td>.76 (.30 – 1.92)</td>
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<td>.99 (.89 – 1.10)</td>
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<tr>
<td>MSPSS</td>
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<td>1.00 (.97 – 1.04)</td>
<td>.947</td>
</tr>
<tr>
<td>3MS</td>
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<td>.98 (.92 – 1.04)</td>
<td>.439</td>
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<td>PHQ-9 (categorical)</td>
<td>1.66 (.80 – 3.43)</td>
<td>.173</td>
<td>2.36 (.80 – 7.01)</td>
<td>.122</td>
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</tbody>
</table>

| Medication Adherence    | .99 (.98 – .998)    | .019      | .99 (.97 – 1.00)         | .142      |

*Abbreviations:* NYHA = New York Heart Association; Charlson = Charlson Comorbidity Index; PROMIS = Patient-reported Outcomes Measurement Information System (short-form anxiety scale); MPSS = Multidimensional Scale of Perceived Social Support; 3MS = Modified Mini-Mental Status Examination; PHQ-9 = Patient Health Questionnaire—9.
Table 6. Multivariate Cox Proportional Hazard Ratios of depression severity and mortality.

<table>
<thead>
<tr>
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<th>All-Cause Mortality</th>
<th>Cardiovascular Mortality</th>
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<td>Sex</td>
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<td>NYHA</td>
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<tr>
<td>Charlson</td>
<td>1.03 (.89 – 1.19)</td>
<td>.695</td>
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<td>.018</td>
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<td>PHQ-9 (continuous)</td>
<td>1.09 (1.01 – 1.71)</td>
<td>.028</td>
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<td></td>
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<td>Age</td>
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</tr>
<tr>
<td>Sex</td>
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</tr>
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<td>NYHA</td>
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<td>PHQ-9 (continuous)</td>
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</tr>
<tr>
<td>Medication Adherence</td>
<td>.99 (.98 – .997)</td>
<td>.015</td>
</tr>
</tbody>
</table>

*Abbreviations:* NYHA = New York Heart Association; Charlson = Charlson Comorbidity Index; PROMIS = Patient-reported Outcomes Measurement Information System (short-form anxiety scale); MSPSS = Multidimensional Scale of Perceived Social Support; 3MS = Modified Mini-Mental Status Examination; PHQ-9 = Patient Health Questionnaire—9.

### 3.3. Secondary Analyses

A series of analyses were also conducted treating PHQ-9 scores as a continuous variable to assess the dose-response relationship between depressive symptoms and mortality.
**Depressive symptoms and medication adherence.** Hierarchical multiple linear regression was conducted to examine the relationship between depressive symptoms and medication adherence. In the first block, the linear combination of demographic and clinical covariates explained 6.7% of the variability in medication adherence, $F(7, 295) = 3.03, p < .01$. Specifically, higher perceived social support ($\beta = .17, p < .01$) was associated with higher medication adherence. In the second block, adding PHQ-9 scores accounted for an additional 1.9% of the variance in medication adherence and improved model fit, $\Delta F(1, 294) = 6.18, p < .05$.

**Depressive symptoms, medication adherence, and all-cause mortality.** Univariate analysis indicated no relationship between depression and all-cause mortality ($HR = 1.04; 95\% CI: .99 – 1.10$). Following adjustment for covariates, higher depressive symptoms were related to increased all-cause mortality risk ($HR = 1.09; 95\% CI: 1.01 – 1.17$).

Multivariate analyses examining relationships among medication adherence and mortality were also performed. Higher medication adherence was associated with decreased mortality risk in multivariate analyses after adjustment for covariates and depressive symptoms ($HR = .99; 95\% CI: .98 - .997$). When medication adherence was added to the model, depressive symptoms were no longer significantly related to mortality risk ($HR = 1.07; 95\% CI: .99 – 1.16$). This represents a 21.49% decrease in the log-HR.

**Depressive symptoms, medication adherence, and cardiovascular mortality.** Finally, Cox proportional hazards models were conducted to examine relationships among depressive symptoms, medication adherence, and cardiovascular mortality. No univariate relationship emerged between depressive symptoms and cardiovascular mortality ($HR = 1.03; 95\% CI: .94 – 1.12$). Similarly, depressive symptoms were not related to cardiovascular mortality following
adjustment for covariates (HR = 1.11; 95% CI: .98 – 1.25). A fully adjusted model including medication adherence showed no relationship between medication adherence and mortality risk (HR = .99; 95% CI: .97 – 1.00).

3.4. Sensitivity Analyses

A series of Cox proportional hazards models adjusting for age, sex, NYHA class, and comorbidity, revealed that a PHQ-9 score of ≥ 4 was the first point at which PHQ-9 scores significantly predicted survival (HR = 2.27; 95% CI: 1.13 – 4.56). Controlling for age, sex, NYHA class, comorbidity, and PHQ-9 scores, analyses examining medication adherence indicated that medication adherence of ≥ 85 yielded a significant difference between mortality rates (HR = .54; 95% CI: .29 - .97).
IV. Discussion

The present study investigated the impact of medication adherence on the relationship between depressive symptoms and mortality risk in patients with HF. It was hypothesized that depressive symptoms would be inversely related to medication adherence. In addition, it was hypothesized that medication adherence would attenuate the relationship between depressive symptoms and mortality. Consistent with the primary hypothesis, the presence of at least mild depressive symptoms (PHQ-9 ≥ 5) was associated with lower medication adherence and increased all-cause and cardiovascular mortality risk in multivariable models. In addition, medication adherence was inversely associated all-cause, but not cardiovascular, mortality risk. Medication adherence attenuated the relationship between the presence of at least mild depressive symptoms and all-cause mortality. In an analysis that treated depressive symptoms as a continuous variable, depressive symptoms were positively associated with all-cause, but not cardiovascular, mortality. Medication adherence also reduced the effect of depressive symptoms on all-cause mortality to the null value.

4.1. All-cause Mortality

In the current sample, approximately one-third of participants reported at least mild depressive symptoms. This prevalence is similar to meta-analytic reports suggesting that approximately 21.5% of HF patients report clinically significant symptoms of depression, though some report rates of at least mild depressive symptomology as high as 60% (Pihl et al., 2005). Although changes in depressive symptomology and the timing of the onset of depressive
symptoms were not assessed in the current study, these findings reveal that depressive symptoms are prevalent in patients with HF. Similar to Rutledge et al. (2006), in the present sample, individuals reporting elevated depressive symptoms were more likely to be women, younger, and higher NYHA class. Unlike Rutledge et al., (2006), the present results found that minority participants reported higher rates of depression compared to Caucasian participants. In addition, individuals with fewer years of education, higher levels of anxiety, lower perceived social support, and lower medication adherence also reported higher rates of depressive symptomology.

The mortality rate in the current study was lower than expected. Similar studies of HF with follow-up periods of 12 months (Jiang et al., 2004), 18 months (Coyne et al., 2011), and 32 months (Faller et al., 2007) reported mortality rates of 15.9%, 27.4%, and 26% respectively. The low mortality rate may be attributed to recruitment of a well-characterized sample of patients who are well-managed and closely followed by their cardiologist. Nonetheless, the current evidence supports that the presence of at least mild symptoms of depression conferred a significant increase in all-cause and cardiovascular mortality risk, with individuals reporting elevated depressive symptoms experiencing mortality at over twice the rate of individuals who did not report elevated symptoms. Similarly, Rutledge and colleagues (2006) reported approximately a 2-fold all-cause mortality risk for depressed individuals with HF and Gathright and Hughes (in preparation) found an effect similar to the current study.

In addition to increased mortality risk associated with the presence of at least mild depressive symptoms, a graded associated between depression severity and all-cause mortality risk emerged. Each 1-point increase in depressive symptoms corresponded to nearly a 10% increase in all-cause mortality risk. The current findings add to a large body of research demonstrating the association between increasing depression severity and poor prognosis.
(Adams et al., 2012; Junger et al., 2005; Lesman-Leegte et al., 2009; Murberg & Furze, 2004; Zuluaga et al., 2010).

In line with the study’s hypotheses, depressive symptoms were inversely associated with medication adherence in individuals with HF. There are several potential explanations for this relationship. First, depression is associated with concentration difficulties, reduced memory, and impairment in executive function (Garcia et al., 2011; McDermott & Ebmeier, 2009; Snyder, 2013), which may also impact medication adherence. Attention and concentration difficulties, linked to depression, may lead to forgetfulness and poor memory for events such as medication-taking behavior. Although recent research has indicated that impairment in memory, but not executive function, is related to poorer medication adherence in HF (Dolansky et al., in press), others have found a relationship between executive function and medication adherence in community-dwelling older adults (Insel, Morrow, Brewer, & Figueredo, 2006). Impairment in executive function may interfere with adherence for individuals with more complex medication regimens. However, this has not been tested.

Second, symptoms of depression including amotivation and fatigue may impede adherence to treatment recommendations. An exploration of relationships among depression, anxiety, and fatigue in HF revealed that depression and anxiety were associated with different aspects of fatigue (Falk, Patel, Swedburg, & Ekman, 2008). Individuals with anxiety displayed more mental fatigue (Falk et al., 2008). Depression was linked to fatigue-related reductions in activity, motivation, and functioning (Falk et al., 2008). Falk et al. (2008) suggested that depression may interfere with activity because of decreased energy necessary to follow through with self-care activities. The directionality of these co-morbid factors needs clarification. Third, maladaptive thinking styles prevalent in depression may contribute to poorer adherence. A
review indicated that HF patients with depression where more likely to employ coping methods such as denial and disengagement as opposed to active coping, acceptance, and planning-related coping strategies (Allman, Berry, & Nasir, 2009; Klein, Turvey, & Pies, 2007). This is unfortunate, as problem-focused coping strategies appear to be related to better self-care activities such as medication adherence (Li & Shun, 2016). In addition, aspects of emotion-focused coping such as acceptance, social support seeking, and emotion support, are related to better physical self-care (i.e., medication and dietary adherence, daily weighing, exercise; Li & Shun, 2016). In a systematic review, Li and Shun (2016) offered that facilitating certain emotion-focused coping strategies, such as acceptance-based coping, may promote patient use of problem-focused coping strategies to maintain their physical self-care activities.

However, no studies to date have explicitly tested differences in how somatic versus cognitive symptoms of depression may relate to medication adherence. Given that somatic symptoms appear to be more strongly related to prognosis, developing increased understanding of how depression impacts medication adherence warrants increased attention.

This study did not explore the direction of the relationship between depressive symptoms and medication adherence, and the relationship may be bidirectional. A recent, secondary analysis of 667 CHD patients from the Heart and Soul study explored the directionality of the relationship between depressive symptoms and health behaviors and lifestyle factors (i.e., physical activity, medication adherence, sleep quality, smoking status, body mass index, and waist to hip ratio) in a 5 year prospective cohort study (Sin, Kumar, Gehi, & Whooley, 2016). After adjustment for covariates including baseline health behaviors and lifestyle factors, severity of depressive symptoms continued to demonstrate a negative association with physical activity, medication adherence, and sleep quality. Although baseline medication adherence also predicted
change in depressive symptoms, the relationship did not persist following adjustment for depressive symptoms at baseline (Sin et al., 2016). Thus, it appears likely the depressive symptoms do contribute to worsening medication adherence over time.

In addition to the inverse relationship between depressive symptoms and medication adherence, higher medication adherence predicted decreased mortality risk. Hazard ratios are dependent on the scaling of variables. Thus, effects should be interpreted with caution. As medication adherence increased 1%, mortality risk decreased by 1%. As changes in the hazard rate occur exponentially rather than additively, a 10% increase in medication adherence reflects a 12% decrease in mortality risk. This finding has been well-documented (Fitzgerald et al., 2011; Granger et al., 2005; Miura et al., 2001; Wu et al., 2008a). Furthermore, the current findings suggest that at least 85% adherence is needed to demonstrate improved all-cause mortality risk. Interestingly, in a similar study, Wu and colleagues (2009) found that ≥ 88% adherence was associated with better event-free survival in 135 HF patients at 3.5 years of follow-up. Although we found that adherence less than 88% was associated with improved prognosis, both our results and Wu et al.’s suggest that adherence may need to reach slightly higher rates than the 80% adherence rate commonly used to define adequate adherence.

Significant effort and attention is required to consistently adhere to the prescribed regimen, and medication adherence often decreases as regimen complexity increases (Caldeira, Vaz-Carneiro, & Costa, 2014). In the present sample, individuals were required to manage complex regimens. The number of prescribed medications ranged from 2 to 24, with an average of approximately 10 medications (SD = 2.48) per individual. Many of the prescribed medications require alternating patterns of dosing and it has been suggested that at least 80% adherence is needed to convey adequate effectiveness of the medication regimen (Wu et al., 2009).
Furthermore, these medications are intended for continued use to optimize the cardioprotective benefit of the medication rather than single or short-term use; however, adherence tends to be poorer for medications that require persistent use (Gilberg et al., 2003). As a result, deviations from the regimen limit the effectiveness of the regimen and lead to worse prognosis.

Both depression and poor medication adherence represent modifiable, prognostic risk factors. The relationship between depression and risk for poor prognosis in patients with HF is likely impacted by a number of physiological changes that occur in both CVD and depression, as well as behavioral factors (Joynt, Whellan, O’Connor, 2004; Kop, Synowski, & Gottlieb, 2011; Whooley et al., 2008; Zuluaga et al., 2010). Prior research exploring these mechanisms of action has suggested physical inactivity to be an important behavioral factor (Whooley et al., 2008; Zuluaga et al., 2010). Whooley et al. (2008) demonstrated that physical inactivity was the largest behavioral factor impacting the relationship between depressive symptoms and risk of experiencing cardiac events, reducing the age-adjusted log HR by 31%. Self-reported medication non-adherence reduced the age-adjusted log HR by 5.3%. The current investigation, which incorporated objectively-measured medication adherence, found a much larger impact on the association between depressive symptoms and all-cause mortality.

Only one study has tested these relationships in HF. In a study of 433 HF patients that assessed various behavioral and psychosocial contributors to mortality, depressive symptoms predicted increased mortality risk at 5.7 year follow-up (Zuluaga et al., 2010). The association was primarily driven by comorbidity, physical activity, and disability in instrumental activities of daily living (Zuluaga et al., 2010). Although medication adherence was not assessed in this study, medication management is a component of instrumental activities of daily living. Limitation in instrumental activities of daily living was assessed using the Lawton-Brody Index,
which measures functional abilities and skills related to independent living. One item addresses an individual’s ability to independently and correctly manage their medications. Thus, the ability to independently manage one’s medications possibly contributed to these findings.

However, limited research has examined the impact of objectively-measured medication adherence on this relationship specifically, though Wu and colleagues (2013) found strong evidence to suggest that depression and poor objectively-measured medication adherence have a synergistic effect on cardiac event-free survival in HF. The current findings build on Wu and colleagues’ report and present the first investigation of the impact of objectively-measured medication adherence on the relationship between depression and mortality in patients with HF. It appears that, consistent with the hypothesis, medication adherence does play an important role. As others have suggested that physical inactivity is another important behavioral contributor, future research is needed to concomitantly explore whether physical inactivity and objectively-measured medication adherence independently impact prognosis in depressed HF patients.

4.2. Cardiovascular Morality

Many of the relationships that emerged when examining all-cause mortality were not statistically significant when exploring the associations with cardiovascular mortality. Only PHQ-9 scores ≥ 5 significantly predicted cardiovascular mortality after adjustment for demographic and medical covariates. However, when medication adherence was added to the model, neither depression nor medication adherence were significant predictors. Although medication adherence trended towards significance in univariable analysis, no other significant relationships between the primary variables of interest and cardiovascular mortality emerged. This was likely a result of the low rate of cardiovascular deaths leading to limited power to detect an effect as prior meta-analytic findings have suggested increased cardiovascular mortality.
associated with the presence of depressive symptomology in HF (Gathright & Hughes, in prep; Fan et al., 2014). In an analysis of 48,117 HF patients identified through hospital records as receiving psychotropic treatment for depression prior to HF diagnosis, Macchia and colleagues (2008) suggested that increased rates of 1-year all-cause mortality among patients previously treated for depression were largely due to increased rates of vascular events (i.e., MI, stroke, transischemic attack), which could be attributed to treatment differences. At baseline, depressed patients were prescribed anticoagulants less often and diuretics and digoxin more often. Over the 1 year follow-up, depressed patients were less likely to receive ACE inhibitors, and although rates of exposure to beta-blockers did not differ among depressed and non-depressed patients, depressed patients were treated with both drug classes for less time throughout the follow-up period (Macchia et al., 2008). Although adherence was not assessed, these findings support that differences in use of evidence-based treatments, whether prescribed or due to non-adherence, may be linked to increased rates of cardiac-related events and mortality.

Continued exploration of the impact of medication adherence to cardioprotective medications is needed. Additionally, as patients may differentially adhere to medications based on inconvenience of the dosing regimen or negative side effects (e.g., increased urination associated with diuretic use), future investigation should seek to understand how different adherence rates across medications may impact the relationship between depression and prognosis. General Discussion

4.3. Limitations and Future Directions

Limitations of the current study warrant mention. First, the mortality rate in the current study was lower than expected. Although the study detected an effect for the all-cause mortality analysis, the particularly small event rate for cardiovascular mortality may have limited the
ability to observe a true effect. Future studies may benefit from larger sample sizes and/or longer follow-up periods. Second, only four HF medications were monitored. Many participants in the present study were prescribed more than 4 medications, and past research indicates that adherence rates may differ across medications. Additional research is needed to understand whether different adherence rates across medications differentially impact the relationship between depression and mortality. Furthermore, a longer monitoring period may be beneficial. Third, the directionality of the relationship between depressive symptoms and medication adherence could not be established given the current study design. Finally, history of depression was not assessed. It will be important for future research to explore whether recurrent depressive episodes or newly onset depression following development of CVD is differentially related to prognosis. In addition, changes over time in depressive symptoms were not investigated in the current study, but may be associated with changes in mortality risk.

4.4. Conclusions

The present study demonstrated that medication adherence contributes to the relationship between depression and all-cause mortality risk in individuals with HF. Future research is needed to explore how depression and medication adherence relate to cardiovascular-specific outcomes in larger samples or in samples with longer follow-up. Whether concurrent improvements in depressive symptoms and medication adherence improve outcomes is unknown. Healthcare providers should continue to screen patients for depressive symptoms and monitor changes in mood, as even mild symptoms of depression can indicate risk for poor medication adherence and prognosis. In addition, HF patients experiencing depressive symptomology may benefit from psychoeducation on the impact of depression on medication adherence and prognosis, though research has yet to explicitly examine this.
REFERENCES


Jiang, W., Alexander, J., Christopher, E., Kuchibhatla, M., Gaulden, L. H., Cuffe, M. S., ... & O'Connor, C. M. (2001). Relationship of depression to increased risk of mortality and
rehospitalization in patients with congestive heart failure. *Archives of Internal Medicine, 161*(15), 1849-1856.


Sin, N. L., Kumar, A. D., Gehi, A. K., & Whooley, M. A. (2016). Direction of Association Between Depressive Symptoms and Lifestyle Behaviors in Patients with Coronary Heart Disease: the Heart and Soul Study. *Annals of Behavioral Medicine, 1-10.*


World Health Organization.


