MODERATORS AND CONTEXTUAL FACTORS IN THE RELATIONSHIP BETWEEN DEPRESSION AND MEDICATION ADHERENCE IN HEART FAILURE

A dissertation submitted to Kent State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy

by

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<tr>
<td>AHA</td>
<td>American Heart Association</td>
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<tr>
<td>BDI</td>
<td>Beck Depression Inventory</td>
</tr>
<tr>
<td>CHARM</td>
<td>Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity</td>
</tr>
<tr>
<td>CR</td>
<td>cardiac rehabilitation</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>CBT</td>
<td>cognitive behavioral therapy</td>
</tr>
<tr>
<td>CHF</td>
<td>congestive heart failure</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
</tr>
<tr>
<td>$d$</td>
<td>Cohen’s measure of effect size for comparing two sample means</td>
</tr>
<tr>
<td>$\Delta$</td>
<td>Greek letter delta, referring to increment of change</td>
</tr>
<tr>
<td>EF</td>
<td>ejection fraction</td>
</tr>
<tr>
<td>ENRICHD</td>
<td>Enhancing Recovery in Coronary Heart Disease Patients</td>
</tr>
<tr>
<td>$f^2$</td>
<td>effect size index for a multiple correlation</td>
</tr>
<tr>
<td>HF</td>
<td>heart failure</td>
</tr>
<tr>
<td>HART</td>
<td>Heart Failure Adherence Retention Trial</td>
</tr>
<tr>
<td>HF-ACTION</td>
<td>Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>IHD</td>
<td>ischemic heart disease</td>
</tr>
<tr>
<td>KCCQ</td>
<td>Kansas City Cardiomyopathy Questionnaire</td>
</tr>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
</tr>
<tr>
<td>$M$</td>
<td>mean</td>
</tr>
<tr>
<td>MEMS</td>
<td>Medication Event Monitoring Systems</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini Mental Status Exam</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>$N$</td>
<td>total sample size</td>
</tr>
<tr>
<td>$n$</td>
<td>subsample size</td>
</tr>
<tr>
<td>$p$</td>
<td>statistical abbreviation referring to probability</td>
</tr>
<tr>
<td>PTSD</td>
<td>posttraumatic stress disorder</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>$r$</td>
<td>estimate of the Pearson product-moment correlation coefficient</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>SADHART</td>
<td>Sertraline Antidepressant Heart Attack Randomized Trial</td>
</tr>
<tr>
<td>$SD$</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SCID</td>
<td>Structured Clinical Interview for DSM Disorders</td>
</tr>
<tr>
<td>$t$</td>
<td>sample value of the $t$-test statistic</td>
</tr>
</tbody>
</table>
T2DM  type 2 diabetes mellitus
WHO  World Health Organization
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I am very grateful for the many individuals who have been influential in the pursuit of this dissertation and my overall educational goals. First, I would like to express my sincere gratitude for my advisor and dissertation committee chair, Dr. Joel Hughes, for his mentorship during not only the formulation of this dissertation, but also throughout my graduate training. Second, I would like to acknowledge all of the members of the Heart ABC team for their assistance in executing this dissertation project. Third, I would like to thank my first-grade teacher, Mrs. Levy, my undergraduate advisor, Dr. Sheldon Solomon, and my grandfather, Louis Premock, and my parents for fostering my curiosity over the course of my lifetime. Most importantly, I wish to extend my heartfelt appreciation to my family and friends for their support and encouragement during the dissertation process and every other phase of my education.
INTRODUCTION

Within the United States, 83.6 million individuals are estimated to have one or more types of cardiovascular disease (CVD) including hypertension (American Heart Association [AHA], 2013). CVD is the leading cause of death for adults in the United States and is also the leading cause for healthcare expenditures in the United States: the total costs associated with CVD were estimated to be $312.6 billion in 2009 (2013). Much of the costs involve rehospitalization, which frequently follows a failure to properly self-manage one’s CVD; 5.8 million hospital discharges in 2010 were attributed to CVD, and this was the leading number of hospital discharges among the top 10 diagnostic groups (2013). In 2009, one in nine death certificates issued in the United States mentioned heart failure (HF; 2013).

There are numerous subtypes of CVD, and pathophysiology varies based on the subtype. These include myocardial infarction (MI), coronary heart disease (CHD), and congestive heart failure (CHF). A MI, otherwise known as a heart attack, is when blood supply to the heart is interrupted, causing part of the heart muscle tissue (the myocardium) to die. MI is a type of ischemic heart disease (IHD). Approximately every 34 seconds an individual in the United States suffers a coronary event, and roughly every minute an American will die of one (AHA, 2013). CHD, a narrowing or blockage of the coronary arteries, is typically caused by atherosclerosis. MI and IHD can cause HF. All subtypes of CVD are associated with burden on patients and caregivers.
One particular subtype of CVD, HF, is extremely debilitating and has a major impact on the mental and physical lives of HF patients and their families (Luttik, Jaarsma, Moser, Sanderman, & van Veldhuisen, 2005). In CHF, poor ventricular function or myocardial damage over time causes HF, which leads to decreased stroke volume, decreased cardiac output, vasoconstriction, sodium and fluid retention, and further stress on the ventricular wall that results in worsened ventricular function (Jackson, Gibbs, Davies, & Lip, 2000). Individuals with HF experience fatigue, shortness of breath, and edema (2013). Adequate self-management is complex and includes dietary sodium restriction, increase or maintenance of physical activity levels, symptom monitoring, fluid restrictions (for some patients), and managing a complex system of numerous medications (Luttik, Jaarsma, Moser, Sanderman, & van Veldhuisen, 2005).

Many individuals with CVD experience depression (Frasure-Smith & Lespérance, 2006), and this is associated with poorer outcomes (Barth, Schumacher, & Hermann-Lingen, 2004). Interventions designed to improve depression have not reduced mortality rates (Berkman et al., 2003). Medication nonadherence may help explain why depressed CVD patients experience such poor outcomes; depressed CVD patients may not take their medications as consistently as nondepressed CVD patients (Kronish et al., 2006). There are numerous factors that influence medication adherence, and these factors likely influence the relationship between depression and medication adherence in CVD patients. Previous research does not account for moderators that may reduce adherence in the context of this relationship. This study explored the moderators of the relationship
between depression and medication adherence in CVD in a sample of older adults with heart failure.

**Cardiovascular Disease and Depression**

Depression is elevated in patients with CVD. The estimates of depression in CVD vary depending on the specific disease processes and method of assessment. Almost 50% of patients with CVD will have major or minor depression at some point in the course of CVD (Carney & Freedland, 2008). In individuals hospitalized for MI, about 20% met criteria for a major depressive episode based on a structured interview, and 31.1% had significant depressive symptoms according to self-report measures (Thombs et al., 2006). Individuals hospitalized for unstable angina, bypass surgery, valve surgery, and angioplasty have depression at similar prevalence rates to individuals hospitalized for acute MI (Frasure-Smith & Lesperance, 2006), whereas individuals with HF appear to display a slightly increased prevalence—particularly if they are screened through self-report measures (Rutledge, Reis, Linke, Greenberg, & Mills, 2006). In a study of over 800 participants with HF, over one-third met the criteria for major depression during post-MI hospitalization according to a diagnostic interview (Powell et al., 2005).

Mechanisms for the relationship of depression in CVD are unknown, but may include autonomic imbalance, hypercoagulability, endothelial and vascular effects in women, inflammation, and indirect causation from behavior and nonadherence (Hayes, 2009).

Depression is related to poorer clinical outcomes and greater mortality in CVD. Both depressive symptoms and clinical depression are unfavorably related to CHD (Barth, Schumacher, & Herrmann-Lingen, 2004). Worsening depression symptoms are
associated with a poorer prognosis in HF (Sherwood et al., 2011). Depression symptoms are associated with adverse prognosis, and those on antidepressants experience worse clinical outcomes (Sherwood et al., 2007). In general, persistent depression symptoms are associated with poor adherence across a variety of health behaviors including quitting smoking and attending cardiac rehabilitation (CR; Kronish et al., 2006). Major depressive disorder is associated with poorer rates of CR completion and adherence (Swardfager et al., 2011). Depression’s effect on self-management behavior, including medication adherence, likely contributes to rehospitalization and mortality. Depression is a strong predictor of mortality after 12 years in adults with CHF (Testa et al., 2011). Further, antidepressant medication alone does not eliminate the relationship between depressive symptoms and mortality (Chung, Dekker, Lennie, & Moser, 2013). These trends are demonstrated despite treatment for depression: when CVD patients are treated for depression with cognitive behavioral therapy (CBT) and sertraline but do not respond their risk of mortality is high six months or later following an MI (Carney et al., 2004). No one mechanism has been implicated as the sole influence in the relationship between depression and CVD (Joynt, Whellan, & O’Connor, 2004).

**Summary of CVD Prevalence and the Relationship Between CVD and Depression**

In summary, CVD is the leading cause of death for American adults, and it is the leading cause for healthcare expenditures in the United States (AHA, 2013). Although the risk factors for CVD and health behaviors that promote heart health are well established, many adults remain at risk for developing one of numerous pathologies associated with CVD (2013). At least 50% of the adults that develop CVD will also experience major or
minor depression during the course of their disease (Carney & Freedland, 2008), and
depression not only predicts poor outcomes but also increased mortality in types of CVD
like HF (Testa et al., 2011). For many patients, these risks remain despite receiving
treatment for depression (Carney et al., 2004; Chung, Dekker, Lennie, & Moser, 2013).

Lessons from ENRICHD and SADHART

Two major studies, Enhancing Recovery in Coronary Heart Disease Patients
(ENRICHD) and Sertraline Antidepressant Heart Attack Randomized Trial (SADHART),
tried to improve depression in CVD patients through psychotherapy and medication.
The ENRICHD trial tested the hypothesis that treatment of depression and low social
support early after an acute MI would reduce death and nonfatal recurrent infarctions
(Carney et al., 2003). Depression was treated with CBT and with a selective serotonin
reuptake inhibitor (SSRI) when CBT alone did not significantly reduce depressive
symptoms after five weeks (Berkman et al., 2003).

CBT improved depression and/or low perceived social support compared to usual
care, but there was no treatment effect on event-free survival (Berkman et al., 2003). An
interpretation of a statistical trend suggested that CBT might have been worse than usual
care for women (Berkman et al., 2003). Additionally, although the female participants
were older and had more medical comorbidities, they were similarly responsive to
treatment as compared to male participants (Berkman et al., 2003).

According to follow-up analyses, after adjusting for all-cause mortality, baseline
BDI score, and the use of an SSRI, patients who experienced their first major depressive
episode at the time of MI had poorer survival (18.4% all-cause mortality) than those with
recurrent major depressive disorder (11.8% all-cause mortality; Carney et al., 2009). Dickens and colleagues (2008) confirmed this finding in another sample. Furthermore, researchers determined that individuals who experienced their first major depressive episode following a MI as well as individuals who experienced a recurrent episode upon MI had significantly poorer survival than nondepressed patients (Carney et al., 2009). There were no significant differences between the groups that experienced their first major depressive episode and those that experienced a recurrent major depressive episode (Carney et al., 2009). Furthermore, upon five-year follow-up, individuals experiencing major or minor depression were at higher risk for all-cause mortality compared to the nondepressed individuals (Carney et al., 2008).

The second major study, SADHART, tested the safety and efficacy of sertraline in the treatment of depression following MI (Glassman, Bigger, & Gaffney, 2009). Through a double-blind, placebo-controlled, randomized trial comparing safety and efficacy of sertraline to placebo in 369 acute coronary syndrome with major depression, sertraline appeared to be safe and to work best if the participant had a history of depression (Glassman, Bigger, & Gaffney, 2009). Additionally, baseline depression severity and failure of depression to improve substantially during treatment with either the study drug or placebo were strongly and independently associated with long-term mortality (Glassman, Bigger, & Gaffney, 2009). Additionally, in a sub-study of patients with HF, remission of depression symptoms was associated with stronger improvements in quality of life (QoL), social functioning, and physical functioning (Xiong et al., 2012). Furthermore, marked improvements of depression were associated with improved
adherence to study medication as validated by pill counts (Glassman, Bigger, & Gaffney, 2009).

**Summary of Lessons Learned from ENRICHD and SADHART**

SSRIs and CBT appeared to reduce depression and improve other contextual factors related to depression, but they did not decrease risk of mortality (Carney et al., 2008). Although improvements in depressive symptoms were associated with improvements in medication adherence in SADHART, marked improvements of depression did not fully perfect adherence rates (Glassman, Bigger, & Gaffney, 2009). It appears that although some outcomes improve when depression is treated, the occurrence of depression is detrimental to CVD patient outcomes such as rehospitalization and mortality.

**Depression and Hospitalization or Rehospitalization**

Across CVD patients, depression is associated with hospitalization or rehospitalization. Depression predicts repeated HF hospitalizations (Johnson et al., 2012; Moser, Doering, & Chung, 2005) as well as rehospitalization after acute MI (Reese et al., 2011). According to a meta-analysis by van Melle and colleagues, post-MI depression was related to all-cause mortality, cardiac mortality, and new cardiac events (2004). Furthermore, acute MI patients with depressive symptoms experienced more emergency department visits and hospitalizations, were hospitalized sooner, and spent more days in the hospital compared to acute MI patients without major or minor depression after 42 months post-hospitalization (Reese et al., 2011).
The Heart Failure Adherence and Retention Trial examined whether an intervention of self-management skills and HF-specific education reduced a patient’s likelihood of future hospitalizations (Johnson et al., 2012). Depression was measured using the Geriatric Depression Scale (Yesavage et al., 1983), and medication adherence was measured using Medication Event Monitoring Systems (MEMS; MWV Healthcare, Richmond VA) electronic pill caps on a single medication (typically an angiotensin II receptor antagonist, β-blocker, or diuretic; Johnson et al., 2012). Medication adherence was monitored for one month; it was measured as the proportion of pills taken compared to the prescribed amount per day, and adherence was dichotomized at 80% (2012). Depression strongly predicted the average number of HF-related hospitalizations after controlling for illness severity, HF severity, socioeconomic factors, physician adherence to evidence-based medication regimens, patient adherence to drug therapy, and patient adherence to salt restriction (2012). Furthermore, individuals with depression were hospitalized for HF 1.45 times more often than nondepressed patients (2012).

**Depression and Mortality**

The presence of depressive symptoms in patients with CVD is predictive of increased risk of death. Depression is a risk factor for mortality after coronary artery bypass grafting (CABG; Blumenthal et al., 2003) in CHD patients (Barth, Schumacher, & Herrmann-Lingen, 2004), in HF patients (Freedland, Carney, & Rich, 2011; Testa et al., 2011), and after MI (Carney et al., 2003). Major depression is associated with increased mortality three and 12 months following hospitalization for CVD as well as with hospital readmission three and 12 months post-hospitalization (Jiang et al., 2001). Additionally,
worsening depressive symptoms are associated with mortality one year after initial assessment (Sherwood et al., 2011), which highlights the need to frequently assess a patient’s depressive symptoms. Currently, the mechanisms governing the relationship between depression and mortality are poorly understood (Joynt, Whellan, & O’Connor, 2004).

Independent predictors of depressive symptoms in the hospital post-MI include pre-MI vital exhaustion, history of depressive disorder, history of MI, living alone, poor performance on exercise tolerance testing, and female gender (Spijkerman, van den Brink, Jansen, Crijs, & Ormel, 2005). Independent predictors of one-year post-discharge depressive symptoms are history of depressive disorder, poor ejection fraction (EF), longer hospital stay, female gender, and pre-MI vital exhaustion (Spijkerman, van den Brink, Jansen, Crijs, & Ormel, 2005). Furthermore, depression present at the time of hospitalization for chronic HF is significantly associated with decreased survival after a twelve-year follow-up, where survival was inversely associated with depression severity measured by the Beck Depression Inventory (BDI; Adams et al., 2012).

Treating depression does not eliminate the relationship between depression and mortality in CVD. According to findings from the ENRICHD trial, patients who do not respond to CBT and sertraline are at a high risk for mortality six months or later following a MI (Carney et al 2004). Furthermore, antidepressants do not necessarily eliminate the relationship between depressive symptoms and mortality (Chung, Dekker, Lennie, & Moser, 2013). Insufficiently treated depression and treatment-resistant depression following MI were associated with mortality after controlling for β-blocker
use, sociodemographics, anxiety disorders, mortality factors, and health service utilization compared to treated patients (Scherrer et al., 2012). In general, persistent depressive symptoms are associated with poor adherence across a variety of health behaviors including quitting smoking and attending CR, and failure to adhere to these important behaviors is associated with increased mortality (Kronish et al., 2006).

Summary of the Damaging Effects of Depression on Patient Outcomes in CVD

In total, depression predicts rehospitalization after acute MI (Reese et al., 2011) and repeated HF hospitalizations (Johnson et al., 2012; Moser, Doering, & Chung, 2005). According to the Heart Failure Adherence and Retention Trial, depression predicted objectively measured medication adherence, and individuals with depression were hospitalized for HF 1.45 times more often than nondepressed patients (Johnson et al., 2012). Depression is associated with increased mortality, and worsening depressive symptoms are associated with mortality one year after initial assessment (Sherwood et al., 2011). Not only does depression contribute to poor outcomes, but also it negatively contributes to a likely mechanism in the relationship between depression and death in CVD: insufficient medication adherence.

Cardiovascular Disease and Medication Adherence

Medication adherence is the extent to which a patient follows his or her provider’s recommendations about their day-to-day treatment such as timing, dosage, and frequency of medication administration (Bosworth et al., 2011). American patients tend to overuse short-term medications such as antibiotics and underuse medication for chronic illness.
such as depression and CHF (Gilberg, Laouri, Wade, & Isonaka, 2003). HF patients who adhere to recommendations of evidence-based pharmacotherapy regimens demonstrate improved outcomes compared to individuals who do not persist with the recommended regimen (Gislason et al., 2007). Nevertheless, medication adherence in CVD patients is sub-optimal. Measurement of medication adherence and interventions targeting medication nonadherence is rare in routine clinical practice (Ho, Bryson, & Rumsfeld, 2009).

Following hospital discharge, there appears to be a steady decrease in adherence to cardiovascular medications (e.g., statins, β-blockers; Ho, Bryson, & Rumsfeld, 2009). Within HF, estimates of medication adherence range from 40-60%, though previous estimates have ranged from 10-93% (Wu, Moser, Lennie, & Burkhart, 2008). One study of HF patients measured five years after an index HF hospitalization found adherence rates of 79% for renin-angiotensin inhibitors, 65% for β-blockers, 56% for spironolactone, and 83% for statins according to prescription refill data (Gislason et al., 2007). In the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) trial, 11% of patients took fewer than 80% of the prescribed pills (Granger et al., 2005). According to Heart Failure Adherence and Retention Trial, 37% of HF patients failed to take their medication at least 80% of the time (Calvin et al., 2012).

Gehi, Haas, Pipkin, & Whooley completed the Heart and Soul Study examining psychosocial factors and health outcomes in CHD outpatients (2005). Participants completed self-reports of their depressive symptoms, the severity of their symptoms, and
medication adherence using multiple-choice questions (2005). Nonadherence was defined as taking medication 75% or less of the time, forgetting to take prescribed medications once per week or more, or deciding to purposely skip medication once per week or more (2005). In the sample of 940 individuals, 22% had current depression, and these individuals were more likely to be female, unmarried, and low SES compared to nondepressed participants (2005). Using self-reported adherence, 7% reported not taking medications as prescribed (2005). Depressed individuals were more likely to not take medications as prescribed and to decide to skip medications after controlling for covariates (2005). The relationship between depression and forgetting to take medications was no longer significant after controlling for covariates (2005).

**Factors Influencing Medication Adherence in CVD**

The factors contributing to medication nonadherence in CVD are not well established (Aggarwal & Mosca, 2010). The World Health Organization notes that nonadherence can be preventable (e.g., forgetting) or nonpreventable (e.g., life-threatening adverse effects), and health care systems, medical conditions, patients, the therapy itself, and socioeconomic factors can all contribute to medication nonadherence (World Health Organization [WHO], 2003). Nonadherence in CVD is associated with disease related complications, hospitalizations, disability, and increased mortality (Ansell, 2008). In a sample of HF patients, lapses in attention, excessive daytime sleepiness, and two or more medication doses per day predicted steep declines in objectively measured medication adherence using MEMS (Riegel et al., 2012). According to the Heart Failure Adherence and Retention Trial, New York Heart
Association (NYHA) class III patients, individuals with asthma, and individuals with renal disease were less likely to adhere to an evidence-based HF medication regimen than those with less severe disease as evidenced by MEMS (Calvin et al., 2012).

Psychological and emotional factors, like depressive symptoms, appear to influence medication adherence behavior more than previously thought (Bane, Hughes, & McElnay, 2006). A study using self-reported medication adherence revealed depressed patients reported poorer medication adherence than their non-depressed peers; additionally, anxiety also negatively influenced self-reported medication adherence (Dempe et al., 2013).

Previous research may have underestimated the complexity of adherence behavior. For instance, a model recently created by Brown and colleagues is one of the first to fully recognize some of the potential determinants of medication adherence behavior (2012). In this conceptual model of atrial fibrillation patients’ adherence to oral anticoagulants, components include the following: predisposing, moderating, and contextual factors; knowledge base and reinforcement; short- and long-term motivation; personalized system, habit formation, and system adaptation; and a self-efficacy loop (Brown et al., 2012). This model is additive to the literature because it encompasses many factors that previously were singled out in theoretical understandings of medication adherence and in interventions designed to improve medication adherence behaviors. For example, patient-articulated reports of medication management strategies (e.g., receiving a pharmacy-initiated reminder to refill a prescription, or remembering to refill a
prescription upon seeing a near-empty pill bottle) do not explain differences in medication adherence (Kripalani, Gatti, & Jacobson, 2010).

**Medication Adherence and Mortality**

Medication nonadherence may lead to rehospitalization or death (Ansell, 2008). Among surveyed patients, caregivers, cardiologists, and HF nurses, respondents noted nearly one third of the readmissions for HF patients could likely have been prevented if adherence was higher (Annema, Luttik, & Jaarsma, 2009).

In a study by Wu, Moser, Chung, & Lennie (2008a), the authors aimed to determine the indicators of medication adherence that predict event-free survival in 134 HF patients. Adherence was measured objectively using MEMS and by self-report with the Medical Outcomes Studies Specific Adherence Scale (2008a). The MEMS system assessed: the percentage of prescribed doses taken (dose-count); the percentage of days the correct number of doses was taken (dose-days); and the percentage of doses taken on schedule (dose-time; 2008a). Events were operationalized as emergency department visits, rehospitalization, and mortality (2008a). According to Cox regressions, dose-count and dose-days predicted event-free survival after controlling for relevant clinical variables. Self-reported adherence did not predict outcomes (2008a). Medication nonadherence, specifically as measured by dose-count and dose-day, are predictive of event-free survival (2008a). Follow-up analyses determined barriers to medication adherence (measured through a barriers subscale of a self-report questionnaire), ethnicity, and perceived social support predicted dose-count adherence while NYHA functional class, barriers to medication adherence, financial status, and perceived social support
predicted dose-day adherence (2008b). It is important to note self-reported adherence failed to predict event-free survival (2008a).

Summary of Medication Adherence in CVD

Medication adherence is the extent to which a patient follows his or her provider’s recommendations about their day-to-day treatment such as timing, dosage, and frequency of medication administration (Bosworth et al., 2011), and nonadherence is rampant in CVD patients even though better medication adherence is associated with better outcomes in CVD (Ansel, 2008; Gislason et al., 2007). According to self-report, depression is associated with not taking medications as prescribed and deciding to skip medications (Gehi, Haas, Pipkin, & Whooley, 2005). The elements complicating adherence in CVD are not well established (Aggarwal & Mosca, 2010). Numerous studies have targeted nonadherence (e.g., Rich, Gray, Beckham, Wittenberg, & Luther, 1996; Wu, Corley, Lennie, & Moser, 2012), though few targeted depression, which may suppress adherence behavior. Medication nonadherence contributes to cardiac events and mortality (Wu, Moser, Chung, & Lennie, 2008a). Before the literature examining the relationship between depression and medication adherence can be understood, the measurement of medication adherence must be reviewed. The types of measurement used within CVD research have implications for what is known about medication adherence, as well as how medication adherence specifically within CVD patients should be studied.
Measurement of Medication Adherence

Hansen and colleagues urge researchers to consider the disease and population when determining what measurement of medication adherence to use (2009a). There is no perfect tool for measuring adherence, but electronic monitoring appears to be the most accurate tool for CVD patients according to a literature review (Wu, Moser, Lennie, & Burkhart, 2008). The evidence suggests that whereas self-reported adherence may be adequate in simple disease processes, objective measures of medication adherence provide the most prudent insight into the complex requirements for adequate CVD self-management.

Methods of Measurement

Adherence can be described as direct or indirect, and both categories have strengths and drawbacks (Osterberg & Blaschke, 2005). Direct methods include directly observed therapy; measurement of the biological marker in the blood; and measurement of the level of medicine or metabolite in the blood (Osterberg & Blaschke, 2005). Although these methods are reliable, they are limited in their practicality within routine clinical use (Ho, Bryson, & Rumsfeld, 2009). Indirect methods include patient questionnaires; pill counts; self-reports; electronic medication monitors; measurement of physiological markers; patient diaries; rate of prescription refills; and assessment of the patient’s clinical response (Osterberg & Blaschke, 2005). There are drawbacks to most types of measurement. For example, although pill counts are easy to perform and frequently used, pill counts do not capture the timing of medication taking, and they are
easy for patients to manipulate (e.g., by disposing of pills; Ho, Bryson, & Rumsfeld, 2009).

Electronic pharmacy data is a common medication adherence measurement method. Using electronic pharmacy data, researchers track the frequency with which an individual procures their prescription over time (Ho, Bryson, & Rumsfeld, 2009). Through determining the proportion of days covered and the medication possession ratio, an adherence ratio with a maximum 1.0 or a ratio that can have a value of >1.0 to account for oversupplies can be determined respectively (Ho, Bryson, & Rumsfeld, 2009). However, this requires individuals to obtain medications from a closed pharmacy system and it fails to capture the timing of doses (Ho, Bryson, & Rumsfeld, 2009).

Many researchers utilize self-report measures of adherence, such as the Morisky scale (Morisky, Green, & Levine, 1986). The Morisky scale is a validated, four-item self-report adherence measure. Self-report measures, albeit convenient, can be biased by social desirability, leading patients to present a more optimistic view of their health behaviors to researchers and clinicians (Ho, Bryson, & Rumsfeld, 2009). Many researchers justify using self-report adherence because they note it has been predictive in previous studies (e.g., Gehi, Haas, Pipkin, & Whooley, 2005). However, self-reported adherence has been validated in samples that are very different from CVD patients, such as hypertension patients (Haynes et al., 1980) and tuberculosis patients (Blumberg et al., 2005). Conversely, recent research suggests objective measures may be necessary for accurate adherence measurement in complex disease such as CVD (Shi et al., 2010). According to a meta-analysis, correlations between adherence rates measured by self-
report questionnaires and MEMS are much lower in CVD-related conditions like hypertension than in other diseases like HIV (Shi et al., 2010); this may be due to different boundary conditions created by the complex nature of adequate CVD self-management.

One of the most popular forms of telemonitoring of medication adherence is MEMS caps, a medication pill bottle with a microchip-equipped lid that passively measures medication adherence by electronically date- and time-stamping each bottle opening (Cook, Schmiege, McClean, Aagaard, & Kahook, 2012). MEMS caps are easy to use, and they are one of the leading objective measurement techniques in adherence research (2012). However, MEMS suffer from drawbacks such as reactivity and technological failure (2012). Therefore, to properly use this technology, researchers should do the following: use a one or two month run-in period to minimize measurement reactivity; corroborate MEMS data with another measure of adherence; report MEMS data continuously or use cut-offs determined by pharmacological properties and consequence of nonadherence to the medication; assess MEMS data using multilevel modeling; and properly train patients to use MEMS to improve their accuracy as an adherence measurement tool (2012). Also, contrary to the belief that objective measurement is too burdensome for CVD patients (e.g., Bauer et al., 2012), patients accept real-time electronic medication adherence monitoring (Haberer et al., 2012).
Comparing Methods of Medication Adherence in CVD

Comparing Self-Report to MEMS Caps

Studies comparing self-reported to objectively measured medication adherence in CVD patients have demonstrated significant differences in adherence levels based on the type of medication adherence measurement strategies used. Previous studies have found a correlation between self-reported adherence and adherence measured by MEMS caps, though not in CVD (Shi et al., 2010). The correlation of methods in studies on hypertensive adults was .26 and .29, while HIV and other disorders yielded significantly higher correlations (Shi et al., 2010). A study of hospitalized cardiac patients employed electronic monitoring and found nonadherence rates three times greater than in a study that utilized self-report, which suggests similar CVD patients dramatically overestimated their level of medication adherence when they were asked to self-report their medication adherence (Rieckmann et al., 2006a).

Straka, Fish, Benson, and Suh assessed the accuracy of patient-kept diaries compared to MEMS tracking three times daily isosorbide dinitrate medication for IHD (1997). According to this study, self-reporting did not correspond with electronic monitoring in this population (Straka, Fish, Benson, & Suh, 1997). In the sample of 68 outpatients, 67% of patients overestimated their compliance when they used self-reported diaries, and an average of 30% of the self-reported diary entries were recorded in error compared to the data produced by the MEMS (1997). In the case of a complicated medication regimen (e.g., contains a medication taken three times daily), self-reports of medication adherence should be critically evaluated (1997).
In Hansen et al. (2009b), researchers sought to evaluate the influence of depressive symptoms on HF patient medication adherence as monitored by self-reports and MEMS. HF patients’ medication adherence was measured both through self-report as well as MEMS. Over one third of the 117-person sample screened positive for depression, and mean adjusted self-reported medication adherence was 75% in depressed patients whereas it was significantly different from nondepressed patients, who reported adhering to their medications 81% of the time (2009b). Depression significantly predicted self-reported adherence (2009b). Electronically measured adherence was lower than self-reported adherence. According to electronic monitoring, there was no statistically significant difference in rates of medication adherence among depressed (71%) and nondepressed (69%) participants (209b). The authors noted the type of measurement (self-reported verses electronically measured) influenced the type of conclusions researchers could draw about the relationship between depression and HF medication adherence (2009b).

In another comparison of self-report to objectively measured medication adherence in 37 HF patients, patients’ medication adherence was measured across 18 months following hospital discharge using MEMS and the Revised HF Compliance Questionnaire (Nieuwenhuis, Jaarsma, van Veldhuisen, & van der Wal, 2012). According to self-report 100% of participants reported that medication adherence is both highly important to them and that they always adhere to their medications 100% of the time (2012). However, according to MEMS, only 76% of patients adhered to their medication at least 88% of the time, demonstrating that patients’ values do not predict medication-
taking behavior and that individuals with CVD may have difficulty accurately predicting their true rate of medication adherence (2012). The 88% cutoff was chosen given its ability to predict event-free survival in HF patients as evidenced by Wu and colleagues (2009). In that longitudinal study of 135 HF patients, medication adherence was measured by MEMS and researchers collected outcomes up to 3.5 years later (2009). Through the use of Kaplan-Meier plots with log-rank tests, Cox survival analyses, and receiver operating characteristics curves, Wu and colleagues determined that event-free survival was most likely to occur when participants adhered to their medications at least 88% of the time as determined by the percentage of prescribed doses taken (dose count) or the percentage of days the correct dose was taken (dose day; 2009). This was confirmed in a Cox regression model controlling for age, gender, EF, NYHA class, comorbidity, angiotensin-converting enzyme inhibitor use, and β-blocker use (2009). Adherence rates exceeding 88% appear to be optimally specific and sensitive (2009).

Comparing Self-Report to Blood Serum Digoxin Concentration

In a sample of HF patients prescribed digoxin, individuals’ medication adherence was assessed using a self-report measure and the measurement of serum digoxin concentration in their blood (Muzzarelli et al., 2010). Poor adherence was defined as adhering to medication 75% or less of the time (Muzzarelli et al., 2010). At follow-up, the proportion of individuals with poor adherence was 15% as determined by the questionnaire, 20% as determined by serum digoxin concentration, and 25% when both methods were combined (Muzzarelli et al., 2010). This suggests that objective
measurement better predicts medication adherence levels than self-report, but a combination of methods may be advantageous (Muzzarelli et al., 2010).

**Dichotomizing Adherence with a Cut-Point**

Dichotomizing adherence (over or under 80%) is likely inappropriate in CVD patients (Wu et al., 2009). Researchers frequently dichotomize adherence based on the convention from the HIV/AIDS literature, in which 80% and above is considered “adherent” since 80% adherence is thought to provide optimal virologic suppression. This somewhat arbitrary cut point has been used widely throughout literature reviews and clinical trials (Ho, Bryson, & Rumsfeld, 2009). The proper cut point should be determined per each medication’s formulation and the specific disease condition (Ho, Bryson, & Rumsfeld, 2009). Given Wu and colleagues’ finding that event-free survival was maximized for HF patients that adhered to their medications at least 88% of the time (2009), all CVD patients may need to exceed 80% adherence in order to maximize their quality of life and chances for event-free survival. Moreover, a recent study found low-density lipoprotein cholesterol and blood pressure continue to reduce with adherence levels exceeding 80%, suggesting the optimal level of adherence to medication for cardiovascular conditions may be beyond the 80% cutoff (Bryson, Au, Young, McDonell, & Fihn, 2007). Continuous—rather than dichotomous—measures of medication adherence obtained by objective measurement techniques appear to be most appropriate within CVD. Future studies that use an 80% cut point should also report continuous adherence values (Ho, Bryson, & Rumsfeld, 2009).
Summary of Issues Concerning Medication Adherence Measurement in CVD

Shi and colleagues suggest objective measures may be necessary for accurate adherence measurement in complex disease such as CVD (2010). Furthermore, patients appear to accept using electronic monitoring devices such as popular MEMS caps (Haberer et al., 2012). Discrepancies between adherence rates derived from electronic monitoring versus self-reports may be attributed to the complex nature of proper CVD self-management or measurements that were limited to a portion of the entire medication regimen. Also, some self-report measures of adherence may lend themselves to inflated reports of adherence more than others given a small number of items within the questionnaire and the wording of the items. Numerous studies dichotomize adherence with a cut-point, although most do not used a medically-derived cut point; dichotomizing adherence with a cut-point and failing to report continuous levels of adherence impedes researchers’ ability to synthesize adherence research and draw conclusions. The previous literature review provides evidence for the relationship of depression and medication adherence in CVD, which will now be examined in hopes of highlighting one of the greatest barriers to improved outcomes and targets for intervention for CVD patients.

The Relationship of Depression and Medication Adherence in Cardiovascular Disease

It appears that depression complicates CVD patients’ ability to adhere to their medications properly. Depression makes it more difficult for patients to comply with recommended health advice: for example, depression predicts failure to complete a 12-week phase-II CR program (Casey, Hughes, Waechter, Josephson, & Rosneck, 2008).
Persistent depressive symptoms are associated with poor adherence to health behaviors (Kronish et al., 2006) and high risk for mortality (Carney et al., 2004; Scherrer et al., 2012). Importantly, poor medication adherence is bad for outcomes in CVD, where adherence under 88% is associated with increased risk of mortality (Wu et al., 2009).

A landmark study examining the relationship between major depression and medication adherence in adults with CVD involved a depression diagnosis assigned by diagnostic interview and objective adherence to 81mg aspirin measured by an unobtrusive electronic monitor in 55 older adults (Carney, Freedland, Eisen, Rich, & Jaffe, 1995). None of the patients in this sample were prescribed antidepressants. Nondepressed patients adhered to their medications 69% of the days they were monitored; conversely, depressed patients in the sample adhered to their medication 45% of the days monitored indicating a statistically significant difference between groups. All patients reported they understood the importance of adhering to daily aspirin use, and none of the participants reported side effects from the medications. This study did not examine the mechanisms influencing the question of why depression affected adherence, although it showed clinically significant differences between depressed and nondepressed CVD patients’ adherence to vitally important cardiac medication.

Another landmark study assessing this relationship tested whether improvements in depressive symptoms preceded improved adherence to aspirin over three months in 172 acute coronary syndrome patients (Rieckmann et al., 2006a). Aspirin adherence was measured using MEMS and depression was assessed with the BDI during hospitalization and one and three months after hospitalization (2006a). Adequate adherence was defined...
as taking aspirin as prescribed at least 80% of the monitored days (2006a). Individuals who refused to be in the study had significantly higher depression questionnaire scores (2006a). Depression severity was associated with nonadherence in a graded manner: 15% of non-depressed, 29% of mildly depressed, and 37% of moderately to severely depressed patients were nonadherent (2006a). Severely depressed patients were 3.7 times more likely to be nonadherent than non-depressed patients after controlling for potential confounders (2006a). Furthermore, adherence increased in patients whose depressive symptoms improved, and they decreased in patients whose depressive symptoms worsened (2006a). According to follow-up analyses in 165 patients by Rieckmann and colleagues, the mean percentage of days that patients properly adhered to their aspirin regimen was significantly lower among persistently depressed patients than in remittent depressed and persistently nondepressed patients (2006b). These results remained after controlling for medical comorbidities and baseline depressive symptom severity (2006b). Patients whose BDI scores remitted below 10 after three months post-hospitalization were significantly more adherent than persistently depressed patients, ultimately becoming equally as adherent as persistently nondepressed patients (2006b). Although depression has deleterious effects on adherence, improvements in depressive symptoms produced remarkable improvements in adherence (2006b). However, improvements in depression did not perfect adherence rates, suggesting other factors influence this relationship.

The relationship between depression and medication adherence in cardiovascular disease is likely a complicated one, and appears to be moderated by additional factors.
Although treating depression appears to improve medication adherence, it does not appear to perfect medication adherence rates. To truly impact medication adherence, treatment must take into account the moderators influencing this relationship.

Potential Moderators of the Relationship Between Depression and Medication Adherence in Cardiovascular Disease

It is likely that the relationship between depression and medication adherence is moderated by additional factors. Demographic, social, and medical variables may offer insight into this complex relationship. These moderators were selected on the basis of available literature that suggests their involvement in this relationship. There are nine potential moderators: gender, socioeconomic status (SES), age, social support, marital status, comorbidities, overall health status/disease severity, functional capacity, and complex medical regimens (see Figure 1).

Gender

Relationship to Depression in CVD

Male and female CVD patients exhibit numerous gender differences regarding depression. There is a 2:1 risk ratio of depression prevalence for women compared to men in the general population (Kessler, 2003). In CVD, although it appears women may be more likely to be depressed than men (Gottlieb et al., 2004), the gender gap of prevalence rates appears to be much smaller compared to the general population. Extensive evidence supports gender differences in CVD and depression in the following domains: cardiac physiology, cardiac pathophysiology, age of CVD onset, CVD risk,
CVD symptoms, traditional CVD risk factors, and CVD outcomes (Möller-Leimkühler, 2007). Probable gender differences in CVD and depression include psychosocial CVD risk factors, depression as a CVD risk factor, CVD management, and depression as a consequence of CVD according to a large literature review (2007).

Some research has illuminated findings that have important implications for treating men with CVD. For example, depression is harder to predict in men (Koivula, Halme, & Åstedt-Kurki, 2010). Low-income non-white male patients with HF have poor
health perception and more depressive symptoms than do white men and white and non-white women from various socioeconomic statuses (Macabasco-O’Connell, Crawford, Stotts, Stewart, & Froelicher, 2010).

Other research has depicted important trends impacting women with CVD. In a sample of 75 depressed outpatients with HF, women were more likely (64%) to be depressed than men (44%; Gottlieb et al., 2004). Depression was assessed using the BDI (2004). However, another study of 231 German HF outpatients found no gender differences in rates of major depression (13% of sample) or minor depression (17% of sample) according to results rendered from the PHQ-9 (Faller et al., 2007). Numerous studies have demonstrated the effects of depression on QoL for women with CVD. For example, female gender is associated with greater impairments in QoL one year after CABG (Bute et al., 2003). Also, female patients and caregivers are more vulnerable to having their QoL negatively impacted than men (Luttik, Lesman-Leegte, & Jaarsma, 2009). Norris, Hegadoren, & Pilote found depression has a greater impact on health-related QoL one year following MI on women compared to men (2007). Correspondingly, lower social support is associated with more depressive symptoms in the year following MI, and this relationship is stronger for women than men (Leifheit-Limson et al., 2010). Additionally, CVD with comorbid depression prior to retirement was strongly associated with ill-health retirement in women but not men according to an Australian sample of 20,655 adults (Paradise, Naismith, Davenport, Hickie, & Glozier, 2012).
Gender differences in depressive symptomatology have been extensively researched. For example, a 2012 study by Eastwood and colleagues had a twofold purpose: it (1) compared prevalence and severity of depressive symptoms in men and women with HF; and (2) defined gender differences in depression symptom predictors. Depression was assessed with the PHQ-9 in this robust sample of 622 HF patients (2012). Financial status, functional capacity, perceived control, health perceptions, and anxiety predicted depression symptoms in men, and BMI, perceived control, and anxiety predicted depression in women (2012). Future prevention efforts can target perceived control and anxiety for both genders, and they can also target gender-specific predisposing factors in an attempt to prevent depression in HF patients.

Likewise, a study conducted by Hsich and colleagues examined sex and EF differences in in-hospital mortality and risk factors for survival in 51,428 hospitalized HF patients (2012). Women were more likely to be older, have hypertension, anemia, depression, or valvular heart disease, and they were less likely to have CAD, ischemic cardiomyopathy, atrial fibrillation, peripheral vascular disease, hyperlipidemia, or tobacco use (2012). There were no differences in in-hospital mortality between genders, and the risk factors predicting in-hospital death were the same between genders and those with preserved or reduced EFs (2012).

Relationship to Medication Adherence in CVD

Some studies suggest medication adherence is reduced in female CVD patients compared to men. McSweeney, Pettey, Lefler, & Heo note that women are underrepresented in HF clinical trials, and this may be due to the trend that they tend to
exhibit preserved left ventricular ejection fraction (LVEF), which is an exclusion criterion for many trials (2012). They also note evidence-based medications are underutilized for women, and there may be gender-based pharmacodynamic differences in medication benefits, where men benefit more and women experience more damaging side effects from some medications used to treat HF (2012). Additionally, according to a meta-analysis of 53 studies of statin adherence, women had 10% greater odds of nonadherence compared to men (Lewey et al., 2013). However, in a retrospective follow-up of 7,247 elderly CHF patients’ prescription claims, women had higher digoxin compliance rates (Monane, Bohn, Gurwitz, Glynn, & Avorn, 1994).

Most studies control for gender rather than examine gender differences. Altogether, there is minimal research that examines gender differences in medication adherence in CVD patients. Given the available research, it is possible that since women tend to experience more depression than men with CVD, they may also exhibit poorer medication adherence. However, rigorous studies need to examine such speculation, particularly given the effect this could have on interventions and health outcomes.

**Summary and Conclusions**

Depressed patients are more likely to be women, who may have worse adherence than men due to their depression. Future research must test whether female gender is associated with worse medication adherence in depressed CVD patients. Despite the lack of available data, gender is still a possible moderator. Women may have other family members to care for in addition to themselves, which may make it harder to adhere. Women may be more likely to experience a major depressive episode in the context of
CVD (given the 2:1 risk ratio of women and men developing depression), and depressed women with CVD are more likely to experience reduced QoL and social support. Depressed women, given their reduced QoL and social support, may not adhere as well as men.

Also, some research measures depressive symptoms whereas others quantify these symptoms into minor or major depression. These variations contribute to variations in findings. Furthermore, women are less likely to be included in research. Although some research focuses solely on women, future research should aim to include an equal number of both sexes so rates of depression and medication adherence can be confidently compared between men and women. Researchers should also continue to examine gender differences among those that consent to participate in a study versus those who decline.

Many research studies control for gender rather than examine the differences between these groups. Further research is needed to determine gender-specific barriers to medication adherence, especially within depressed CVD patients. Due to limited research and methodological inconsistencies within available research, the role of gender as a moderator of depression and medication adherence in CVD requires further evaluation. Factors commonly associated with gender roles, such as caregiving responsibilities, may further reduce medication adherence in depressed women with CVD compared to depressed men with CVD. Gender may moderate this relationship, and the magnitude of the effect may minimally favor depressed men’s adherence over women’s.
Socioeconomic Status

SES is generally conceptualized as a household’s social and economic standing in relation to others based on education, occupation, and income (Adler et al., 1994). SES is best understood as a gradient rather than a threshold, and low SES appears to be linked to higher morbidity and mortality across nearly all illness and condition (1994). Factors that may moderate the association between SES and health include macroeconomic contexts, social factors, immediate social environments, biological predispositions, biological processes, individual psychological factors, and individual behavioral factors (Adler & Ostrove, 1999).

Relationship to Depression in CVD

Lower SES is associated with more disability, poorer access to health care, and higher psychiatric morbidity (Lorant et al., 2003). Specifically, low-SES individuals are more likely to be depressed than high-SES individuals (Lorant et al., 2003). In low and middle-income countries, wealth and education are inversely associated with angina, depression, and comorbidity prevalence (Hosseinpoor et al., 2012). Although it appears depression is related to SES in CVD, more current research is needed to further explore this finding.

Relationship to Medication Adherence in CVD

According to the World Health Organization, SES may contribute to medication nonadherence (2003). Limited data on SES demonstrates SES appears to predict certain aspects of medication adherence in HF patients. In a 2008 study by Wu, Moser, Chung,
& Lennie, researchers collected ethnicity, level of education, and financial status in a patient/family interview from 134 HF patients (2008). These patients’ medication adherence was monitored with MEMs for three months (2008). Dose-count, dose-days, and dose-time were calculated based on adherence data (2008). Among other factors, minority ethnicity predicted poorer dose-count adherence, and financial status predicted dose-day and dose-time (2008). These researchers suggest the interaction between race and income, rather than race alone, may be related to adherence (2008). Also, this study included few participants with low incomes. Future research should incorporate individuals from a broad range of SES to determine which SES-related factors affect medication adherence the most.

**Summary and Conclusions**

Individuals with lower income should be considered at higher risk for medication nonadherence (Wu, Moser, Chung, & Lennie, 2008). SES is a contributing factor to medication nonadherence (WHO, 2003). Conversely, higher SES may buffer the effects of depression on medication adherence. Additionally, studies of depression in CVD patients from a variety of SES are needed, but existing research suggests SES is broadly related to depression across a variety of health conditions (Lorant et al., 2003). Studies using SES as a gradient, or using SES at all, are lacking (Adler, 1994). Adler noted SES is typically used as a control variable rather than as a predictor itself (1994). Many of the other potential moderators have also been used as control, rather than predictor, variables. Nevertheless, the existing research suggests there may be utility in examining the role of
SES as a predictor of poor medication adherence in CVD patients that experience depressive symptoms.

**Age**

Age may also moderate the relationship between depression and medication adherence.

**Relationship to Depression in CVD**

In advanced forms of CVD such as HF, age appears to play a significant role in the prevalence of depression. In a study of 155 HF outpatients (mostly NYHA class III), 48% were classified as depressed as defined by a BDI score equal to or greater than 10 (Gottlieb et al., 2004). Only 7% of patients were receiving an antidepressant medication, but 48% were depressed (Gottlieb et al., 2004). In that sample, depressed HF patients tended to be younger, and these younger patients also reported worse QoL, bodily pain, mental health, and general functioning (Gottlieb et al., 2004). Furthermore, for every 10 years above age 64, the likelihood of demonstrating depressive symptoms decreased 26%, and for every 10 points below the mean score for vitality (energy level and well-being) the likelihood of having depressive symptoms increased by 90% (Gottlieb et al., 2004). Therefore, age appeared to play a major role in the prevalence of depressive symptomatology in outpatients with HF.

Rohyans & Pressler found similar results for age (2009). In their sample of Midwestern HF outpatients, a score of 10 or greater on the PHQ-9 indicated a likelihood of depression. The mean age of participants was 61.3 years and the majority were NYHA
class III (2009). Twenty-eight percent of the outpatients had scores indicating a likelihood of depression; a significant inverse correlation between age and depressive symptoms illustrated that younger outpatients reported more depressive symptoms than older outpatients (2009).

In a study by Hinz, Kittel, Karoff, & Daig (2011), the researchers administered the Hospital Anxiety and Depression Scale to CR patients at the start of the CR program and to a random sample of German adults. Sixty-one percent of the cardiac patients were depressed as compared to approximately 49% of the general population (2011). In the general sample, anxiety and depression increased with age, but in the cardiac patient sample both anxiety and depression peaked in middle age (around ages 50-59; 2011). Most of the items that contributed to the age differences appeared to represent worrying about the future and the subjective experience of psychomotor retardation (2011). This publication supports the idea that middle age CVD patients are especially vulnerable to depression compared to younger and older CVD patients. Considering depression’s effects on adherence, middle age adults with CVD pay require greater medication adherence support than their older and younger peers.

**Relationship to Medication Adherence in CVD**

Research on the relationship of age to medication adherence suggests results that conflict with what researchers have theorized. Some researchers suggest younger individuals may have poor medication adherence because they might experience lower perceived risk of future negative cardiovascular events (Aggarwal & Mosca, 2010). In an empirical study of adherence to amiodarone and amiodarone placebo following MI, being
over 70 years old predicted adherence in the 20th percentile confirmed by pill count over two years in 569 participants (Irvine et al., 1999). These individuals took less than 66% of the pills dispensed to them over two years (1999). Furthermore, individuals over 70 years of age were more likely to have declined participation in this study (1999). Future research on medication adherence in young through old CVD patients is needed.

**Summary and Conclusions**

Presently, it is unclear if age moderates the relationship between depression and medication adherence in CVD. It is still possible that this moderation exists, but future research is needed. Young age may buffer the negative effects of depression on adherence because younger CVD patients may have more resources to deal with both their depression and barriers to adherence. Future research must test whether young age acts as a buffer. Future research may consider using a difference score of the patient’s current age and the age at which they were diagnosed with CVD. It may be that individuals who have been diagnosed with CVD for years have created self-management strategies as opposed to individuals who were recently diagnosed and still adjusting to a self-management protocol. Also, age should be reported continuously rather than categorically to maximize the ability to compare findings across studies.

The literature reveals discrepancies among studies that evaluate age’s relationship to depressive symptoms in CVD. Gottlieb and colleagues (2004) and Rohyans and Pressler found a negative relationship between age and depressive symptoms in HF outpatients (2009), whereas Hinz, Kittel, Karoff, & Daig found depression peaked in middle age among CR participants (2011). These variations can in part be due to the
studies’ considerable methodological flaws. Future studies should diagnose depression using uniform procedures and cut-offs when using self-report tools.

The disconnect between researchers’ hypotheses about medication adherence and observable trends is embodied in this line of research. Some researchers believed depressed patients were more likely to be younger and demonstrate worse adherence (Aggarwal & Mosca, 2010). They believed that younger participants might have trouble appreciating the importance and impact of their medications due to worry and hopelessness about the future (2010). The researchers believed older patients were less likely to be depressed, which may help them achieve better adherence (2010). However, empirical studies demonstrated older participants were more likely to demonstrate poor adherence (Irvine et al., 1999).

**Social Support and Marital Status**

Social support refers to the functions rendered as a result of social relationships, including but not limited to emotional concern, instrumental assistance, or information (Arthur, 2006). Social support typically comes from spouses, relatives, and friends. Social support is generally measured through short self-report questionnaires. One of the most popular questionnaires is the Multidimensional Scale of Perceived Social Support (Zimet, Powell, Farley, Werkman, & Berkoff, 1990), in which the rater assesses dimensions of the patient’s close social relationships, including having someone to talk to in a time of need and knowing people care about them. Marital status is self-reported and typically considered an indicator of social support.
**Relationship to Depression in CVD**

Studies have well documented the relationship between social support and depression in CVD. Patients with higher perceived social support tend to have lower depression scores (Barefoot et al., 2003). Social support and depressive symptoms predict mortality in coronary artery disease (CAD) patients (Brummett et al., 2005). In patients with mild HF, depression is associated with male sex, few social ties, and low social support (Tsuchihashi-Makaya, Kato, Chishaki, Takeshita, & Tsutsui, 2009). Numerous studies in the past decade have examined the relationship between social support and depression in CVD. There is strong evidence that the interaction of depression and social support not only produces impairment, but also it can contribute to an early death.

A sub-study of ENRICHD by Barefoot and colleagues examined how aspects of social support relate to depressive symptoms following MI in the hospital and two weeks after discharge (2003). According to baseline Hamilton Rating Scale for Depression scores, 28% of the 196 participants demonstrated depressive symptoms, 17% showed symptoms at follow-up, and 75% stayed in the same category across time (2003). In this sample, 16% saw their depression improve over the two weeks while 9% saw it worsen (2003). According to BDI scores, 37% exhibited depressive symptoms at baseline and the prevalence was 27% at follow-up, with 27% improved over time, 13% worsened, and 59% remained the same (2003). The two measures of depression had fair to moderate agreement (2003). Individuals with high social support scores—especially scores that reflected perceived support—had lower depression scores at baseline; the Beck cognitive scale revealed that high levels of perceived support and low levels of social conflict were
related to fewer depression symptoms at follow-up (2003). In this study, the method of measurement appeared to impact the results. Given the differences in observed relationships depending on the measures used, multiple measures of depression and social support should be used in future studies so the relationships between these constructs can be fully documented and understood (2003).

Positive spousal support is a common aspect of social support. One study sought to evaluate the effect of marital status on mortality over four years in 166 depressed and non-depressed HF patients (Chung et al., 2009). The researchers determined the presence or absence of depression by using a cutoff score of 14 on the BDI-II, which was entered into Kaplan-Meier and Cox regression analyses (2009). In this study, 56% of the participants were married, 33% had depressive symptoms, and levels of depression were similar across married and unmarried participants (2009). Married participants lived longer than unmarried participants even after accounting for depression (2009). Another study examined the relationship of depression, social support, and event-free survival in 220 HF patients over four years (Chung, Lennie, Dekker, Wu, & Moser, 2011). Participants completed the BDI-II and the Multidimensional Perceived Social Support Scale (2011). Both depression and social support independently predicted event-free survival (2011). Depressed participants with low perceived social support had 2.1 times higher risk of events than non-depressed patients with high-perceived support (2011). These findings indicate that depression and poor perceived social support decrease the chances of event-free survival in HF patients.
**Relationship to Medication Adherence in CVD**

There is a relationship between social support and medication adherence in CVD, and this relationship appears to have implications for event-free survival. It appears unmarried CVD patients are less adherent. A study by Wu and colleagues determined if medication adherence mediated the relationship between marital status and event-free survival in 136 HF patients (2012). Medication adherence was tracked with MEMS over three months, and the amount of time for which patients were followed to determine cardiac events was not specified (2012). Unmarried participants had worse cardiac event-free survival, they were two times more likely to experience an event, and they were more likely to adhere less than 88% of the time (2012). Marital status did not significantly predict event-free survival after entering medication adherence into the model; marital status and event-free survival appear to be mediated by dichotomized medication adherence (2012b). Future medication adherence interventions should specifically target unmarried patients because they are at higher risk for nonadherence (2012).

**Summary and Conclusions**

There are no studies that explicitly test a moderating effect for social support on depression and adherence. However, previous research suggests depression may interact with low social support in a negative manner. Depressed patients are less likely to experience high social support, but social support may buffer the deleterious effects of depression on medication adherence. Being married may buffer depression’s potential negative influence on medication adherence because the benefits of marriage may include
an additional caregiver, additional income, and additional positive social support. Future research should directly test whether social support moderates the relationship between depression and medication adherence in CVD patients.

Most studies assume that social relationships are positive and neglect the effects of adverse close relationships (de Vogli, Chandola, & Marmot, 2007). Future studies should examine the quality of the support. Additionally, future studies should disentangle spousal support from platonic friendship-based support. These types of support may also differ from familial support (e.g., having one’s children as caregivers). Future research should incorporate objective measures of caregiver and patient adherence to understand the broad influence of social support on outcomes of patients and their supporters.

Discrepancies within the depression and social support in CVD literature prompt the need for future research. Multidimensional measures of social support are preferable given the multifaceted nature of social support. Methodological flaws mar some of the existing literature in this area. Although there appears to be a relationship between depression, social support, and outcomes, more research designs that investigate the specific elements and direction of this relationship are necessary.

Comorbidities

Comorbidities refer to the presence of other diseases in addition to CVD. Any additional diagnosis is considered to be comorbid. Common comorbid conditions include type 2 diabetes mellitus (T2DM), diabetic neuropathy, hypertension, hypercholesteremia, sleep apnea, depression, generalized anxiety disorder, autoimmune disorders, chronic pain, and infectious diseases. Comorbidities are typically assessed via chart review, tests
to confirm pathology, questionnaires, or verbal reports from the patient, their family, or their care provider. They are associated with significant increases in mortality risk, particularly for older adults with HF (Ahluwalia et al., 2011). Also, 40% of older adults with HF have five or more additional chronic conditions (Page & Lindenfeld, 2012).

**Relationship to Depression in CVD**

Comorbidities present challenges for CVD patients, and they appear to become more problematic when combined with depression. Comorbidities and depression are associated with hospital admissions in newly diagnosed HF patients (Chaudhry, McAvay, Chen, Whitson, Newman, Krumholz, & Gill, 2013). In one study, impaired QoL and depressive symptoms were most prevalent among HF patients with comorbidities and without comorbidities as compared to a sample of community dwelling elderly (Lesman-Leegte, Jaarsma, Coyne, Hillege, van Veldhuisen, & Sanderman, 2009).

T2DM is one of the most commonly studied comorbidities in CVD patients. In patients with CVD, depression predicts smoking and T2DM (Nair, Farmer, Gongora, & Dehmer, 2012). Patients with T2DM and depression were at significantly increased risk for new-onset MI as opposed to individuals with T2DM or depression alone (Bot, Pouwer, Zuidersma, van Melle, & de Jonge, 2012; Scherrer et al., 2011). According to a study of 1,008 female CVD patients over age 60, the 18% of the sample with T2DM had greater functional impairment than those without T2DM (Janevic, Janz, Connell, Kaciroti, & Clark, 2011). Depressive symptoms were generally significantly higher in the group with T2DM, and women with T2DM experienced greater physical impairment after 18 month of follow-up (Janevic, Janz, Connell, Kaciroti, & Clark, 2011). Overall, it
appears CVD patients with T2DM experience poorer outcomes than CVD patients without T2DM.

Obstructive sleep apnea is another commonly studied comorbidity many CVD patients experience. Between 30-50% of CHD patients report at least mild obstructive sleep apnea (Carney et al., 2006). Although sleep apnea is not more common in depressed CVD patients than in nondepressed CVD patients, depressed CVD patients experience longer obstructive sleep apneic episodes in men and women and with a higher frequency of episodes in men according to a two night sleep study (2006). Obstructive sleep apnea has dramatic deleterious effects on treatment for depression. Obstructive sleep apnea can limit the efficacy of CBT for depression following MI (Freedland, Carney, Hayano, Steinmeyer, Reese, & Roest, 2012) as well as sertraline supplemented with omega-3 fatty acid in patients with CHD (Roest et al., 2012). Obstructive sleep apnea, when combined with depression after MI, is interactively associated with adverse clinical outcomes (recurrent MI or death; Hayano et al., 2012).

**Relationship to Medication Adherence in CVD**

There is limited research on the relationship of comorbidities to medication adherence in CVD, though it appears self-care is complicated by comorbidities (Dickson, Buck, & Riegel, 2011). In the Heart Failure Adherence and Retention Trial, individuals with comorbidities (asthma and renal disease) were less likely to be adherent according to MEMS monitoring (Calvin et al., 2012).

Dunbar-Jacob, Bohachick, Mortimer, Sereika, & Foley conducted a key study examining medication adherence in individuals with CVD and comorbidity (2003). The
study determined medication adherence rates among three groups of adults over age 62 who experienced comorbid conditions including CVD (2003). Individuals were monitored for three weeks using electronic monitoring in all 169 individuals (2003). The percentage of prescribed doses taken, the percentage of days with the correct number of doses taken, and the percentage of doses taken within the correct timing interval were calculated to describe adherence behavior (2003). The group with the poorest adherence had both CVD and rheumatoid arthritis (2003). In this sample, 88.77% of prescribed doses were taken, participants took the correct number of doses 76.40% of the time, and 64.02% of doses were taken in the correct timing interval (2003).

**Summary and Conclusions**

Depressed individuals have comorbidities that make it difficult to manage their medications. No studies have examined whether a certain number of comorbidities predict depression. Although the present analyses will be exploratory, it appears that amongst depressed CVD patients, those with a greater number of comorbidities, as well as those with more pervasive or disruptive comorbidities may have poorer medication adherence. Depressed CVD patients with comorbidities that require complex self-management may demonstrate significantly worse medication adherence than those with comorbidities that are easy to manage. Individuals with complicated comorbidities that reduce life expectancy as well as depression may have a harder time adhering to medication given increased physical symptoms and increased hopelessness. Individuals with less comorbidity appear to be less depressed and display better medication adherence rates. T2DM, obstructive sleep apnea, and rheumatoid arthritis are three
frequently assessed comorbidities. Future research should question whether comorbidities complicate the relationship between depression and medication adherence in CVD. Future research should examine the influence of specific common conditions that are frequently comorbid with CVD. Furthermore, the optimal way to quantify comorbidities (e.g., number of comorbidities, a weighted score that accounts for more complicated mandatory self-management strategies) is yet to be determined.

**Overall Health Status and Disease Severity**

Within CVD, NYHA class (which is also a marker of self-reported functional capacity), LVEF, B-type natriuretic peptide, and peak oxygen consumption during cardiopulmonary testing frequently determine health status and disease severity. Although cardiopulmonary testing is the optimal measure of health status and disease severity, it is strenuous for participants, as well as timely and costly for researchers. Therefore, self-report measures are frequently substituted for objective measures of overall health status and disease severity. A commonly used self-report measure of health status is the Kansas City Cardiomyopathy Questionnaire (KCCQ; Green, Porter, Bresnahan, & Spertus, 2000). Another one of the most common ways to measure disease severity in HF patients is NYHA class and LVEF, which can be considered to be a combination of objective and subjective disease severity. Most measures of disease severity that require any self-report include at least some aspects of functional capacity. Functional capacity will be discussed later as its own moderator.
**Relationship to Depression in CVD**

Overall health status and disease severity appears to be related to depression in CVD. In a sample of 75 depressed outpatients with HF, patients classified as NYHA functional class III and IV (signifying greater impairment) were significantly more likely to score as depressed than those who were class II; NYHA class III patients were equally likely to be depressed as class IV patients (Gottlieb et al., 2004). Furthermore, LVEF did not predict depression in this sample (Gottlieb et al., 2004). In another study of HF outpatients, adults in class III and IV had significantly more depressive symptoms than adults in class I and II (Rohyans & Pressler, 2009). Furthermore, depressive symptoms predict short-term declines in overall health status (Rumsfeld et al., 2003) and symptom burden (de Jong, Moser, & Chung, 2005) in HF patients.

In a study of 168 patients with CAD, patients were split into preserved LVEF groups (>50%) and impaired (<50%) groups (Dogdu et al., 2012). Patients also completed the BDI (2012). Depression scores were significantly higher in the impaired group than in the preserved group, and these scores were important risk factors for left ventricular dysfunction in the preserved group of patients (2012). According to this study, in CAD patients, depression symptoms were influential for patients with both preserved and impaired left ventricular function (2012).

In the Heart Failure And a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial, investigators sought to test whether depressive symptoms measured by the BDI were better associated with patient perception of disease severity than with objective markers of HF severity (Gottlieb et al., 2009). Patient perception of
disease severity was assessed with the KCCQ, and objective measures of HF severity included EF, B-type natriuretic peptide, and peak oxygen consumption through cardiopulmonary exercise testing (2009). Depression was assessed with the BDI, according to which 43% of the sample of over 2,000 patients was depressed (2009). Increased depressive symptoms were associated with more subjective symptoms of HF as reported on the KCCQ (2009). Moreover, NYHA class, cardiopulmonary exercise training test duration, peak respiratory exchange ratio, and six-minute walk test were slightly related to BDI scores (2009). However, together those characteristics showed an $R^2$ of 0.086 in the model, leading the authors to believe unmeasured noncardiac factors played a major role in depression (2009). Altogether, depression was associated with patient perceptions of disease severity and minimally related to objective assessments of disease severity in HF patients (2009).

In a study of 75 Italian CVD patients, mediators of the relationship between illness severity (LVEF) and depression (through questionnaires) were examined (Greco et al., 2013). The relationship between LVEF and depression was moderated by self-efficacy beliefs about managing cardiac risk factors, identity illness perception, and perceived social support, suggesting interventions may target these constructs in future depression interventions for CVD patients (Greco et al., 2013). Another study of Italian CVD patients by the same group of researchers tested the (1) impact of illness severity on depression and health/life satisfaction, and (2) mediation of illness perception and self-efficacy beliefs in managing cardiac risk factors (Steca et al., 2013). In that study, 172 patients’ LVEF was recorded upon hospital discharge and they completed psychological
questionnaires one week later (Steca et al., 2013). LVEF was positively associated with all other variables, except that it was negatively associated with depression (Steca et al., 2013). Illness severity, depression, and health satisfaction were mediated by illness perception and self-efficacy, but disease severity and life satisfaction were unrelated (Steca et al., 2013). Future depression interventions in CVD patients may attempt to improve illness perception and self-efficacy beliefs in order to improve overall QoL in this population.

**Relationship to Medication Adherence in CVD**

There is minimal research on the relationship between illness severity and medication adherence in CVD. Recent research suggests the need for further examination of the magnitude that disease severity may negatively influence medication adherence in CVD patients. As previously mentioned, according to the HART trial, NYHA class III patients were less likely to adhere to their medications at least 80% of the time (Calvin et al., 2012). Additionally, the 37% of patients who failed to properly adhere to their medication as recorded by MEMS were more likely to be a minority or a higher NYHA class (2012).

**Summary and Conclusions**

Disease severity likely moderates the relationship between depression and medication adherence. The literature demonstrates illness worsens as depression worsens too. The limited research on medication adherence and illness severity finds sicker patients achieving poorer rates of medication adherence. It is also possible that depressed
patients are more prone to experience health declines, which likely entails medication changes and contributes to poorer adherence. Depressed individuals with greater disease severity likely exhibit poorer medication adherence, whereas healthier depressed CVD patients may adhere better. Furthermore, CVD patients with greater illness severity may also experience more comorbidity, which may further suppress their medication adherence. Sicker patients may also have more medications to keep track of or they may be older, which can further impair their ability to properly adhere. Individuals with CVD and reduced motivation, self-efficacy, and internal locus of control may not engage in the regular health behaviors that would maintain their health. As such, these same individuals may experience greater illness severity and, ultimately, poorer medication adherence partially as a byproduct of reduced motivation, self-efficacy, and internal locus of control. These constructs warrant further investigation. Given previous research, it appears the method of disease severity assessment plays an important role in the ultimate conclusions researchers can draw about the role of disease severity in outcomes. Future research should target how different assessment methods differentially impact findings.

Many of the aforementioned studies draw a relationship between depression and objective measures of disease severity, although Gottlieb and colleagues (2009) found this to be truer for subjective measures of disease severity. At face value, this appears to contradict existing literature. However, both NYHA class and six-minute walk test are strongly influenced by motivation and patient perception, and they also represent self-reported measures of functional capacity. The role of motivation and subjective experience of fatigue appear to influence many aspects of depression and disease.
severity. However, other studies (e.g., Dogdu et al., 2012) have documented a relationship between LVEF, an objective measure of disease severity, and depression. Yet, LVEF is influenced by physical activity habits, which can be influenced by motivation and other subjective experiences. Therefore, the indirect effects of subjective symptom experiences likely influence objective measures of disease severity, ultimately causing the observed disparity.

**Functional Capacity**

Functional capacity refers to one’s ability to perform basic physical and occupational tasks. Commonly, CVD patients experience diminished functional capacity such as dyspnea upon walking long distances, difficulties with intimate relations, and problems completing strenuous housework. Because of physical barriers, many individuals report occupational impairment as well. Functional capacity is assessed through cardiopulmonary testing, the six-minute walk test (Guyatt et al., 1985), and the Duke Activity Status Index (Hlatky et al., 1989). Self-report measures are adequate when determining physical limitations, but older adults tend to over-report reduced physical functional capacity even when their objective physical performance improves or does not worsen between measurements (Dolansky & Moore, 2008). Functional capacity focuses more on disability whereas overall health status or disease severity quantifies the extent of pathology.
**Relationship to Depression in CVD**

Reduced functional capacity, particularly occupational limitation, is common among CVD patients, and it appears to be related to depressive symptoms. Both men and women with CVD report similar levels of disability despite women reporting more depressive symptoms (Scott & Collings, 2012). In 105 women with CAD, women who were still working had fewer depressive symptoms and higher social support than nonworking women (Blom et al., 2007). In one study, employed individuals with CVD and depression were eight times as likely to experience work impairment as a reference group, and they reported the greatest likelihood of workplace absenteeism (O’Neil, Williams, Stevenson, Oldenburg, & Sanderson, 2012). There was also a trend of depression severity being associated with poorer return-to-work outcomes six and 12 months following MI (O’Neil, Sanderson, & Oldenburg, 2010).

Depressive symptoms progressively increase as HF outpatients increase their instrumental activities of daily living (Friedman, Lyness, Delavan, Li, & Barker, 2008). Patients report reduced functional capacity following CHF diagnosis, which tends to be associated with worse self-reported executive dysfunction and depressive symptoms (Foster et al., 2011). Remission of depressive symptoms is associated with improved physical functional capacity (Xiong et al., 2012).

Additionally, CVD significantly predicted depression in urban Taiwanese older adults (Chiu, Chen, Huang, & Mau, 2005). Shen and colleagues found that depression and anxiety predicted decline in HF patients’ physical health functioning (2011). One study by Song, Moser, and Lennie found that dyspnea on exertion, ankle swelling,
fatigue, and depressive symptoms were independently associated with functional status in
women (2009). The study also found that only dyspnea on exertion influenced functional
status of men with HF (2009).

A 2010 study by Kurdyak and colleagues examined the association between
depression and mortality following acute MI. The authors used a prospective cohort
design: they obtained a measure of self-reported depression and gained access to no less
than 12 years’ of previous hospitalization data in 1,941 adults (2010). The researchers
discovered that patients with more depressive symptoms tended to be younger, were
more likely to be women, and had lower household incomes (2010). Additionally, the
severely depressed patients had greater incidences of T2DM, hypercholesterolemia, and
smoking history, and they had a higher number of non-cardiac comorbidities (2010).
Furthermore, moderately and severely depressed individuals were more likely to have
been prescribed nitrates upon discharge from the index acute MI hospitalization
compared to mildly and nondepressed patients (2010). Depression was strongly
correlated with mortality two years following hospital discharge for the index MI (2010).
As depression severity scores increased, self-reported cardiac functional status scores as
measured by the Duke Activity Status Index also increased (2010). After adjusting for
age, sex, income, and self-reported cardiac functional status, self-reported cardiac
functional status emerged as the main factor determining increased mortality in depressed
patients (2010). Therefore, the negative impacts to cardiac functional status merit further
examination. Future intervention efforts might be fruitful in reducing patient mortality for
situations in which acute MI leads to depression.
An acute MI typically lessens an individual’s independence and causes his or her physical function to decline, although rates of incidence have not been clear until a recent study by Dodson and colleagues (2012). That nationwide United States-based study examined 2,002 individuals. Researchers surveyed participants about their independence and physical function at the time of their acute MI and one year following (2012). According to regression analyses, 43% of patients experienced health status declines (2012). In that sample, 12.8% experienced independence loss, 15.2% had physical function decline, and 15% experienced both; independence loss was predicted by unmarried status, nonwhite race, uninsured status, end-stage renal disease, female sex, and depression. Physical function decline was predicted by uninsured status, lack of CR referral, and absence of pre-MI angina (2012). Depression was one of the only modifiable predictors of independence loss (2012).

**Relationship to Medication Adherence in CVD**

There are no available studies of the relationship between medication adherence and functional capacity. It is possible that functional capacity may impair ability to obtain medications from pharmacies or even from within one’s home. Further research should investigate whether or not functional capacity influences medication adherence in CVD.

**Summary and Conclusions**

Diminished functional capacity is related to increased depressive symptoms. Further research in this area is needed, though, as the number of depressive symptoms does not appear to explain the relationship between depression and disability. Depressed
individuals with diminished functional capacity may have more difficulties adhering to medication, yet depressed individuals with improved functional capacity may adhere better. This could be because diminished functional capacity may make it more difficult for individuals to obtain prescriptions, to take medications on time, and to manage a large number of medications in a single day. These obstacles to adherence have been observed in qualitative patient interviews, and should be examined in relation to reliable measures of functional capacity. Future studies should examine the relationship between functional capacity and medication adherence.

**Complex Medical Regimens**

Complex medical regimens are associated with noncompliance in a variety of populations (Coleman et al., 2012a). Using multivariate meta-regression analyses of individuals with chronic disease, Coleman and colleagues demonstrated that adherence was higher for once-daily medications than for medications prescribed to be administered multiple times each day (2012a). That finding was magnified when more stringent definitions of adherence were used; it was present when studies were limited to prospective designs assessing adults with chronic CVD through at least one month with an electronic monitoring device (2012b).

Unlike individuals who take just a few once-daily medications, individuals with CVD typically are prescribed several medications each day; some medications need to be taken multiple times each day or come with complex instructions. For example, although individuals who are prescribed nitrates should observe a 10-12 hour nitrate-free period each day, a study by Straka, Fish, Benson, & Suh found 74% of CVD patients prescribed
nitrates three times daily failed to comply with proper nitrate recommendations (1996). Depending on a medication’s pharmacological properties, improper dosing (e.g., overdosing) could be more dangerous than skipping doses.

Of the many tools that researchers use to measure a medical regimen’s complexity, one such tool is the Medication Regimen Complexity Index (George, Phun, Bailey, Kong, & Stewart, 2004). This tool generates a complexity score that encompasses the complexity of the entire prescribed regimen.

Relationship to Depression in CVD

No publications were found that examined the relationship between depression and complex medical regimens in CVD. Theoretically, it is logical that CVD patients being treated for depression with pharmacotherapy may have more complex medications regimens due to the addition of medication targeting their mood symptoms. This could result simply in additional medication, which would not dramatically complicate the regimen. Conversely, if extensive precautions must be taken to avoid side effects or to properly incorporate the medication into the regimen while avoiding potential adverse drug interactions, then adding precautions would present measurable challenges to self-management. However, depressed CVD patients may also experience additional comorbidities that nondepressed CVD patients are less likely to experience, which could greatly complicate the medical regimen. Future research should examine the interplay between complex medical regimens for CVD and depression.


**Relationship to Medication Adherence in CVD**

Dunbar-Jacob, Bohachick, Mortimer, Sereika, & Foley found an inverse relationship between adherence and daily dosing frequency (2003). Specifically, adherence declined as doses per day increased in their sample of adults with CVD and at least one comorbid condition (2003). They found adherence was 95.2% for medications taken once daily, 84.1% for medications taken twice daily, and 77.9% for medications taken three or four times daily (2003). As previously mentioned, Coleman and colleagues found adherence to be higher for once-daily medications than medications taken two, three, or four times daily according to electronic monitoring (2012b). Moreover, an analysis of 1,077,474 CVD patients revealed medication possession ratios were higher for medication prescribed once-daily than medication prescribed twice-daily (Bae et al., 2012).

However, another study found no differences in adherence between once-daily versus twice-daily carvedilol in HF patients using MEMS (Udelson et al., 2009). The authors noted this was surprising and contradictory to hypotheses and previous research (2009). This may be due to a high baseline adherence to prescribed therapy, a very high standard of care in the specialized HF clinic from which patients were sampled, and measurement reactivity (2009). Furthermore, another study of prescription claims of the New Jersey Medicaid program found elderly CHF patients who took more medications were also more compliant with their medications (Monane, Bohn, Gurwitz, Glynn, & Avorn, 1994). Nevertheless, Udelson and colleagues recommend a once daily regimen when possible for the reasons of simplicity, safety, fewer side effects, and the trend that
HF patients acquire more medications over time, which ultimately further complicates their already complex regimens (2009).

**Summary and Conclusions**

Depressed patients with more complex medication regimens may exhibit poorer medication adherence than depressed patients with simpler regimens. Having a simpler medication regimen may reduce the effect of depressive symptoms on medication adherence and overall self-management. However, almost no research has been done to examine this hypothesis. Depression may lower motivation to adhere and decrease concentration needed for medication self-management. Depression may also contribute to the worsening of other disease processes, which require troubleshooting and increased hypervigilance to adequate self-management. Currently, researchers can look elsewhere in the literature to further explain this poorly understood moderator within the context of depressed CVD patients. The field of behavioral medicine must devote more attention to the relationship between medication complexity and medication adherence before confidently asserting that a moderating relationship exists.

**The Current Study**

There appears to be clinically significant differences between depressed and nondepressed CVD patients’ adherence to medication (Carney, Freedland, Eisen, Rich, & Jaffe, 1995). However, no investigations have explored demographic, social, and medical moderators of this relationship using telemonitoring. Since depression and poor medication adherence are both associated with poor outcomes, it would be advantageous
to understand what factors can positively influence medication adherence in a depressed HF patient sample as a way of improving clinical outcomes and quality of life. The current study aims to identify whether certain demographic, social, and medical variables moderate the relationship between depressive symptoms and medication adherence in HF patients.

The proposed study will examine the following primary hypotheses:

1. Demographic factors, including gender, SES, and age will moderate the relationship between depression and medication adherence in HF. Depressed females will have poorer medication adherence than depressed males. Additionally, high SES will buffer the deleterious effects of depressive symptoms on medication adherence in the current sample. Lastly, older depressed adults will have poorer medication adherence than younger depressed adults.

2. Social factors, including social support and marital status, will moderate the relationship between depression and medication adherence in HF. High social support or being currently married and not separated will buffer the effects of depressive symptoms on medication adherence.

3. Medical variables, including comorbidities, overall health status/disease severity, functional capacity, and medication regimen complexity, will moderate the relationship between depression and medication adherence in HF. Depressed individuals with greater Charleson Comorbidity Index scores will have poorer medication adherence. Depressed individuals with poorer health status/worse disease severity will have poorer medication adherence than their healthier peers.
Depressed individuals with decreased functional capacity will have poorer medication adherence than depressed individuals with better functional capacity, and depressed individuals with higher Medication Regimen Complexity Index scores will have poorer rates of medication adherence.
METHOD

Kent State University, Summa Health System’s Akron City Hospital, and Case Western Reserve University’s University Hospital institutional review boards previously approved the protocol for this study. Participants were recruited through two cardiology services, informational letters, and advertisements. The present study is a part of a larger study entitled Heart Adherence, Behavior, and Cognition (ABC), a longitudinal observational study examining the effects of medication adherence and cognition on outcomes in HF.

Before consenting to participate, participants were provided with full verbal and written descriptions of the study’s procedures and were given the opportunity to have questions or concerns addressed by research staff. Participants enrolled in the study granted the researchers permission to gather information from their medical records. Research staff obtained the following information from the clinical database: diagnosis of systolic heart failure, gender, and age.

Participants

The present study includes 305 older adults who were enrolled in the Heart ABC study. Participants were recruited from both inpatient services and the associated outpatient cardiology clinic of two medical centers in northeast Ohio. They were eligible for participation if they were between 50-85 years of age, English-speaking, had a history of systolic HF class II or III for at least three months confirmed by medical chart review.
within 12 months of study enrollment, and lives within 30 miles of either study site. The individual was also only eligible if they were willing to allow research staff into their home for the study visits and to allow research staff to install a telehealth device in their home. Exclusion criteria included class IV HF, a history of neurological disorder (e.g., stroke, Alzheimer’s disease, severe head injury producing loss of consciousness of 10 minutes or more), history of significant psychological problems (e.g., schizophrenia, substance abuse within past five years), developmental disability that interferes with daily living, renal failure requiring dialysis, history of untreated sleep apnea (diagnosed through a formal sleep study), history of coronary artery bypass grafting within the past three months, or terminal illness where the individual was expected to expire within the next six months. Additionally, the individual could not have been a telehealth or home healthcare nursing patient through which a professional managed their medication regimen.

**Measures**

**Depression**

Depressive symptoms were assessed using the Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer, & Williams, 2001). The PHQ-9 is the depression module of a self-administered diagnostic instrument for common mental disorders (2001). A score of 5, 10, 15, or 20 represents mild, moderate, moderately severe, and severe depression respectively (2001). The PHQ-9 was collected at baseline and again three weeks post-
baseline. The mean of the two scores represents the individual’s level of depression. The score will be used as a continuous variable.

Medication Adherence

Medication adherence was determined using a protocol developed for the present study. Adherence data was collected using a medication pillbox connected to the participants’ telephone lines in their homes. Through this connection, the box transferred data throughout the day to an online server. The pillbox was set-up in the participant’s home two weeks after baseline and was picked up six weeks after baseline so that the monitoring period was four weeks long. There was a one-week run-in period followed by three weeks of monitoring. In order to minimize measurement reactivity, only the last three weeks of monitoring are used in calculations. Common heart failure medications were chosen to fill each of the four bins on the pillbox. The types of medications were chosen to fill the pillbox bins were beta-blockers, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, diuretics, aspirin, aldosterone antagonists, Plavix, and statins. One medication was chosen from each of the preceding classes, with preference for inclusion in ascending order (i.e., a beta blocker was chosen first, then an ACE, then ARB, then diuretic, and only then aspirin if one of the previous types was unavailable). The pillbox was not alarmed; instead, participants were instructed to take their medications from the pillbox immediately before ingesting them as per their typical medication schedule, which they provided to the researchers at the beginning of the study.
Following data collection, the first week of monitoring data (data collected during the one-week run-in) was removed to minimize measurement reactivity. A daily adherence value was calculated by dividing the number of medication taking events (a medication bin opened and closed in the pillbox) by the number of medication taking events that were supposed to occur that day across all four medications (primary outcome measure). The mean of this value across each of the four medications per day per individual represents their daily medication adherence value, and all 21 days’ values were averaged to determine the overall medication adherence rate. The Cronbach’s alpha for these values will be reported to reflect the internal consistency and to estimate the reliability of the mean adherence rates.

**Gender**

This information was acquired during the medical chart review necessary for enrollment and it was also self-reported at baseline. This variable was dummy-coded in analyses.

**SES**

SES was determined according to the protocol outlines in Roux et al (2001). Upon scheduling their study home visits, research staff recorded each participant’s zip code. Using the zip code, each neighborhood’s socioeconomic environment is summarized using information including income, education, and occupation for block groups of 1,000 people as defined by the U.S. Census (2001). The final score is z-scored.
Age

This information was acquired during the medical chart review necessary for enrollment and it was also self-reported at baseline. This variable was z-scored in moderation analyses.

Social Support

Social support was measured using The Multidimensional Scale of Perceived Social Support (Zimet, Dahlem, Zimet, & Farley, 1988). This scale has good internal reliability across a variety of populations, and its three-subscale structure (family, friends, and significant other) has been confirmed with strong factorial validity (Zimet, Powell, Farley, Werkman, & Berkoff, 1990). The scale’s 12 items are rated on a 7-point Likert scale ranging from very strongly disagree to very strongly agree (Zimet, Dahlem, Zimet, & Farley, 1988). The scale measures perceived support from family, friends, and a significant other (Zimet, Dahlem, Zimet, & Farley, 1988), and the measure is reliable (α = .88). The scale was administered at baseline and again three weeks post-baseline. In this study, the mean of the scores from both administrations is the perceived social support score, and the mean was standardized.

Marital Status

Marital status was self-reported during the baseline study visit. This variable was dummy-coded in analyses (i.e., currently married or not).
Comorbidities

Comorbidities were quantified using The Charlson Comorbidity Index (Charlson, Szatrowski, Peterson, & Gold, 1994). The Charlson combines age and comorbidities to estimate the relative risk of death (1994). Each one point increase in the age-comorbidity score approximately corresponds to one less decade of life (1994). This comorbidity index is preferable to a comorbidity count in this sample because it weights the comorbidities by effects on mortality, where conditions associated with greater reductions in lifespan are given more weight. During the baseline appointment, participants freely reported their comorbidities. Following the study visit, their Charlson score was computed and standardized.

Overall Health Status and Disease Severity

Heart failure severity was measured by NYHA Functional Classification (NYHA, 1979), which was assessed at baseline. NYHA Classification consists of four classes of heart failure severity: I (established but symptomless cardiac disease), II (mild symptoms and slight activity limitations), III (marked limitations and comfortable only at rest), and IV (severe limitations with symptoms even while at rest). Classes I and II are classified as one group, and classes III and IV are classified as a more severe group for the purposes of data analysis.

Functional Capacity

Functional capacity was measured using the Duke Activity Status Index (DASI; Hlatky et al., 1989), which was collected three weeks post-baseline. The DASI is
comprised of 12 items assessing personal care, ambulation, household tasks, sexual function, and recreational activities. Each item is weighed based on its metabolic cost. Higher scores reflect better functional capacity. DASI scores are significantly correlated with peak oxygen uptake (Hlatky et al., 1989). This variable was z-scored in moderation analyses.

**Medication Regimen Complexity**

The Medication Regimen Complexity Index (George, Phun, Bailey, Kong, & Stewart, 2004) was collected at baseline. This 65-item measure assesses the number of drugs in the regimen, dosage frequency, special instructions for medications, and type of medication (2004). These factors are weighted and summed to quantify medication regimen complexity, with higher scores indicating more complex regimens. During validation, these scores were significantly correlated the total number of medications but not factors like age or gender (2004). The final scores were standardized.

**Procedure**

All study subjects provided informed consent prior to beginning any part of the study. Participants were evaluated at four time points over the course of six weeks (baseline, time two, time three, time four). At each time point, the study procedures were completed in one visit. Participants provided medical history information through self-report measures. SES was determined by using zip codes that were provided at the time of enrollment. Participants provided the following information at baseline: depressive symptoms, gender, age, social support, marital status, comorbidities, overall health
status/disease severity, and medication regimen. Two weeks after baseline, the pillbox was installed in the participant’s home. Three weeks after baseline, depression and social support were measured again. Functional capacity was also assessed three weeks following baseline. Six weeks following baseline, at the final study home visit, the pillbox was collected marking the end of the medication adherence data collection period. Participants then completed telephone follow-up interviews, though data from those interviews were not used in the present study.

Power Analyses

Power analyses were completed using G-Power Version 3.1.6 (Faul, Erdfelder, Buchner, & Lang, 2009). It was estimated the following six moderator variables would be used in analyses in the regressions described above: gender, SES, social support, marital status, comorbidities, and complex medical regimens. In order to attain the critical F value, $F(2,139) = 4.76$, in a multiple regression with two moderators, with .01 alpha, when power is .80, and the estimated effect size is .15 (medium effect size for F-test multiple regression), a sample size of 143 is needed. This indicates that the present sample of 305 would allow adequate power to detect significant associations among the study variables.

Statistical Analysis Strategy

All statistical analyses were performed using IBM© Statistical Package for the Social Sciences (SPSS© version 20.0 statistical software (IBM Corporation). For all analyses, the criterion for statistical significance was set at $p < .01$. In addition, Cohen’s $d$
values of 0.2, 0.5, and 0.8 were considered to be the minimum thresholds for small, medium, and large effect sizes respectively (Cohen, 1992). Pearson’s \( r \) values of .10, .30, and .50 were considered to be the minimum thresholds for small, medium, and large effect sizes respectively. Finally, \( f^2 \) values of .02, .15, and .35 were considered to be minimum thresholds for small, medium, and large effect sizes respectively.

**Preliminary Analyses**

Prior to conducting analyses, descriptive analyses, such as frequencies, percentages, means and standard deviations, were used to describe the sample of participants. Next, the assumptions of regression analyses were tested. Normality was tested using histograms, a normal probability plot, residuals plots, skewness, and kurtosis. Linearity of the relationship between dependent and independent variables was tested with a bivariate scatterplot and a residual plot. If the data were not linear, it would be transformed. Homoscedasticity was tested using residuals plots as well as scatterplots of both depression and medication adherence. Multicollinearity and singularity was tested through bivariate correlations.

**Primary Analyses**

Bivariate correlations were used to assess the relationship between study variables. We expected higher depression symptoms scores would be associated with lower medication adherence rates. Each of the moderators were then added into the bivariate correlations. Moderation assumes the moderator is independent of the predictor and outcome variables. All potential moderators were still be entered into hierarchical
linear regressions. However, in the case of a moderator correlated to the independent variable (depressive symptoms) or the dependent variable (medication adherence), the results would have been interpreted as the moderator functioning as a contextual factor rather than a moderating variable.

First, depressive symptoms and medication adherence values were entered into a hierarchical linear regression. Next, hierarchical linear regression was used to examine if moderators influence the potential relationship between depression and medication adherence. Gender, SES, age, social support, marital status, Charleson Comorbidity Index score, overall health status/disease severity, functional capacity, and Medication Regimen Complexity Index score were each entered into the regression as sole moderators. In contrast to standard multiple regression where all independent variables are entered into the equation at once, hierarchical multiple regression includes independent variables that are entered in a stepwise fashion. No demographic variables were entered into the first step of the regression equation. Instead, the main effects were entered into the first step and the interaction terms were entered after. The alpha level was .05.

The first regression solely included depression predicting medication adherence. The second regression solely used gender as a moderator. The third used SES as a moderator. The fourth regression looked at age as a moderator. The next regression only included social support as a moderator. The sixth regression used marital status as a moderator. The seventh included comorbidities as a moderator. The eighth utilized overall health status/disease severity as a moderator. The ninth used functional capacity, and the tenth used medication regimen complexity as a moderator. Therefore, no
moderation included more than one moderator. In the event of significant regression results, the residuals were plotted to determine the nature of the significant interactions. Furthermore, separate regressions and follow-up tests were conducted for significant results (e.g., if gender was significant, separate interactions would be run for men and women) in order to understand the nature of the interactions if necessary.
RESULTS

Participant Screening and Recruitment

A total of 1003 patients were screened according to the study’s eligibility criteria. Among the 1003 patients who met the eligibility criteria, 628 (62.61%) refused participation. Fifty-three participants dropped out sometime during the course of data collection due to expiration, inability to contact, or severe worsening of illness. Ultimately, 174 participants were enrolled through Akron City Hospital and 201 were enrolled through University Hospitals Cleveland. Three participants were missing almost all data due to dropping out or expiring prior to completing the first visit, so they were excluded. As a result, 372 participants’ data were initially considered for inclusion in the final sample. See Table 1 for participant enrollment and attrition.

Examination of Data Distributions

The distributions of the continuous-level variables were examined for possible violations of univariate normality based on inspection of skewness and kurtosis statistics, histograms, a normal probability plot, residuals plots, bivariate scatterplots, and bivariate correlations. Missing data was excluded. Additionally, medication adherence values that likely reflected refusal to use the device rather than poor adherence (<10%) were excluded from the present analyses, leaving 305 cases included in final analyses (see Table 1). Otherwise, the data was normal, and no transformations were necessary.
Table 1. Participant Enrollment and Attrition

<table>
<thead>
<tr>
<th>Description of Participant Enrollment</th>
<th>Total</th>
<th>Summa</th>
<th>UH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>375</td>
<td>174</td>
<td>201</td>
</tr>
<tr>
<td>Approached</td>
<td>1003</td>
<td>458</td>
<td>545</td>
</tr>
<tr>
<td>Refused</td>
<td>628</td>
<td>284</td>
<td>344</td>
</tr>
<tr>
<td>Drop-outs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 1</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Visit 2</td>
<td>14</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Visit 3</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Visit 4</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Excluded</td>
<td>70</td>
<td>35</td>
<td>35</td>
</tr>
</tbody>
</table>

Note: Summa = Akron City Hospital, Summa Health System, Akron, Ohio; UH = University Hospitals Cleveland, Cleveland, OH; Participants were excluded from the present analyses for missing data, dropping out, illness/expiration, statistical outliers, and refusing to provide information.

Characteristics of Study Participants

Sociodemographics

The sociodemographic characteristics of the final sample (N = 305) are presented in Table 2. Briefly, the majority of participants were male (60.7%), Caucasian (n = 73.1%), and married (60.3%). The mean age of participants was 68.36 years (SD = 9.59). Participants completed an average of some college. The mean PHQ-9 score was 4.15 (SD = 4.46), and 29.9% of the sample reported experiencing at least mild symptoms, as defined by a PHQ-9 score of 5 or greater.
Table 2. *Sociodemographic Characteristics of the Sample (N = 305)*

<table>
<thead>
<tr>
<th></th>
<th>M (SD)</th>
<th>Range (min-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.36 (9.6)</td>
<td>50-85</td>
</tr>
<tr>
<td>MMSE†</td>
<td>27.11 (2.29)</td>
<td>19-30</td>
</tr>
<tr>
<td>PHQ-9 total score (raw) ‡</td>
<td>4.15 (4.46)</td>
<td>0-26</td>
</tr>
<tr>
<td>Medication adherence (%)</td>
<td>81.03 (20.46)</td>
<td>10-100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>n % of sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>Caucasian (non-Hispanic)</td>
</tr>
<tr>
<td>African American</td>
</tr>
<tr>
<td>Native American or Alaska Native</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Employment Status</td>
</tr>
<tr>
<td>Retired</td>
</tr>
<tr>
<td>Retired but work part-time</td>
</tr>
<tr>
<td>Retired but work full-time</td>
</tr>
<tr>
<td>Work part-time</td>
</tr>
<tr>
<td>Work full-time</td>
</tr>
<tr>
<td>Homemaker</td>
</tr>
<tr>
<td>Marital Status</td>
</tr>
<tr>
<td>Married</td>
</tr>
<tr>
<td>Divorced</td>
</tr>
<tr>
<td>Widow/Widower</td>
</tr>
<tr>
<td>Never married</td>
</tr>
<tr>
<td>Separated relationship</td>
</tr>
<tr>
<td>Highest Educational Level Achieved</td>
</tr>
<tr>
<td>8th grade or less</td>
</tr>
<tr>
<td>9-11th grade</td>
</tr>
<tr>
<td>High school</td>
</tr>
<tr>
<td>Technical or trade school</td>
</tr>
<tr>
<td>Some college</td>
</tr>
<tr>
<td>Bachelors degree</td>
</tr>
<tr>
<td>Masters degree</td>
</tr>
</tbody>
</table>

†MMSE data were not available for 2 participants.

‡PHQ-9 total score data was not available for 1 participant.
Preliminary Analyses

**Depressive Symptoms**

Depressive symptom scores ranged from 0-26, and the mean was 4.15 ($SD = 4.46$). Participants’ depressive symptoms were consistent with subclinical levels of mild depressive symptoms. Nearly one-third of the sample (29.2%) experienced at least mild depressive symptoms. Participants’ symptoms ranged from nonexistent (0.00) to severe (>20.00). The measure was internally consistent ($\alpha = .86$).

**Medication Adherence**

Medication adherence scores ranged from 10.30-100%, and the mean was 81.03 ($SD = 20.46$). The median was 89.67. The measure was internally consistent ($\alpha = .95$).

**Moderators**

The moderator variables were normal and no transformations were necessary. Although many of the moderators were related to depressive symptoms, medication adherence, and other moderators, only two were at least moderately correlated.

Increased depressive symptoms was moderately related to decreased social support $r(298) = -.33$, $p < .01$. Also, increased depressive symptoms was moderately associated with increased disease severity, $r(302) = .33$, $p < .01$. Please see Tables 3, 4, and 5 for correlations of moderators with the predictor and outcome variables.
### Table 3. Depressive Symptoms, Demographic Moderators, and Medication Adherence: Correlations and Descriptive Statistics

<table>
<thead>
<tr>
<th></th>
<th>PHQ-9</th>
<th>Med</th>
<th>Gender</th>
<th>SES</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>304</td>
<td>305</td>
<td>305</td>
<td>298</td>
<td>305</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>--</td>
<td>-17**</td>
<td>.14*</td>
<td>-.13*</td>
<td>-.14*</td>
</tr>
<tr>
<td>Med</td>
<td>--</td>
<td>-.04</td>
<td>.14*</td>
<td>.15**</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>--</td>
<td></td>
<td>-.19**</td>
<td>-.08</td>
<td></td>
</tr>
<tr>
<td>SES</td>
<td>--</td>
<td></td>
<td></td>
<td>.26**</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>4.15</td>
<td>81.03</td>
<td>0.39</td>
<td>0.08</td>
<td>68.36</td>
</tr>
<tr>
<td>SD</td>
<td>4.46</td>
<td>20.45</td>
<td>0.49</td>
<td>4.24</td>
<td>9.59</td>
</tr>
<tr>
<td>Range</td>
<td>0.00-26.00</td>
<td>10.30-100.00</td>
<td>0.00-1.00</td>
<td>-10.00-10.00</td>
<td>50-85</td>
</tr>
</tbody>
</table>

*p < .05  **p < .01

**Note:** Abbreviations: Med: medication adherence. M: mean. SD: 1 standard deviation.

### Table 4. Depressive Symptoms, Social Moderators, and Medication Adherence: Correlations and Descriptive Statistics

<table>
<thead>
<tr>
<th></th>
<th>PHQ-9</th>
<th>Med</th>
<th>Social</th>
<th>Marital</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>304</td>
<td>305</td>
<td>301</td>
<td>305</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>--</td>
<td>-17**</td>
<td>-.33**</td>
<td>-.16**</td>
</tr>
<tr>
<td>Med</td>
<td>--</td>
<td></td>
<td>.10</td>
<td>.02</td>
</tr>
<tr>
<td>Social</td>
<td>--</td>
<td></td>
<td></td>
<td>.29**</td>
</tr>
<tr>
<td>Marital</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>4.15</td>
<td>81.03</td>
<td>69.68</td>
<td>0.60</td>
</tr>
<tr>
<td>SD</td>
<td>4.46</td>
<td>20.45</td>
<td>12.74</td>
<td>0.49</td>
</tr>
<tr>
<td>Range</td>
<td>0.00-26.00</td>
<td>10.30-100.00</td>
<td>25.50-84.00</td>
<td>0.00-1.00</td>
</tr>
</tbody>
</table>

*p < .05  **p < .01

Table 5

Depressive Symptoms, Medical Moderators, and Medication Adherence: Correlations and Descriptive Statistics

<table>
<thead>
<tr>
<th>PHQ-9</th>
<th>Med</th>
<th>Comorbid</th>
<th>Severity</th>
<th>Functional</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>304</td>
<td>305</td>
<td>305</td>
<td>305</td>
<td>290</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>--</td>
<td>-.17**</td>
<td>.05</td>
<td>.33**</td>
<td>-.12*</td>
</tr>
<tr>
<td>Med</td>
<td>--</td>
<td>-.06</td>
<td>-.09</td>
<td>.12*</td>
<td>-.07</td>
</tr>
<tr>
<td>Comorbid</td>
<td>--</td>
<td>.07</td>
<td>.04</td>
<td>.18**</td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td>--</td>
<td>.00</td>
<td>.05</td>
<td>.25**</td>
<td></td>
</tr>
<tr>
<td>Functional</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regimen</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>4.15</td>
<td>81.03</td>
<td>3.29</td>
<td>0.66</td>
<td>33.92</td>
</tr>
<tr>
<td>SD</td>
<td>4.46</td>
<td>20.45</td>
<td>1.73</td>
<td>0.48</td>
<td>14.89</td>
</tr>
<tr>
<td>Range</td>
<td>0.00-10.30</td>
<td>1.00-11.00</td>
<td>0.00-1.00</td>
<td>1.75-58.20</td>
<td>4.00-26.00</td>
</tr>
</tbody>
</table>

*p < .05 **p < .01


Depressive Symptoms and Medication Adherence

The results of these regression analyses are presented in Table 6. Depressive symptoms predicted medication adherence ($\Delta R^2 = .03, F (1, 303) = 9.04, p = .003; f^2 = .03$, corresponding to a small effect size).

Table 6. Depressive Symptoms Predicting Medication Adherence

<table>
<thead>
<tr>
<th>Model</th>
<th>b</th>
<th>SE</th>
<th>$\beta$</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>80.954</td>
<td>1.159</td>
<td>69.847</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>-3.521</td>
<td>1.171</td>
<td>-1.70</td>
<td>-3.007</td>
<td>.003*</td>
</tr>
</tbody>
</table>

Note. N = 304. $\Delta R^2 = .029, F (1, 303) = 9.042, p = .003.$
**Demographic Moderators**

Gender, SES, and age were individuals entered into hierarchical linear regression models individually.

**Gender.** The results of these regression analyses are presented in Table 7. Depressive symptoms were negatively related to medication adherence ($t (300) = -2.857, p = .005; f^2 = .03$, corresponding to a small effect size). Gender was unrelated to medication adherence ($t (300) = -.409, p > .05; f^2 = .03$, corresponding to a small effect size). Gender did not moderate the relationship between depressive symptoms and medication adherence ($t (300) = 1.032, p > .05; f^2 = .00$, corresponding to less than a small effect size).

**Table 7. Gender as a Moderator of Depressive Symptoms Predicting Medication Adherence**

<table>
<thead>
<tr>
<th>Model</th>
<th>b</th>
<th>SE</th>
<th>β</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>81.335</td>
<td>1.500</td>
<td>54.208</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>-3.456</td>
<td>1.183</td>
<td>-.167</td>
<td>-2.921</td>
<td>.004*</td>
</tr>
<tr>
<td>Gender</td>
<td>-.959</td>
<td>2.395</td>
<td>-.023</td>
<td>-.400</td>
<td>.689</td>
</tr>
<tr>
<td>Intercept</td>
<td>81.177</td>
<td>1.508</td>
<td>53.831</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>-.465</td>
<td>1.598</td>
<td>-.221</td>
<td>-2.857</td>
<td>.005*</td>
</tr>
<tr>
<td>Gender</td>
<td>-.980</td>
<td>2.395</td>
<td>-.023</td>
<td>-.409</td>
<td>.683</td>
</tr>
<tr>
<td>Dep*Gender</td>
<td>2.455</td>
<td>2.378</td>
<td>.080</td>
<td>1.032</td>
<td>.303</td>
</tr>
</tbody>
</table>

*Note. N = 304. Dep*Gender = the interaction between depression and gender. ΔR² = .003, F (3, 300) = 3.415, p > .05.*
**SES.** The results of these regression analyses are presented in Table 8. Depression was negatively related to medication adherence ($t(293) = -2.694, p = .007; f^2 = .04$, corresponding to a small effect size). SES was positively related to medication adherence ($t(293) = 1.996, p = .047; f^2 = .04$, corresponding to a small effect size). However, SES did not moderate the relationship between depressive symptoms and medication adherence ($t(293) = -.806, p > .05; f^2 = .00$, corresponding to less than a small effect size).

Table 8. **SES as a Moderator of Depressive Symptoms Predicting Medication Adherence**

<table>
<thead>
<tr>
<th>Model</th>
<th>b</th>
<th>SE</th>
<th>$\beta$</th>
<th>$t$</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>80.857</td>
<td>1.175</td>
<td>68.788</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>-3.204</td>
<td>1.191</td>
<td>-.155</td>
<td>-2.691</td>
<td>.008*</td>
</tr>
<tr>
<td>SES</td>
<td>.575</td>
<td>.280</td>
<td>.118</td>
<td>2.056</td>
<td>.041*</td>
</tr>
<tr>
<td>Intercept</td>
<td>80.817</td>
<td>1.189</td>
<td>67.977</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>-3.216</td>
<td>1.193</td>
<td>-.155</td>
<td>-2.694</td>
<td>.007*</td>
</tr>
<tr>
<td>SES</td>
<td>.565</td>
<td>.283</td>
<td>.116</td>
<td>1.996</td>
<td>.047*</td>
</tr>
<tr>
<td>Dep*SES</td>
<td>-.073</td>
<td>.298</td>
<td>-.014</td>
<td>-.246</td>
<td>.806</td>
</tr>
</tbody>
</table>

*Note. N = 297. Dep*SES = the interaction between depression and SES. $\Delta R^2 = .000, F(3, 296) = 4.396, p > .05.$*

**Age.** The results of these regression analyses are presented in Table 9. Depressive symptoms were negatively related to medication adherence ($t(300) = -2.640, p = .009; f^2 = .05$, corresponding to a small effect size). Age was positively related to medication adherence ($t(300) = 2.201, p = .029; f^2 = .05$, corresponding to a small effect size). Age did not moderate the relationship between depressive symptoms and medication adherence ($t(300) = -.087, p > .05; f^2 = .00$, corresponding to less than a small effect size).
Table 9. *Age as a Moderator of Depressive Symptoms Predicting Medication Adherence*

<table>
<thead>
<tr>
<th>Model</th>
<th>b</th>
<th>SE</th>
<th>β</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>81.059</td>
<td>1.153</td>
<td></td>
<td>70.322</td>
<td>.000</td>
</tr>
<tr>
<td>Depression</td>
<td>-3.169</td>
<td>1.174</td>
<td>-.153</td>
<td>-2.699</td>
<td>.007*</td>
</tr>
<tr>
<td>Age</td>
<td>2.589</td>
<td>1.175</td>
<td>.125</td>
<td>2.203</td>
<td>.028*</td>
</tr>
<tr>
<td>Intercept</td>
<td>81.044</td>
<td>1.168</td>
<td></td>
<td>63.391</td>
<td>.000</td>
</tr>
<tr>
<td>Depression</td>
<td>-3.194</td>
<td>1.210</td>
<td>-.155</td>
<td>-2.640</td>
<td>.009*</td>
</tr>
<tr>
<td>Age</td>
<td>2.590</td>
<td>1.177</td>
<td>.125</td>
<td>2.201</td>
<td>.029*</td>
</tr>
<tr>
<td>Dep*Age</td>
<td>-.111</td>
<td>1.270</td>
<td>-.005</td>
<td>-.087</td>
<td>.931</td>
</tr>
</tbody>
</table>

*Note. N = 304. Dep*Age = the interaction between depression and age. ΔR² = .000, F (3, 303) = 4.658, p > .05.*

**Social Moderators**

Social support and marital status were entered into hierarchical linear regression models individually.

**Social support.** The results of these regression analyses are presented in Table 10. The measure was internally consistent (α = .94). Depressive symptoms were negatively related to medication adherence ($t$ (296) = -2.891, $p = .004$; $f^2 = .03$, corresponding to a small effect size). Social support was unrelated to medication adherence ($t$ (296) = 1.100, $p > .05$; $f^2 = .03$, corresponding to a small effect size). Social support did not moderate the relationship between depressive symptoms and medication adherence ($t$ (296) = -1.524, $p > .05$; $f^2 = .01$, corresponding to less than a small effect size).

**Marital status.** The results of these regression analyses are presented in Table 11. Depression was unrelated to medication adherence ($t$ (300) = -1.554, $p > .05$; $f^2 = .03$, corre
corresponding to a small effect size), as was marital status ($t(300) = -.062, p > .05; f^2 = .03$, corresponding to a small effect size). Marital status did not moderate the relationship between depressive symptoms and medication adherence ($t(300) = -.742, p > .05; f^2 = .00$, corresponding to less than a small effect size).

Table 10. Social Support as a Moderator of Depressive Symptoms Prediction Medication Adherence

<table>
<thead>
<tr>
<th>Model</th>
<th>b</th>
<th>SE</th>
<th>β</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>80.808</td>
<td>1.173</td>
<td>-152</td>
<td>68.878</td>
<td>.000</td>
</tr>
<tr>
<td>Depression</td>
<td>-3.158</td>
<td>1.255</td>
<td>-152</td>
<td>-2.516</td>
<td>.012*</td>
</tr>
<tr>
<td>SocSup</td>
<td>1.029</td>
<td>1.247</td>
<td>0.50</td>
<td>.826</td>
<td>.410*</td>
</tr>
<tr>
<td>Intercept</td>
<td>80.353</td>
<td>1.208</td>
<td>-168</td>
<td>66.511</td>
<td>.000</td>
</tr>
<tr>
<td>Depression</td>
<td>-3.853</td>
<td>1.333</td>
<td>-168</td>
<td>-2.891</td>
<td>.004*</td>
</tr>
<tr>
<td>SocSup</td>
<td>1.393</td>
<td>1.267</td>
<td>0.68</td>
<td>1.100</td>
<td>.272</td>
</tr>
<tr>
<td>Dep*SocSup</td>
<td>-1.273</td>
<td>.836</td>
<td>-0.97</td>
<td>-1.524</td>
<td>.129</td>
</tr>
</tbody>
</table>

*Note. N = 300. SocSup = social support. Dep*SocSup = the interaction between depression and social support. ΔR^2 = .008, F (3, 299) = 3.932, p > .05.

Table 11. Marital Status as a Moderator of Depressive Symptoms Predicting Medication Adherence

<table>
<thead>
<tr>
<th>Model</th>
<th>b</th>
<th>SE</th>
<th>β</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>81.046</td>
<td>1.849</td>
<td>-171</td>
<td>43.823</td>
<td>.000</td>
</tr>
<tr>
<td>Depression</td>
<td>-3.533</td>
<td>1.189</td>
<td>-171</td>
<td>-2.973</td>
<td>.003*</td>
</tr>
<tr>
<td>Marital</td>
<td>-1.54</td>
<td>2.402</td>
<td>-0.04</td>
<td>-0.64</td>
<td>.949</td>
</tr>
<tr>
<td>Intercept</td>
<td>80.899</td>
<td>1.861</td>
<td>-128</td>
<td>43.462</td>
<td>.000</td>
</tr>
<tr>
<td>Depression</td>
<td>-2.636</td>
<td>1.696</td>
<td>-128</td>
<td>-1.554</td>
<td>.121</td>
</tr>
<tr>
<td>Marital</td>
<td>-1.49</td>
<td>2.402</td>
<td>-0.04</td>
<td>-0.62</td>
<td>.951</td>
</tr>
<tr>
<td>Dep*Marital</td>
<td>-1.765</td>
<td>2.379</td>
<td>-0.61</td>
<td>-0.742</td>
<td>.459</td>
</tr>
</tbody>
</table>

*Note. N = 304. Marital = marital status. Dep*Marital = the interaction between depression and marital status. ΔR^2 = .002, F (3, 303) = 3.184, p > .05.
Medical Moderators

Comorbidities, overall health status/disease severity, functional capacity, and complex medical regimens were individuals entered into hierarchical linear regression models individually.

Comorbidities. The results of these regression analyses are presented in Table 12. Depressive symptoms were related to medication adherence \((t (300) = -2.972, p = .003; f^2 = .03, \text{corresponding to a small effect size})\). Comorbidities were not related to medication adherence, \((t (300) = -.916, p > .05; f^2 = .03, \text{corresponding to a small effect size})\). Comorbidities did not moderate the relationship between depressive symptoms and medication adherence \((t (300) = .374, p > .05; f^2 = .00, \text{corresponding to less than a small effect size})\).

Table 12. Comorbidities as a Moderator of Depressive Symptoms Predicting Medication Adherence

<table>
<thead>
<tr>
<th>Model</th>
<th>b</th>
<th>SE</th>
<th>(\beta)</th>
<th>(t)</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>80.911</td>
<td>1.160</td>
<td>69.762</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>-3.462</td>
<td>1.172</td>
<td>-0.168</td>
<td>-2.953</td>
<td>.003*</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>-1.197</td>
<td>1.200</td>
<td>-0.057</td>
<td>-0.998</td>
<td>.319</td>
</tr>
<tr>
<td>Intercept</td>
<td>80.886</td>
<td>1.163</td>
<td>69.526</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>-3.510</td>
<td>1.181</td>
<td>-0.170</td>
<td>-2.972</td>
<td>.003*</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>-1.118</td>
<td>1.220</td>
<td>-0.053</td>
<td>-0.916</td>
<td>.360</td>
</tr>
<tr>
<td>Dep*Comorbidities</td>
<td>.539</td>
<td>1.439</td>
<td>.022</td>
<td>.374</td>
<td>.709</td>
</tr>
</tbody>
</table>

Note. \(N = 304\). Dep*Comorbidities = the interaction between depression and comorbidities. \(\Delta R^2 = .000, F (3, 303) = 3.383, p > .05\).
**Overall health status/disease severity.** The results of these regression analyses are presented in Table 13. Neither depressive symptoms \( t(300) = -0.597, p > .05; f^2 = .03, \) corresponding to a small effect size) nor overall health status/disease severity \( t(300) = -0.726, p > .05; f^2 = .03, \) corresponding to a small effect size) were related to medication adherence. Overall health status/disease severity did not moderate the relationship between depressive symptoms and medication adherence \( t(300) = -0.495, p > .05; f^2 = .00, \) corresponding to less than a small effect size).

### Table 13. Overall Health Status/Disease Severity as a Moderator of Depressive Symptoms Predicting Medication Adherence

<table>
<thead>
<tr>
<th>Model</th>
<th>b</th>
<th>SE</th>
<th>( \beta )</th>
<th>( t )</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>81.919</td>
<td>2.065</td>
<td></td>
<td>39.674</td>
<td>.000</td>
</tr>
<tr>
<td>Depression</td>
<td>-3.286</td>
<td>1.244</td>
<td>-0.159</td>
<td>-2.642</td>
<td>.009*</td>
</tr>
<tr>
<td>HS</td>
<td>-1.463</td>
<td>2.588</td>
<td>-0.034</td>
<td>-0.565</td>
<td>.572</td>
</tr>
<tr>
<td>Intercept</td>
<td>82.614</td>
<td>2.498</td>
<td></td>
<td>33.070</td>
<td>.000</td>
</tr>
<tr>
<td>Depression</td>
<td>-2.102</td>
<td>3.126</td>
<td>-0.090</td>
<td>-0.597</td>
<td>.551</td>
</tr>
<tr>
<td>HS</td>
<td>-2.102</td>
<td>2.895</td>
<td>-0.049</td>
<td>-0.726</td>
<td>.468</td>
</tr>
<tr>
<td>Dep*HS</td>
<td>-2.102</td>
<td>2.895</td>
<td>-0.071</td>
<td>-0.495</td>
<td>.621</td>
</tr>
</tbody>
</table>

*Note. N = 304. HS = overall health status/disease severity. Dep*HS = the interaction between depression and overall health status/disease severity. \( \Delta R^2 = .001, F(3, 303) = 3.188, p > .05. \)*

**Functional capacity.** The results of these regression analyses are presented in Table 14. The measure was internally consistent \( (\alpha = .77). \) Depressive symptoms were negatively related to medication adherence \( t(290) = -2.620, p = .009; f^2 = .03, \) corresponding to a small effect size). However, functional capacity was unrelated to medication adherence \( t(290) = -0.119, p > .05; f^2 = .03, \) corresponding to a small effect size). Functional capacity did not moderate the relationship between depressive
symptoms and medication adherence ($t(290) = -.583, p > .05; f^2 = .00$, corresponding to less than a small effect size).

Table 14. **Functional Capacity as a Moderator of Depressive Symptoms Predicting Medication Adherence**

<table>
<thead>
<tr>
<th>Model</th>
<th>$b$</th>
<th>SE</th>
<th>$\beta$</th>
<th>$t$</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>80.863</td>
<td>1.188</td>
<td>68.065</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>-3.440</td>
<td>1.321</td>
<td>-.166</td>
<td>-2.605</td>
<td>.010*</td>
</tr>
<tr>
<td>Fxn</td>
<td>-.043</td>
<td>1.325</td>
<td>-.002</td>
<td>-.032</td>
<td>.974</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model</th>
<th>$b$</th>
<th>SE</th>
<th>$\beta$</th>
<th>$t$</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>80.544</td>
<td>1.309</td>
<td>61.512</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>-3.773</td>
<td>1.440</td>
<td>-.182</td>
<td>-2.620</td>
<td>.009*</td>
</tr>
<tr>
<td>Fxn</td>
<td>-.159</td>
<td>1.342</td>
<td>-.008</td>
<td>-.119</td>
<td>.906</td>
</tr>
<tr>
<td>Dep*Fxn</td>
<td>-.766</td>
<td>1.315</td>
<td>-.037</td>
<td>-.583</td>
<td>.561</td>
</tr>
</tbody>
</table>

*Note. N = 294. Fxn = functional capacity. Dep*Fxn = the interaction between depression and functional capacity. $\Delta R^2 = .001, F(3, 293) = 2.824, p > .05.$

**Complex medical regimens.** The results of these regression analyses are presented in Table 15. The measure was internally consistent ($\alpha = .72$). Depressive symptoms were negatively related to medication adherence ($t(285) = -2.301, p = .022; f^2 = .03$, corresponding to a small effect size), but complex medical regimens were unrelated to medication adherence ($t(285) = -.308, p > .05; f^2 = .03$, corresponding to a small effect size). Complex medical regimens moderated the relationship between depressive symptoms and medication adherence ($t(285) = -2.713, p = .01; f^2 = .03$, corresponding to a small effect size). Adding the moderator to the model accounted for 2.4% of the additional variance ($\Delta R^2 = .02, F(1,2) = 7.358, p = .007; f^2 = .03$, corresponding to a small effect size). For individuals with high levels of depressive symptoms, having a more complex medication regimen lowered medication adherence by
5.90%. Depressive symptoms had no significant impact on medication adherence in individuals with minimally complex medication regimens. To test the significance

<table>
<thead>
<tr>
<th>Model</th>
<th>b</th>
<th>SE</th>
<th>β</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>81.281</td>
<td>1.181</td>
<td>68.812</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>-3.254</td>
<td>1.194</td>
<td>-2.725</td>
<td>.007*</td>
<td></td>
</tr>
<tr>
<td>CMR</td>
<td>-0.834</td>
<td>1.161</td>
<td>-0.718</td>
<td>.473</td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>81.861</td>
<td>1.188</td>
<td>68.922</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>-2.751</td>
<td>1.195</td>
<td>-2.301</td>
<td>.022*</td>
<td></td>
</tr>
<tr>
<td>CMR</td>
<td>-0.358</td>
<td>1.162</td>
<td>-0.308</td>
<td>.758</td>
<td></td>
</tr>
<tr>
<td>Dep*CMR</td>
<td>-3.089</td>
<td>1.139</td>
<td>-2.713</td>
<td>.007*</td>
<td></td>
</tr>
</tbody>
</table>

Note. N = 289. CMR = complex medical regimens. Dep*CMR = the interaction between depression and complex medical regimens. ΔR^2 = .024, F (3, 288) = 5.506, p = .007.

of the simple slopes, a decomposition test was conducted in accordance with Jaccard, Wan, & Turrisi (1990). Results indicated that the slope for high medication adherence was significantly different from zero (slope = -6.160, t (285) = -3.799, p < .0001; see Figure 2). However, the slope for low medication adherence was not significantly different from zero (slope = -.656, t (285) = -.347, p > .05).

**The Complete Model**

The results of these regression analyses are presented in Table 16. When all the demographic (gender, SES, age), social (social support and marital status), and medical (comorbidities, overall health status/disease severity, functional capacity, and complex medical regimens) variables were entered as predictors into a single block, they collectively predicted medication adherence, (R^2 = .07, F (10, 258) = 1.929, p = .04;
Results indicated that age was positively related to medication adherence, \( t(258) = 2.123, p = .035; f^2 = .07, \) corresponding to a small effect size), after accounting for all the other effects in the model.

![Diagram showing the interaction effect of medication regimen complexity as a moderator of depressive symptoms predicting medication adherence.](image-url)

*Fig. 2* Interaction Effect of Medication Regimen Complexity as a Moderator of Depressive Symptoms Predicting Medication Adherence
Table 16. *Depressive Symptoms and all Demographic, Social, and Medical Variables Predicting Medication Adherence*

<table>
<thead>
<tr>
<th>Model</th>
<th>b</th>
<th>SE</th>
<th>β</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>83.526</td>
<td>3.339</td>
<td>25.013</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>-2.181</td>
<td>1.480</td>
<td>-1.07</td>
<td>-1.474</td>
<td>.142</td>
</tr>
<tr>
<td>Gender</td>
<td>-.631</td>
<td>2.819</td>
<td>-0.015</td>
<td>-0.224</td>
<td>.823</td>
</tr>
<tr>
<td>SES</td>
<td>.465</td>
<td>.310</td>
<td>.097</td>
<td>1.499</td>
<td>.135</td>
</tr>
<tr>
<td>Age</td>
<td>2.948</td>
<td>1.389</td>
<td>.141</td>
<td>2.123</td>
<td>.035*</td>
</tr>
<tr>
<td>SocSup</td>
<td>1.298</td>
<td>1.375</td>
<td>.064</td>
<td>.944</td>
<td>.346</td>
</tr>
<tr>
<td>Marital</td>
<td>-3.204</td>
<td>2.823</td>
<td>-0.076</td>
<td>-1.135</td>
<td>.257</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>-.281</td>
<td>1.304</td>
<td>-.062</td>
<td>-.982</td>
<td>.327</td>
</tr>
<tr>
<td>HS</td>
<td>-.258</td>
<td>2.948</td>
<td>-.006</td>
<td>-.087</td>
<td>.930</td>
</tr>
<tr>
<td>Fxn</td>
<td>.240</td>
<td>1.633</td>
<td>.011</td>
<td>.147</td>
<td>.883</td>
</tr>
<tr>
<td>CMR</td>
<td>-.391</td>
<td>1.74</td>
<td>-.020</td>
<td>-.307</td>
<td>.759</td>
</tr>
</tbody>
</table>

*Note. N = 297. SocSup = social support. Marital = marital status. HS = overall health status/disease severity. Fxn = functional capacity. CMR = complex medical regimens. \( \Delta R^2 = .070, F (10, 268) = 1.929, p = .04. \)
DISCUSSION

Summary of Major Findings

This study provided evidence that depressive symptoms predict medication adherence in a sample of adults with HF. SES and age were positively related to medication adherence. This study also provided evidence that the complexity of a medical regimen moderates the relationship between depressive symptoms predicting medication adherence. However, gender, SES, age, social support, marital status, comorbidities, overall health status/disease severity, and functional capacity did not moderate the relationship between depressive symptoms and medication adherence. In the full model, depressive symptoms, demographic (gender, SES, age), social (social support and marital status), and medical (comorbidities, overall health status/disease severity, functional capacity, and complex medical regimens) variables collectively predicted medication adherence, with age being positively related to medication adherence after accounting for all the other effects in the model.

Potential Explanations

The present study replicated previous findings that depressive symptoms are related to poorer medication adherence in CVD patients (Carney, Freedland, Eisen, Rich, & Jaffe, 1995; Rieckmann et al., 2006a; Rieckmann et al., 2006b). This study found the same findings specifically in a HF sample. There are many possible explanations for this
relationship. Fatigue, a symptom of depression, likely reduces the energy necessary to efficiently manage a HF self-management program. Depressed HF patients have numerous causes of fatigue that may reduce their self-management capabilities. Furthermore, difficulty concentrating, another symptom of depression, may lead HF patients to forget doses or make errors in their medication regimen. Although the present analyses did not include measures of cognition through formal neuropsychological testing, future analyses should examine impairment in cognitive domains such as memory and executive functioning as potential explanations for this relationship. Considering that depression impairs other areas of self-management in CVD, such as adherence to a CR program (Casey, Hughes, Waechter, Josephson, & Rosneck, 2008), these results conform to the existing literature.

Our findings of medication regimen complexity moderating the relationship between depressive symptoms and medication adherence extend the previous literature examining complex medical regimens. In a sample of individuals with chronic illness, meta-regression analyses revealed medication adherence was higher for once-daily medications than medications with multiple daily doses (Coleman et al., 2012a). In patients with CVD, 74% of CVD patients prescribed nitrates three times daily failed to comply with proper nitrate recommendations (Straka, Fish, Benson, & Suh, 1996). Additionally, other studies have found an inverse relationship between adherence and daily dosing frequency (Dunbar-Jacob, Bohachick, Mortimer, Sereika, & Foley 2003). Other studies found no relationship between number of daily doses of carvedilol and medication adherence (Udelson et al., 2009), and no previous studies investigated the
relationship of medication regimen complexity and depressive symptoms in HF patients. Here, medication regimen complexity ranged from 4.0 - 92.5 ($M = 22.28, SD = 12.11$) with higher scores indicating greater complexity. The present study is the first to illustrate a moderation of medication regimen complexity in depressive symptoms predicting medication adherence in HF patients.

Several factors may explain the unanticipated findings of a lack of moderation of gender, SES, age, social support, marital status, comorbidities, overall health status/disease severity, and functional capacity in the present study. Firstly, the present sample contained few individuals with a current major depressive episode; only one-third of the sample reported at least mild depressive symptoms. It is possible these demographic, social, and medical factors moderate the effects of depressive symptoms on medication adherence when depressive symptoms are plentiful and impairing enough to reach the threshold of a current major depressive episode, but not when only a few symptoms are present. Additionally, the present sample had higher medication adherence ($M = 81.03, SD = 20.46$) than previous estimates of 40-60% (Wu, Moser, Lennie, & Burkhart, 2008). Future analyses should examine a larger sample of exclusively low adherers with full major depressive episodes to determine the effects of these possible moderators on a sample of more clinically impaired individuals. It is possible these moderations only exist within more depressed samples.

One aspect of the study design, the exclusion criteria, may have contributed to limited observations of moderating relationships. The exclusion criteria used in the present study were selected to in hopes of including individuals whose adherence was
predominantly governed by factors related to their HF. However, numerous individuals were excluded on the basis of comorbidities that are common within HF patients. For example, individuals who were non-adherent to their sleep apnea self-management plans were excluded from the present study. However, sleep apnea is common amongst HF patients; it is estimated that approximately 49% of individuals with HF also have sleep apnea (Javaheri, 2006). These individuals that are not adherent to their sleep apnea treatments are also likely non-adherers to their medications. This may have contributed to a slight ceiling effect for medication adherence. It is possible that if these individuals had been included, the mean adherence rates would have been closer to the lower rates observed in previous studies (e.g., 40-60% in Wu, Moser, Lennie, & Burkhart, 2008).

Furthermore, in moderation analyses, it is preferable to include moderators that are not strongly correlated with the independent variable. In the present sample, increased depressive symptoms was moderately related to decreased social support $r(298) = -.33$, $p < .01$, and increased depressive symptoms was moderately associated with increased disease severity, $r(302) = .33$, $p < .01$. Although neither social support nor disease severity was strongly correlated with the independent variable, the relationship of these factors to depressive symptoms can partially reduce some of the variance in the moderation models.

These findings are novel for a number of reasons. To date, this is one of the largest examinations of depressive symptoms and objectively measured medication adherence in a HF sample. In addition, the study design (i.e., home visits) allowed for the inclusion of more clinically limited individuals, such as class IV HF patients, who are
typically excluded from studies of HF either through exclusion criteria or inability to travel to research sites due to their medical conditions. Finally, this study demonstrated that even in the case of mild levels of depressive symptoms, medication regimen complexity moderates the relationship between depressive symptoms and medication adherence.

**Limitations**

The current findings are limited in numerous ways. To begin, depressive symptoms were only measured over the course of three weeks. However, depressive symptoms likely vary greatly over the course of HF. The sampling of depressive symptoms over only three weeks impedes the ability to pinpoint how disease duration and progression influence depressive symptoms. There may be some identifiable trends in depression over time following HF diagnosis. For example, depressive symptoms may have a specific relationship with rehospitalization. Also, we are unable to determine whether depressive symptoms degrade medication adherence or vice versa. Secondly, previous incidence of depressive episodes was not assessed, and individuals with a history of depression may have higher rates of depression over time than individuals without a history of depression. Third, results of stress testing to quantify HF severity was unavailable, and HF severity may have an important relationship to depression that the NYHA class system cannot detect due to range restriction (*i.e.*, there only being four classes). Additionally, NYHA class is a predominantly subjective measure of disease severity that may be unduly influenced by poor self-management and depressive symptoms. However, many HF patients may be unable to tolerate stress testing.
Furthermore, the relationship between depressive symptoms and medication adherence may be bidirectional; this should be investigated via longitudinal studies of HF patients. Furthermore, cognition may moderate the relationship between depressive symptoms and medication adherence, so global cognition and independent cognitive domains should be investigated in future studies.

The sample itself also presents some unique limitations. The sample was comprised of predominantly older, white outpatients with class III HF and education beyond a high school diploma. Therefore, these findings may not generalize to other populations. Additionally, the exclusion criteria prohibited inclusion of individuals with sleep apnea and history of neurological problems, which also limits the generalizability of the findings to other HF samples in which comorbidities are numerous. Furthermore, individuals with comprehensive home health care were excluded, which may have limited the inclusion of individuals with more severe HF. HF patients with home health care may have more social interaction and more help with self-management, which could improve depressive symptoms and medication adherence respectively.

Furthermore, the present study did not control for current antidepressant medication use or psychotherapeutic treatment targeting depression. Either of these treatments would likely lower overall PHQ-9 scores. However, participants were not surveyed about whether or not they were currently engaged in depression treatment. Moreover, the present study used a measure (the PHQ-9) that only assessed for current depressive symptomatology. The PHQ-9 does not measure past diagnoses of depression (in remission) or dysthymia. However, a history of depressive symptoms may also
negatively impact self-management. Additionally, depression is partially characterized by multiple somatic symptoms. A clinical interview, rather than a paper-and-pencil measure, is preferable for disentangling somatic symptoms attributed to medical conditions, like HF, or depression. Differences in endorsements of somatic symptoms as compared to cognitive or affective symptoms were not examined in the present study. Future studies should determine if participants are currently received pharmaceutical or psychotherapeutic depression treatment, control for treatment status in statistical analyses, and consider treatment status in the interpretation of their results. They should also consider including a clinical interview to determine the cause of somatic symptoms, which ultimately would improve the accuracy of the attribution to depression or medical conditions.

The recruitment sites and current depressive symptoms may have influenced the types of participants recruited for the study. Participants were recruited from well-run cardiology practices; individuals who receive inferior HF care may have higher levels of depressive symptoms. Recruiting from these two specific cardiology practices may have limited the number of possible participants with worse depressive symptoms. Furthermore, depressed individuals may have refused to enroll in the study due to their own fatigue or disinterest, which would also limit the sample to minimally depressed participants.

**Research and Clinical Implications**

Despite these limitations, these findings contain several important research and clinical implications. First of all, additional prospective studies are needed to determine
the effects of depressive symptoms on adherence over time. Both depressive symptoms and adherence may vary throughout the disease course; ideally, future prospective studies will examine CVD patients before they develop HF to determine how depression and adherence vary over time. This is particularly important considering recent findings have demonstrated that depressive interventions, including psychotherapy and psychotropic medication, may be cardioprotective if they are implemented prior to the onset of CVD (Stewart, Perkins, & Callahan, 2012).

It is possible that lifetime incidence of depression prior to onset of CVD may influence self-management differently than depression that only occurs after a diagnosis of CVD. However, comparisons of the time of onset of depression and its relationship to self-management across the progression of CVD have yet to be investigated. Future studies should examine first incidence of depression as a predictor of adherence behavior; for individuals with a longstanding history of depressive symptoms prior to onset of CVD and specifically HF, self-management may be more difficult due to low self-efficacy, hopelessness, decreased ability to concentrate, and fatigue.

Researchers should also examine the interaction of depressive symptoms and complex medical regimens on medication adherence. For depressed patients, complex medical regimens may exceed the capabilities of the patient’s self-management plan. For all HF patients, simplified but effective medical regimens are best, and this appears to be especially true for HF patients with symptoms of depression. Future research may also consider whether anxious patients would also benefit from simplified medication regimens. Other research should also examine the influence of complex regimens on the
entire HF self-management plan. HF patients, especially those with depressive symptoms, may achieve the best adherence under conditions where their medications, medical appointments, dietary restrictions, fluid restrictions, daily weighing, and management of other chronic conditions when their providers’ expectations for self-management are streamlined into efficient plans. With the increase in electronic medical records and team-based care, ideally it will be easier for providers to work together to determine unified self-management regimens that are as simple as possible. These efforts would collectively decrease patient burden, caregiver burden, rehospitalization, and mortality, as well as increase patient and caregiver quality of life, patient self-management self-efficacy, and cost-efficiency of medical care.

Additional research should investigate methods for improving medication adherence and HF self-management. The present study demonstrated that complex medical regimens moderated the relationship between depressive symptoms, and previous studies have also observed complex medical regimens negatively influencing objectively measured medication adherence. Riegel and colleagues found that taking two or more medication doses per day predicted steep declines in objectively measured medication adherence in a sample of HF patients (2012). Healthcare providers should make every attempt possible to reduce the complexity of the medication regimen (e.g., switching powders to pills, minimizing the number of daily doses, simplifying medication dosing instructions when possible). Furthermore, previous work demonstrated that HF patients with comorbidities, such as asthma or renal disease, and individuals with more severe HF (class III), are particularly susceptible to lower adherence according to
objectively measured medication adherence (Calvin et al., 2012). Individuals with complex comorbidities and increased disease severity may require special attention from healthcare providers and caregivers to achieve necessary rates of medication adherence. Furthermore, providers should make an effort to simplify instructions, educate patients about the reason a medication is prescribed and how it helps the patient, address fears regarding side effects, ask patients what would help them be more adherent, explain how to handle missed or late doses, ask about adherence during every visit, and reward adherence (American College of Preventative Medicine, 2011).

Ideally, efforts to improve HF self-management should extend beyond medication adherence. The average HF self-management plan includes medication adherence, dietary sodium restriction, symptom monitoring, increase or maintenance of physical activity levels, and fluid restrictions for some patients (Luttik, Jaarsma, Moser, Sanderman, & van Veldhuisen, 2005). Furthermore, HF patients must also self-manage their other comorbidities, such as diabetes or renal disease. Previous research indicates the majority of older adults with HF use the Internet (78.2%) and e-mail (71.4%), though only 45% of the sample used the Internet to obtain information on HF (Schprechman et al., 2013). HF patients could benefit from an online portal where multiple providers can coordinate care, post instructions for self-management, inform other providers of changes to the self-management plan, and communicate as a team-based system of care. Furthermore, HF patients may incorporate currently available commercial technology, such as apps and smartphones, into their plans to improve medication and dietary behaviors. Ultimately, insurance companies or physicians should provide online patient portals that include:
health behavior tracking systems that alert the provider when a patient is not adhering to their self-management plan complete with a scale, pillbox, and blood-glucose monitor; provider-patient communication systems; educational modules to teach the patient new skills relevant to their self-management needs; and screening tools that assess for psychological and emotional difficulties, provide referrals, and alert providers to symptoms that may require further evaluation and intervention.

Finally, future studies should examine depressive symptoms and medication adherence in relation to rehospitalization. Rehospitalization is very common in HF, and poor rehospitalization is frequently a result of poor self-management (AHA, 2013). Future studies should examine how depressive symptoms and medication adherence vary before and after rehospitalization. Major depression is independently related to both rehospitalization and mortality in CHF (Jiang et al., 2001). If healthcare providers can detect increases in depressive symptoms or drops in medication adherence before they result in rehospitalization, providers can also hopefully intervene before HF patients’ health declines to the point of expiration.

Conclusions

In summary, the present study sought to examine the influence of depressive symptoms on medication adherence in a sample of patients with HF, and the potential demographic, social, and medical moderators of that relationship. The present study extended previous findings by transcending theoretical assertions and testing the influence of various social, demographic, and medical factors on medication adherence in a large sample of adults with HF. At least 29.2% of the present sample demonstrated at
least mild depressive symptoms as indicated by PHQ-9 scores, with symptoms ranging from nonexistent to severe. Medication adherence scores also ranged greatly (10.30-100%), with average scores ($M = 81.03$, $SD = 20.46$) being higher than previous estimates of 40-60% (Wu, Moser, Lennie, & Burkhart, 2008). The results showed that SES and age were both positively related to medication adherence, and the complexity of the participant’s medication regimen moderated the relationship between depressive symptoms and medication adherence. Furthermore, depressive symptoms, demographic (gender, SES, age), social (social support and marital status), and medical (comorbidities, overall health status/disease severity, functional capacity, and complex medical regimens) variables jointly predicted medication adherence; age was positively related to medication adherence after accounting for all the other effects in the model. These results suggest that complicated medical regimens reduce rates of medication adherence in HF patients within the context of depressive symptoms. Consequently, healthcare providers should aim to simplify self-management guidelines including medication schedules as much as possible and particularly for depressed HF patients. Simplified medication regimens as a part of a larger streamlined self-management plan could ultimately improve quality of life and longevity among HF patients with or without depressive symptoms.
APPENDIX A

IRB CONSENT FORM
INFORMED CONSENT

SUMMA
Health System

KENT STATE
UNIVERSITY

Project Title: Self-management and Cardiac Disease
Principal Investigator: Joel W. Hughes, PhD

Introduction

You are being asked to participate in a research study because you have been diagnosed with heart failure. The purpose of the study is to identify the relationships among cognitive function, self-management, and health services use. Before you can decide whether or not to volunteer for this study, you must be informed of the purpose of the research study, how this study may help you, any risks to you, and what is expected of you. This process is called "informed consent."

You do not have to participate in this study. You may stop your participation in this study at any time without affecting your current or future care at Summa Health System or with its doctors.

If you decide to participate in this study you will be told about any new information learned during the course of the study that might cause you to change your mind about staying in the study.

Why is this study being done?

This study is being done so that we can look at factors which may be associated with how someone with heart failure manages their illness. These factors are things like how you think and what you remember (cognitive function).

We are also interested in how self-management (a patient's ability to manage their care) relates to how they use health services. Patients with heart failure are an important group of people to study because of the high risk of complications and high medical costs associated with heart failure. Information gained from this project will be used to identify patients who have trouble thinking and remembering and to create ways to help patients manage their care.

How many people will take part in this study?

There will be approximately 400 people who participate in this study.

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Who can be in this study?

We will offer participation in this study to people who are 50-85 years of age, who have been diagnosed with heart failure, and who have a telephone at their home.

What is involved in this study?

There will be 4 study visits which will take place at the hospital or in your home over about two months.

Study Visit 1
Study visit 1 will take place during a hospital stay or on the same day as your doctor appointment. During this visit you will complete questionnaires and complete cognitive testing which includes answering questions and performing simple procedures. You will also complete a 2-minute “step test” in which the number of steps you can take in 2-minutes is counted. Altogether, this will take about 60 minutes.

Study Visit 2
Within the 2 weeks after study visit 1, a research assistant will come to your home and will train you on how to use an electronic pill box and weight scale. The research assistant will deliver these devices to your home. The electronic pill box and the weight scale are connected by your telephone line to a computer used by the research team. There will be no extra phone charges. The research assistant will also provide you with a 24-hour urine collection container and will repeat the cognitive testing. This will take 90 minutes.

Study Visit 3
Seven days after study visit 2, the research assistant will return to your home and will collect the 24-hour urine sample, and will provide you with another 24-hour urine collection container. They will perform a pill count to check the accuracy of the electronic pill box, and answer any questions you have since study visit 2. This will take 60 minutes.

Study Visit 4
The research assistant will return to your home 21 days after study visit 3. During Rev 07-23-09

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this visit the research assistant will collect the electronic pill box and weight scale and the 24-hour urine collection. During this visit you will also repeat the cognitive testing. This will take 30 minutes.

Additional Study Procedures
In addition to the study visits, we will be collecting your personal data every month for 12 months. This will consist of making telephone calls to you to collect information, and having you complete a health service use calendar. You will be sent a new health service use log and contacted by telephone every 3 months (for 12 months) to obtain data regarding phone calls to health providers, scheduled and unscheduled medical visits, and re-hospitalizations.

We may like to contact you after the completion of this study for future research studies of health service use and cognitive function. Participation of these future study opportunities is strictly voluntary, and you may refuse to be contacted for further research. Please indicate your interest in being contacted for future studies:

___ Yes, I agree to be contacted for possible future research studies
___ No, I do not want to be contacted for possible future research studies

Assessment of Cognitive Functioning
We will collect information on how you think (cognitive status) at study visits 1, 2, and 4 by asking you to take some short tests. These tests will look at your general thinking ability, memory, ability to pay attention, and ability to quickly make decisions. These tests involve working puzzles, answering questions, learning words, and other simple tasks that are designed to challenge your thinking and memory.

Questionnaires
You will be asked to complete questionnaires that ask about things like your health behaviors, diet, social support and your relationships, depression, anxiety, sleep quality, sleepiness, symptom severity, and knowledge of heart failure self-care. We will also ask about demographic information such as marital status, number of children, lifestyle habits such

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as cigarette smoking and alcohol use, living arrangements, education level, and health literacy.

Some of the questionnaires are completed as an interview, and some are for you to fill out.

Urine Collection
You will be asked to collect urine over the course of 24 hours prior to study visits 3 and 4. You will be asked to store your urine in your refrigerator at home or in a portable cooler which we will provide to you. Urine must be kept cold throughout the 24-hour period. The research assistant will collect the stored urine at the study visit. This urine will be used to provide an estimate of how much salt you eat.

Pill Box
You will be asked to store your medications in an electronic pill box which we will provide to you for your use for 4 weeks (from study visit 2 to study visit 4). You will use the pill box to dispense your medications. We will ask you to complete a pill log to track any changes to how you use the pill box. In addition to tracking your pill use with the electronic pill box, you will also be asked to record any changes to your medications, like skipping doses on purpose.

Daily Weight
We will ask you to monitor your weight daily on a scale which we provide to you.
- We will collect the electronic pill boxes and weight scale from you at the end of Study Visit 4.

Medical Records
We will also be accessing your medical records for heart failure history, etiology (i.e., what may be causing your medical condition), and hospitalization.

Will any of the samples (urine) taken from me be used for other research studies?

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The urine sample we take from you will not be used for any other purposes except those described in this consent form.

**What happens if I discontinue or withdraw from the study?**

You are participating in this study of your own free will and we realize that you can change your mind. You may stop your participation in this study at any time without changing your current or future care at Summa Health System or with its doctors.

**What are the risks of this study?**

Your participation in the study may include the following risks. The questionnaires may make you feel uncomfortable. There is a small risk of falling during or after the 2 minute step test. There may also be a possibility of your personal health information being lost or misplaced. We will also keep any study data we collect from you in a locked cabinet or computer file. Only authorized research personnel will have access to your data.

If we find that you are having changes in feelings of depression or thinking and memory problems we will help you and notify your health care provider.

**Possible benefits:**

There is no direct benefit from participation in this research study. The information that you contribute may benefit other patients with heart failure in the future.

**Options:**

Because of the nature of this research, the only alternative is to not participate in this study.

**Confidentiality:**

Your name will not be used in any written or oral report of the study. A number will be used on all information supplied by you. This information will be known Rev 07-23-09
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only to the study staff.

Costs:

There is no cost to you or your insurance for participation in this study. Any equipment needed will be provided to you free of charge and you will have no financial liability for it.

Compensation:

You will be compensated with a monetary payment of $300 if you complete all the parts of the study. The breakdown of payments is as follows: $50 after visits 1, 2, 3, and 4. $25 for each follow-up telephone call. There are 4 follow-up calls. All together this adds up to $300.

Contact information

________________________ has described to you what is going to be done, the risks, hazards, and benefits involved. The Principal Investigator, Joel Hughes, can also be contacted at 330-672-7721 during the day. If you have a medical emergency please call 911. You may ask any questions you have now. If you have any questions, concerns or complaints about the study in the future, you may also contact them later.

If you have questions about your rights as a research subject, please call the Institutional Review Board (IRB) at Summa Health Systems (330-375-4045). This is a group of people who work to protect research subjects' rights. If you have questions about Kent State University's rules for research, please call the dean of the Division of Research and Graduate Studies at Kent State University (330-672-0700).

Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation.

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in the study. By signing this consent form, you do not waive any legal rights, and
the investigator(s) or sponsor(s) are not relieved of any liability they may have. A
copy of this consent form will be provided to you.

__________________________ Date__________________________

Signature of Participant Printed Name of
Participant

__________________________ Date__________________________

Signature of Person Obtaining Consent Printed Name of Person
Obtaining Consent

(Must be study investigator or individual who has been designated in the
Checklist to obtain consent.)

__________________________ Date__________________________

Signature of Principal Investigator Printed Name of Principal Investigator
(Affirming subject eligibility for the Study and that informed consent has been
obtained.)

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APPENDIX B

HIPAA CONSENT FORM
INFORMED CONSENT

HIPAA Authorization Agreement – Authorization to Use and Disclose
(Release) Health Information for a Research Study
Self-management and Cardiac Disease

State and Federal laws, including the Health Insurance Portability and
Accountability Act (HIPAA), require researchers to protect your health
information. This form describes how researchers, with your authorization
(permission), may use and release (disclose or share) your protected health
information for this research study. Please read this form carefully.

You have been asked to take part in a research study. The study is described to
you in a separate consent form. By signing this HIPAA Authorization Agreement
you are permitting Joel Hughes and his research team to create, get, use, store,
and share protected health information that identifies you for the purposes of this
research. Protected health information may include results of tests, procedures
or surveys that are part of the research, as well as information that can identify
you, such as your name, date of birth and medical record number.

You have the right to see and copy your protected health information related to
the study for as long as the study doctor holds this information. However, to
make sure the scientific findings of this study are accurate, you may not be able
to review some of your records related to this study until after the study is
completed.

Research use of your protected health information

If you sign this form, the researchers may use or share your health information
during the conduct of the research with:
• Each other and with other researchers involved in the study
• Law enforcement or other agencies, when required by law
• Summa Health System's Institutional Review Board (a group of people
  who protect the rights of research subjects)
• The sponsor (funding organization) of this research
• Representatives of government agencies (i.e. Food and Drug
  Administration and the Office of Human Research Protection)
• Authorized representatives from internal hospital operations (i.e. quality
  assurance)

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Description of protected health information that may be used and released (disclosed or shared)

Health information includes all information created and/or collected during the research as described in the research study consent form entitled Self-management and Cardiac Disease. Health information in your medical record may be used and released if it is needed for the research; for example, past medical conditions or medications or information related to illness or hospitalizations that occur during your participation in the research.

Specifically, we will be accessing your medical records for heart failure history, what may be causing your medical condition, and hospitalization.

Protection of your health information

The researchers agree to protect your health information and will only share this information as described in this Authorization and the research consent form.

Summa Health System will make every effort to keep your research records private, but confidentiality cannot be assured with complete confidence. For example, Summa Health System has no control over the use of this information once it is released.

The information about you that is collected in this study will be shared with the study sponsor and may be combined with information gathered from public sources or other research studies. This information may be used by the sponsor for purposes unrelated to this research and could potentially be used to identify you.

Expiration of Authorization

This Authorization does not have an expiration date but can be canceled sooner if you decide to withdraw your permission.

Withdrawal or removal from the study

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You may change your mind and cancel this Authorization at any time. To cancel this Authorization, you must write to:

Joel W. Hughes, Ph.D.
Department of Psychology
P.O. Box 5190
Kent, OH 44242

If you cancel this Authorization, you may no longer be allowed to take part in the research study. Even if you cancel this Authorization, the researchers may still use and disclose health information they have already obtained to maintain the integrity and reliability of the research, and to report any adverse (bad) effects that may have happened to you.

Contact information for questions about my rights under HIPAA

If you have questions or concerns regarding your privacy rights under HIPAA, you should contact the Privacy Officer at 330-375-6665.

Right to refuse to sign this Authorization

You do not have to sign this Authorization. However, because your health information is required for research participation, if you decide not to sign this Authorization form, it will only mean you cannot take part in this research. Not signing this form will not affect your non-research related treatment, payment or enrollment in any health plans, or your eligibility for other medical benefits.

Signature of subject

I have read (or someone has read to me) the above information. I have been given an opportunity to ask questions, and my questions have been answered to my satisfaction. I authorize the use and disclosure of my protected health information for this research. I will be given a signed copy of this Authorization form.

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Printed Name of Subject

Signature of Subject  Date

Signature of Person Obtaining Authorization Agreement  Date

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