2012

Health Literacy, Cognitive Impairment, and Medication Adherence in Veterans with Heart Failure

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Hahn School of Nursing and Health Science

DOCTOR OF PHILOSOPHY IN NURSING

HEALTH LITERACY, COGNITIVE IMPAIRMENT, AND MEDICATION ADHERENCE IN VETERANS WITH HEART FAILURE

By

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A dissertation presented to the

FACULTY OF THE HAHN SCHOOL OF NURSING AND HEALTH SCIENCE

UNIVERSITY OF SAN DIEGO

In partial fulfillment of the

requirements for the degree

DOCTOR OF PHILOSOPHY IN NURSING

November 2012

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ABSTRACT

Health Literacy, Cognitive Impairment, and Medication Adherence in Veterans with Heart Failure

Background: Heart failure (HF) affects 5.8 million people in the United States, costly in terms of patient mortality and morbidity as well as healthcare dollars. One important manifestation of poor HF outcomes is the excessive admission-readmission cycle. Non-adherence to medication is responsible for the majority of HF readmissions. Identification and intervention for key factors contributing to poor medication adherence is critical to improving outcomes. Two such factors prevalent in persons with HF are cognitive impairment (CI) and poor health literacy (HL). There is a paucity of tested interventions designed to improve medication adherence by addressing underlying CI or HL. A recent study tested a pictorial medication sheet to improve medication adherence in veterans with HF and CI, however no information on HL was collected. This new study examines what mediating effects HL may have played in the adherence scores of subjects in the completed study.

Study Aims:

Aim 1. Describe the level of HL in the study population.

Aim 2. Determine the strength and direction of the relationships between reading HL and numeracy HL and selected clinical and demographic variables in the study population.

Aim 3. Determine the direct and indirect effects that reading HL and numeracy HL and other key variables (including the intervention) have upon medication adherence in

cognitively impaired veteran outpatients with HF based on prior data from an interventional study testing a pictorial medication sheet to improve medication adherence.

Study Design

A retrospective, correlational, cross-sectional design was employed to analyze HL scores from medical records with data from the completed study using conventional statistics and structural equation modeling.

Results: 27 subjects with a mean age of 65.3 years (SD 8.2, range 45-80) had evaluable data. HL was less than adequate in 19% of the sample. HL scores were strongly correlated with cognition. HL did not significantly affect relationships between study covariates (cognition scores, depression, number of medications) and medication adherence.

Conclusions and Significance: HL scores were associated with cognitive function scores. More research is needed to evaluate the prevalence and effect of poor HL in veterans with HF upon adherence.

DEDICATION

I dedicate this dissertation to the hundreds of veterans that have granted me the privilege of sharing their struggles with heart failure and their stories about life over the past fifteen years. They have become my teachers--each one of them a true American hero--surely we have walked together on sacred ground.

"And the King will answer and say to them, "Assuredly, I say unto to you, inasmuch as you did for one of the least of these My brethren, you did also unto Me."

--Matthew 25:40

ACKNOWLEDGEMENTS

Research is a collaborative effort, and over the years I have benefitted from the advice and practical help of too many wonderful people to mention here. However, the TARGET study in particular would not have been possible without the steadfast daily support, excellent technical skills, and dedication of my research associate, Christopher J. Firek. The beautifully rendered medication images and the accurate counting of thousands of medications are all the work of his hands. Chris, I look forward to reading your own dissertation in the future!

Being a doctoral student at the University of San Diego Hahn School of Nursing and Health Science has been a privilege from the very first day. Before even considering this adventure, I had the pleasure of meeting Dr. Ann Mayo, who was to become my mentor and dissertation chairperson. Dr. Mayo, it was your example and your words that encouraged me to achieve this goal, how can I ever adequately express my thanks? To my other committee members, Dr. Jane Georges and Dr. Mary Jo Clark: thank you for sharing hours of your time, kind words of advice, expertise, and most of all your own amazing work.

Finally, to my beloved husband, Ken, and our children Kendralyn, Katie, and Brian, who all unfailingly believed in me. This became especially important on those days I did not believe in myself. Thank you for this priceless gift!

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Chapter 1: Introduction

Heart failure (HF) is a complex, chronic medical condition that affects 5.8 million people in the United States, contributing significantly to increased morbidity, mortality, healthcare expenditures, and decreased quality of life (Lindenfeld et al., 2010; Lloyd-Jones et al., 2010). This negative impact of HF is projected to escalate as the American population ages, and is of particular importance to the Veterans' Health Care System (VA), the largest integrated healthcare system in the United States (Heidenreich, 2011; Population Resource Center, 2011). Large clinical trials have demonstrated the success of pharmacologic regimens and lifestyle strategies in improving patient outcomes and have resulted in the development of consensus guidelines (Lindenfeld et al., 2010). However, HF patients tend to be older with multiple comorbidities and may find it difficult to follow these often-complex regimens, thereby losing the benefits of evidence-based care (Heidenreich, 2004; Murray et al., 2007). One particularly important manifestation of poor HF outcomes is the excessive admission-readmission cycle; in the VA system 20% of HF patients are readmitted within 30 days (Heidenreich, 2011). Medication non-adherence is common in persons with HF, and has been shown to be responsible for the majority of readmissions for HF in the United States (Albert, 2008; Esposito, Bagchi, Verdier, Bencio, & Kim, 2009; Ho, Bryson, & Rumsfeld, 2009; Munger, Van Tassell, & LaFleur, 2007; Murray, et al., 2009). Thus identification of, and intervention for, key factors contributing to poor medication adherence has become a primary goal for clinicians and healthcare policymakers.

Medication Adherence

Adherence is a complex issue and depends on multiple patient and healthcare-related factors. The World Health Organization's Multidimensional Adherence Model classifies predictors of poor adherence into five broad domains: socio-economic status, type of healthcare system, prescribed therapy, condition being treated, and individual patient-related factors (Sabate, 2003). However, this model explained less than 20% of poor medication adherence in HF patients, emphasizing the need to identify other contributors to non-adherence in this population (van der Wal & Jaarsma, 2008; Wu, Moser, Chung, & Lennie, 2008). One frequently overlooked factor that may influence all of these domains is the presence of cognitive impairment (CI). Indeed, a recent study in veterans with HF demonstrated a high prevalence (58%, n=251) of clinically unrecognized CI that was significantly associated with poorer medication adherence (Hawkins et al., 2012).

Another factor associated with adherence is poor health literacy (HL). In America, low health literacy is a highly prevalent and clinically under-recognized problem that directly impacts patient's self care skills (Morrow et al., 2006). Poor HL predicts poor medication adherence, but little is known about the prevalence of poor HL in veterans with HF, or the effect of HL on medication adherence in cognitively impaired outpatients with HF (Evangelista et al., 2010; Moser & Watkins, 2008).

Interventions to Improve Adherence

There is a general lack of awareness on the part of providers in regards to the prevalence of CI and poor HL in their patients, and the contribution of these factors to

poor medication adherence (Cameron et al., 2010). Interventions that rely on traditional models of patient education to improve adherence are thus likely to fail in this at-risk population, and there is a paucity of tested interventions that improve outcomes by improving medication adherence (Wu, Corley, Lennie, & Moser, 2012). Novel interventions targeted at key factors contributing to non-adherence are urgently needed.

To address this gap, a pilot study (TARGET) was designed utilizing two interventions addressing CI as the underlying cause of medication non-adherence. The TARGET study enrolled subjects with known CI from an outpatient veteran HF clinic and tested the effectiveness of an intervention to improve medication adherence (Hawkins, Firek & Silvet, 2012). The intervention, a pictorial medication sheet, was designed to address memory problems from underlying cognitive impairment. The primary outcome, medication adherence, was measured from sequential direct 30-day pill counts, using subjects as their own controls. A major limitation in the TARGET study is that no information on HL was collected. HL may actually mediate the relationship between key independent variables (including the intervention) and medication adherence in this study.

Purpose of Study

The purpose of this dissertation research study was to estimate the causal relationships between HL (included in existing outpatient medical records), the intervention, other key variables, and medication adherence in a sample of cognitively impaired outpatient veterans with HF who participated in an interventional pilot study

testing a pictorial medication sheet and alarmed pill box to improve medication adherence.

Using previously-collected data from the TARGET pilot study and the existing outpatient medical records of the TARGET participants, a retrospective, correlational, cross-sectional study design using secondary data was used to answer the study research question: What are the direct and indirect effects that HL and other key variables (including the intervention) had upon medication adherence in cognitively impaired veterans with HF?

Research Aims

The specific aims of the study were to:

Aim 1. Describe the level of HL in the study population.

Aim 2. Determine the strength and direction of the relationships between reading HL and numeracy HL and selected clinical and demographic variables in the study population.

Aim 3. Determine the direct and indirect effects that reading HL and numeracy HL and other key variables (including the intervention) had upon medication adherence in cognitively impaired veteran outpatients with HF based on prior data from an interventional study testing a pictorial medication sheet and alarmed pillbox to improve medication adherence.

Summary

Heart failure is an epidemic facing the American healthcare system, and is projected to grow as the population ages (Heidenreich, 2011; Population Resource

Center, 2011). One manifestation of poor outcomes in HF is the excessive admission-readmission cycle. This is particularly important to the VA healthcare system wherein 20% of veterans with HF are readmitted within 30 days (Heidenreich, 2011). Non-adherence to medication has been shown to be both prevalent in persons with HF, and responsible for the majority of hospital readmissions (Albert, 2008; Esposito, Bagchi, Verdier, Bencio, & Kim, 2009; Ho, Bryson, & Rumsfeld, 2009; Munger, Van Tassell, & LaFleur, 2007; Murray, et al., 2009). Two key factors in poor medication adherence include poor HL and CI (Hawkins, 2012; Morrow, 2006). A recent pilot study was designed to target CI as an underlying cause of medication non-adherence; a major limitation was that no information on HL was collected as part of that study. HL may actually have mediated the relationship between key independent variables (including the intervention) and the outcome measure of medication adherence. This study sought to answer the research question: what are the direct and indirect effects that reading HL and numeracy HL and other key variables (including the intervention) had upon medication adherence in cognitively impaired veteran outpatients with HF based on prior data from an interventional study testing a pictorial medication sheet and alarmed pillbox to improve medication adherence?

Chapter 2: Review of the Literature

This chapter includes a survey of the relevant current literature to provide a context for the study. The research will be situated within an existing theoretical framework, and a brief concept analysis will be included to clarify the main construct of "adherence". The relationships between the study and previous work conducted on the topic will be evaluated, and the current gap in the knowledge that this study sought to answer will be described.

Conceptual Model

The use of a theoretical model helps describe complex systems, and ensures appropriate variables are studied when designing research and clinical interventions. Riegel and Dickson (2008) propose a conceptual model of HF self-care. This model described HF self-care in five stages: stage one: self-care maintenance (symptom monitoring and treatment adherence) and stages two through five: self-care management (recognition of, response to, and evaluation of symptoms). Each stage involves a series of naturalistic, or "real world", decisions made by the patient. Adherence is viewed as only one part of the multifaceted self-care process (Riegel et al., 2009). The authors consider a separate construct, self-care confidence, as moderating and/or mediating all five stages in the model (Riegel & Dickson, 2008).

The HF self-care model was selected to serve as the theoretical framework for this dissertation research as it reflects the complex and iterative nature of daily decisions made by persons living with HF regarding their treatment plan. The presence of CI and/or

poor HL may exert an influence on decision-making at any of the five stages in the model, as well as on the construct of self-care confidence. For the purpose of this study the influence of CI and/or poor HL will be addressed as primarily affecting stage one: treatment adherence, specifically, medication adherence.

Figure 1. Conceptual Model

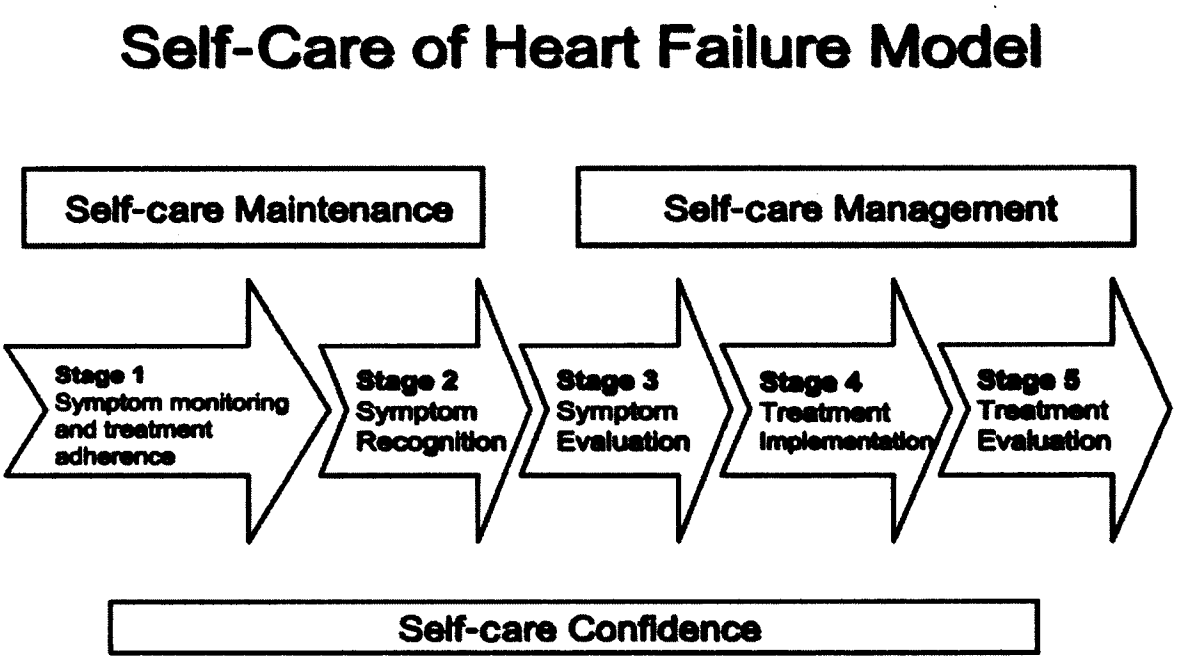

Figure 1. HF self-care in five stages: stage one: self-care maintenance (symptom monitoring and treatment adherence) and stages two through five: self-care management (recognition of, response to, and evaluation of symptoms). Each stage involves a series of naturalistic decisions made by the patient. Adherence is viewed as only one part of the multifaceted self-care process. The construct of self-care confidence moderates and/or mediates the self-care process. From "A Situation-specific Theory of Heart Failure Self-care," by B. Riegel and V. V. Dickson, 2008, *Journal of Cardiovascular Nursing, 23,* p. 192. Copyright 2008 by Lippincott, Williams & Wilkins. Reprinted with permission.

Adherence

Adherence is frequently used to replace an older term, "compliance", when describing the relative success of a patient in following a plan of care. Adherence

suggests a more active, independent role on the part of the patient; compliance is thought to reflect a more paternalistic attitude towards a passive patient (Aronson, 2007; Gould & Mitty, 2010). Closely related to adherence and compliance is a newer term: "concordance". Concordance reflects the ideal partnership between an empowered patient and enlightened provider jointly formulating a plan of care (Carpenter, 2005; Edwards, Davies, & Edwards, 2009). Each of these three terms, when examined closely, gives inference as to why the patient may not successfully follow the plan of care:

1. Non-compliant: patient choosing to not 'obey' the given plan.
2. Non-adherent: something interferes with the ability to adhere, although the intent may be there.
3. Discordant: the patient and the provider did not arrive a mutually agreeable plan.

There is much discussion in the literature regarding the usage of these closely related terms and they are often used interchangeably in journal articles and in clinical practice (Carpenter, 2005). However, adherence is the most frequently used term, and was term chosen by the World Health Organization (Sabate, 2003) and the U.S. National Institute of Health (Adherence Research Network, 2010). In addition, this dissertation research will examine how underlying CI and/or poor HL influence the person's ability to adhere, which most closely matches inference number two, above. Therefore, the term "adherence" will be used in this research proposal.

Importance of medication adherence in HF outcomes

The American healthcare system is facing unprecedented challenges in the demand for and the delivery of care. A key driving force behind many of these changes

is the rapidly aging population; by 2030, there will be about 72.1 million persons over 65 years old, more than twice the number in 2000 (US Department of Health and Human Services, 2012). This shift in demographics brings along an attendant rise in the multiple and progressive chronic diseases often seen in the elderly (Population Resource Center, 2011).

HF serves as an archetypical disease to illustrate these transformational changes in American healthcare. HF has been termed an epidemic due to the increasing numbers of cases, the intensity of care they require, and the direct and indirect costs incurred (Heidenreich, 2011; Lloyd-Jones et al., 2010). Admissions for HF in a recent review of Medicare data showed high in-hospital mortality (4.4%) and high readmission rates; specifically, 60% of patients had one or more readmission for any cause within the first nine months, and 28% were readmitted for heart failure (Aranda, Johnson, & Conti, 2009). In the VA system, up to 20% of patients are readmitted for HF within 30 days (Heidenreich, 2011). This high rate of hospitalization has led to cost estimates of over $37 billion for heart failure care in the VA alone (Heidenreich, 2011). Many of these readmissions may have been prevented if patients were to engage in consistent self-care including adherence to medication (Cutler & Everett, 2010; Heidenreich, 2004; Riegel et al., 2009). Poor adherence to medication in persons with HF is common, with estimates ranging from 33 from 58% (Albert, 2008; Cutler & Everett, 2010; Heidenreich, 2004; Ho, Bryson & Rumsfeld, 2009; Wu, Moser & De Jong, 2009). Healthcare stakeholders recognize this; non-adherence has been termed the next frontier in quality improvement in cardiovascular outcomes research (Heidenreich 2004).

Medication non-adherence in persons with HF. Non-adherence to medication may be the most common cause of HF exacerbations and subsequent hospital readmissions in the United States today; and this is quoted widely in the literature. However, when sources of this quote are closely examined it appears that the reported outcomes, such as hospital readmissions, are often in reference to cardiovascular disease (e.g. hypertension, coronary artery disease, or myocardial infarction) rather than HF alone. (Albert, 2008; Cutler & Everett, 2010; Osterberg & Blaschke, 2005). However, this is not unreasonable as hypertension, coronary artery disease, and prior myocardial infarction are the most common pre-disposing etiologies of HF in America (Lindenfeld et al., 2010).

Esposito et al. (2009) examined medication adherence in persons with HF with healthcare usage and costs in Medicare and Medicaid data in four states. This study showed improved medication adherence was related to fewer hospitalizations and emergency room visits, and that overall treatment costs for those with 95% medication adherence were 15% less than those with adherence between 80 and $\leq$ 95%; $p = < .01$ (Esposito, Bagchi, Verdier, Bencio, & Kim, 2009). Murray et al. (2009) studied pharmacy refill data in a cohort of 192 HF subjects and found medication adherence < 40% to be associated with a three-fold higher incidence of rehospitalizaton for HF than those whose adherence was $\geq$ 80%. Both of these studies utilized pharmacy refill data that may not accurately reflect patient-level adherence, and they did not establish a link to causes of non-adherence.

Definition of cut point for adherence. There is some disparity in defining the cut point for "adherent" versus "non-adherent". Pharmaceutical trials have generally defined taking 80% of study medication as "adherent", although the rationale for this cutoff is not well

defined (Osterberg & Blaschke, 2005). Non-adherence is usually thought of as missing medication doses, however it may manifest in various ways, including underdosing, overdosing, self-imposed drug holidays, and taking medication that is not prescribed—all by the same patient (van der Wal & Jaarsma, 2008). In persons with HF, a minimum medication adherence of 88% has been shown to predict improved event-free survival, and a recent trial found all-cause mortality to be associated with <80% adherence to HF medications (Fitzgerald et al., 2011; Wu, Moser, & De Jong, 2009). One study of medication adherence and CI in veterans with HF found poor adherence to medication (78%) in the overall study cohort; and that adherence significantly worsened (73%, p =. 017) in those subjects with mild CI (Hawkins, 2012).

Measurement of medication adherence. Currently, there is no gold standard used to measure medication adherence. Methods of measuring medication adherence may be described as direct or indirect. Direct methods, which include directly observed therapy and detecting levels of the drug or its metabolite in the serum or the urine, are not practical for routine clinical use (Ho, Bryson & Rumsfeld, 2009; Osterberg & Blaschke, 2005). Indirect methods include asking the patient about adherence, collecting patient questionnaires or diaries, assessing clinical response, performing pill counts, ascertaining rates of refilled prescriptions, and using electronic medication monitors (Lee, 2007; Osterberg & Blaschke, 2005). Recent clinical trials have used electronic devices, such as the Medication Event Monitoring System (MEMS), which register the date and time when caps of medication bottles are removed (Wu, Moser, Chung & Lennie 2008). Such devices have been shown to be valid instruments in measuring adherence of one or two medications in research settings, but are impractical to use when measuring adherence to

the multiple medications prescribed in routine care. Pill counts are relatively easy to perform for any amount of medications, have been correlated in accuracy to electronic monitors, and have been frequently used in randomized controlled clinical trials (Lee, 2007; Smith, Hankins, Hodson & George, 2010).

Interventions to improve adherence

Interventions have been tested to improve medication adherence in persons with HF that largely focused on the healthcare system and providers. In one study of 314 low-income patients with HF, subjects were assigned to usual care or a pharmacist-led intervention for nine months; with a three-month follow up. Adherence improved in the interventional group (78.8% vs. 67.9% in the usual care group) but this effect disappeared once the intervention ceased (Murray et al., 2007). A systematic review of 79 randomized controlled trials confirmed most interventions to improve medication adherence in persons with HF did not have a large or sustained effect. The interventions that did have an effect were complex and required involvement of multiple disciplines (Haynes, Ackloo, Sahota, McDonald & Yao, 2008). Thus, it is not surprising that attention has turned to examining patient-related factors for designing interventions to improve adherence.

Patient-related factors and medication adherence in HF. HF usually occurs later in life in persons with multiple other chronic diseases such as diabetes, coronary artery disease, and depression (Lindenfeld, et al., 2010). These potentially frail patients are confronted with potential polypharmacy and a fragmented medical care system that does not offer reimbursement incentives to the healthcare provider for careful medication reconciliation (Cutler & Everett, 2010).

Moser and Watkins (2008) point out the normative model in American healthcare is the delivery of care on an acute, episodic basis. However, HF is a chronic disease, and daily attention, or adherence, to multiple factors such as taking medications is needed to maintain stability. The patient in the home must manage this ongoing process of self-care. Self-care occurs as a result of a series of decisions made by patients, and thus interventions to improve self-care may fail if little is known about the factors affecting decision-making. The presence of CI and/or poor HL may influence decision-making, but this has not been well studied in veterans with HF.

Cognitive Impairment in HF

For the purposes of this study CI may be defined as ranging from mild to severe (dementia), manifesting as problems with memory, attention, learning, recall, motor speed, reaction times, and executive functioning (Sauve, et al. 2009). CI has been shown to be a frequent condition in patients with HF, far above what is to be expected with normal aging. A population-based study of 1075 persons in Italy found the risk of CI was 1.96-fold greater in those with HF (Cacciatore et al. 1998). A literature review of 22 studies from 1966 to 2006 compared pooled data from 2937 HF patients with 14,848 controls and concluded the odds ratio of HF patients having CI to be 1.62 (Vogels, Scheltens, Schroeder-Tanka & Weinstein, 2007). Another literature review of CI in HF found the prevalence of CI ranged from 30-80% (Bennett & Sauve, 2003). A third review of the literature from 2002-2007 examined 97 longitudinal studies and found the prevalence of CI in HF to be 25% to 50% (Pressler, 2008). This wide variance in prevalence is probably due to the small select samples of very ill hospitalized patients

included in the reviews. Thus these results may not be readily generalized to the outpatient HF population. In addition, instruments used to measure CI varied widely.

More recently, cognition has been studied in outpatients with HF using sophisticated neuropsychogical instruments. One study tested of 414 participants (249 HF, 63 healthy, and 102 medical participants, i.e. those with conditions other than HF); those with HF were found to have 24% more cognitive deficits than the controls. The domains affected were primarily memory, psychomotor speed and executive functioning (Pressler, Subramanian & Kareken, 2010). Another study compared 50 outpatients with HF compared to age-matched controls in the community. All subjects completed neuropsychological testing, and those with HF were found to have a four-fold risk for CI compared to controls (Sauve et al., 2009). None of these studies have evaluated the association of poor HL or medication adherence in persons with HF and CI.

Causal factors for CI in HF. It is unknown if the increased occurrence of CI with HF is due to a direct causal association, or if both conditions are associated with certain patient demographics such as advanced age and co-morbid disease states including diabetes, anemia, sleep apnea, or stroke (U.S. National Library of Medicine, 2012). Previous studies have suggested that low cardiac output, as well as variations in blood pressure are associated with CI, particularly in patients with ischemic cardiomyopathy (Kennelly, Lawlor & Kenny, 2009; Woo, Kumar, Macey, Fonarow & Harper, 2009). Depression is prevalent in persons with HF and is associated with both CI and with poorer overall outcomes (Hawkins et al. 2012, Rutledge, Reis, Linke & Greenberg, 2006). Prior literature has also focused on the association of CI with biomarkers for disease severity, including increased B-type natriuretic peptide (BNP), serum creatinine, and glycated

hemoglobin, as well as derangements in thyroid function, serum vitamin B12, and thiamine levels (Lindenfeld et al., 2010).

Health Literacy

As important as CI may be in contributing to poor medication adherence and thus, poor outcomes, it is only one of many factors. A related, yet separate concept is poor health literacy (HL), which may be described as an individual's capacity to obtain and process basic health information and negotiate the healthcare system well enough to obtain necessary services and make appropriate health decisions (Nielsen-Bohlman, Panzer, & Kindig, 2004). Health literacy is not simply a problem of reading fluency and vocabulary (and thus is not dependent upon educational level), but instead is affected by multiple factors such as the complexity of the information presented, and the patient's contextual knowledge, prior experience, and cognitive and functional abilities (Evangelista, et al. 2010; Nielsen-Bohlman, Panzer, & Kindig, 2004; Moser and Watkins 2008). Numeracy skills, a subset of HL, are less discussed in the literature, yet are critical to managing such common tasks as taking medication. For example, Davis et al. (2006) found 70 % of patients with poor HL could correctly state the instructions on a medication label, yet only 34% could actually demonstrate the number of pills to be taken.

HL is usually categorized in three to five ordinal levels e.g. "below basic" (no more than simple, concrete literacy skills), "basic" (simple and everyday literacy skills), "intermediate" (moderately challenging literacy skills) and "proficient" (complex and challenging literacy skills). Multiple articles cite the extremely high incidence of poor HL in America; and usually reference the seminal National Assessment of Adult Literacy

(NAAL) study, which published data in 2003 showing only 13% of Americans possess HL at the proficient level (National Center for Educational Statistics, 2012). Disproportionately high levels of poor HL were found in vulnerable populations including racial and ethnic minorities, the frail elderly, and those with low incomes lacking health insurance.

Health literacy, CI and outcomes. Healthcare providers remain largely oblivious of the fact that the majority of their patients may have difficulty reading and understanding healthcare information, and continue to provide their patients with written prescription labels, consent forms, test preparation instructions, test results, health questionnaires, and the like. Patients with low literacy are likely to feel anxious and ashamed about communicating with the provider, and also may not tell anyone that they do not understand basic health concepts (Parikh, Parker, Nurss, Baker & Williams, 1996). Poor HL has been associated with poor outcomes such as non-adherence to treatment plans, poor self-care behaviors, poorer physical and mental health, increased risk of hospitalization, and increased mortality (Wolf, Gazmararian, & Baker, 2005). The effect of HL on medication adherence in patients with cardiovascular disease in a large health maintenance organization revealed patients with inadequate HL were at increased risk for poor adherence (odds ratio: 1.37; 95% CI 1.08 to 1.74) compared to those with adequate HL. However, this finding did not achieve statistical significance once adjustments were made for age, race, gender, education and regimen complexity, suggesting another factor may influence adherence (Keller, Wright & Pace, 2008). A study of 492 community dwelling adults with hypertension found that CI greatly reduced the influence of age, education and race on HL scores (Levinthal, Morrow, Tu, Wu, & Murray, 2008).

However, this study enrolled primarily African-American females, and thus may not be generalizable to the VA population of primarily Caucasian males. There is only one interventional study evaluating improving medication adherence in HF by addressing HL; 314 low-income patients were randomized to usual care versus an intervention that included face-to-face support with a pharmacist and materials designed for patients with low health literacy. The interventional arm did show increased adherence, however, this decreased back to baseline once the intervention ceased (Murray, et al. 2007). In addition, only five medications were used in this study, which does not reflect the polypharmacy often found in clinical practice (Hawkins et al., 2012).

Health literacy and veterans with HF. In America, low health literacy is a prevalent and clinically under-recognized problem that directly impacts patient's self care skills, including medication management, and up to 57% of patients with HF may have poor HL (Evangelista et al., 2010; Moser & Watkins, 2008; Morrow, 2006). One study conducted in four VA medical facilities assessed HL in 1,786 veterans. This study showed veterans actually had a lower prevalence of poor HL than what has been reported in the civilian population; specifically only 8.3% had inadequate and 11.8% had marginal skills (Griffin et al., 2010). There are no studies reporting the prevalence of poor HL in the veteran population with HF.

CI and HL in persons with HF. Memory and verbal fluency are decreased in patients with CI (Hawkins et al. 2012; Pressler, Subramanian & Kareken, 2010; & Sauve et al. 2009). Yet, both are needed to negotiate a HF patient's complex medication regimen that often requires thoughtful action based on evaluation of daily vital signs. Memory and verbal fluency have also been found to be associated with poor HL, after controlling for

mild CI (Federman, Sano, Wolf, Siu & Halm 2009). Thus, interventions to improve adherence in patients with low HL should also reduce demands on cognitive abilities. The commonly accepted view that utilizing simple language and a series of illustrations for health information will not help low-literacy patients if the pictures must be mentally integrated to be understood (Morrow, et al. 2006).

Summary

HF is an epidemic threatening to overwhelm American healthcare. Poor medication adherence leads to poor outcomes as evidenced by the excessive admission-readmission cycle for HF. This is particularly important to the VA, the largest managed healthcare system in the U.S. It is becoming increasingly clear that traditional models of patient education to improve adherence are failing. Novel interventions, targeted to improve adherence, and therefore, outcomes, by addressing underlying problems with CI and poor HL are needed. This literature review demonstrates the paucity of research in veterans with HF about the effect of CI and HL on medication adherence. A gap exists in the current knowledge, as nothing has been documented about the prevalence of poor HL in veterans with HF, or the relationship between CI and HL on interventions designed to improve medication adherence in this population.

Significance of Dissertation Research to Advancement of Nursing Knowledge

Unfortunately, there remains a lack of awareness on the part of healthcare providers regarding the negative effects of poor HL and CI on adherence and outcomes in their patients with HF. There is also a paucity of data on how to address these problems in actual clinical practice. Most interventions attempting to increase adherence have

focused on the healthcare system or the provider. In addition interventions have been tested in populations stratified by illness, e. g. HF, coronary disease or hypertension, rather than the unaddressed but underlying patient-related factors such as CI and poor HL. Knowledge about the mediating effect of HL on an intervention targeted to improve MA in veterans with HF and CI will help inform the design and implementation of future interventions. Improved medication adherence will improve outcomes and decrease healthcare costs.

Chapter 3: Methods

Research Aims

The specific aims of the study were to:

Aim 1. Describe level of HL in the study population.

Aim 2. Determine the strength and direction of the relationships between reading HL and numeracy HL and selected clinical and demographic variables in the study population.

Aim 3. Determine the direct and indirect effects that reading HL and numeracy HL and other key variables (including the intervention) had upon medication adherence in cognitively impaired veteran outpatients with HF based on prior data from an interventional study testing a pictorial medication sheet and alarmed pillbox to improve medication adherence.

Research Design

The study was a retrospective, correlational, cross-sectional design using secondary analysis of data from the completed TARGET pilot study. Selected clinical and demographic variables, and reading HL and numeracy HL scores were retrieved from the participant's medical records. The TARGET study did not include information on HL, yet reading HL and numeracy HL scores were available from the participant's medical records. Thus this design was selected to estimate the causal relationships between reading HL and numeracy HL (included in existing outpatient medical records), the intervention, other key variables, and medication adherence in a sample of cognitively

impaired outpatient veterans with HF who participated in an interventional pilot study testing a pictorial medication sheet and alarmed pill box to improve medication adherence.

Participant characteristics

Setting. All study procedures were conducted at a large metropolitan Veteran's Administration facility, which serves an urban population of 246,000 veterans in southern California.

Inclusion and exclusion criteria. All subjects in the pilot study were 18 years old or older, had an established clinical diagnosis of HF, and screened positive for CI using the Saint Louis University Mental Status (SLUMS) exam (Tariq, Tumosa, Chibnall, Perry & Morley, 2006). In order to participate in testing the pictorial medication sheet and alarmed pillbox, participants were required to speak and read English, follow simple directions, be able to see, and have the manual dexterity to take their own medications. Thus persons with severe functional limitations, acutely decompensated HF, dementia requiring a caregiver, or severe mental illness, such as active schizophrenia, were excluded. Subjects were also excluded if they had a life expectancy of less than 6 months.

Sampling Procedures

Sampling method. The sample included subjects (n=40) from the TARGET pilot study. These subjects were recruited as a convenience sample from the investigator's outpatient HF clinic.

Sample size and power analysis. The TARGET study was designed as a pilot study to

test feasibility and effectiveness of the intervention. Thus, no power analysis was conducted.

Data Collection Procedures

Data was retrospectively collected from the TARGET database and the electronic medical record, and entered into an Excel spreadsheet on the investigator's secure, password-protected computer. Subject ID numbers were assigned sequentially, and all data was de-identified. A master subject/linkage log was retained in a separate locked research file in the investigator's office. Any pen-and-paper files related to the study, as well as IRB documents, were maintained in a separate, locked research file in the investigator's office.

Human Subjects Considerations

Prior to any data collection or analysis permission to conduct the study was obtained from both the VA Loma Linda Healthcare System's IRB and the University of San Diego's IRB. As this de-identified, secondary data, no consent will be obtained from the subject.

Measures

Table 1

Variable	Source	Validity/Reliability	Type and Level of Data
Medication Adherence	TARGET study 30-day pill counts	Calculated Change Score (Lee, 2007)	Percent: 100% indicated all pills taken correctly
Health Literacy	S-TOFHLA[1]	Published validity and reliability widely used in clinical practice (Bass, Wilson, & Griffith, 2003).	Score 0-36 reading comprehension Score 0-50 on numeracy subscale
Clinical: EF% [2], selected laboratory values[3], SBP[4], NYHA class[5], etiology of HF, co-morbidities	Clinic chart and data from TARGET study database	N/A	Continuous, ordinal, and dichotomous
Demographic: Age, gender, ethnicity, race, living arrangements, educational level	Clinic chart and data from TARGET study database	N/A	Continuous, ordinal, and dichotomous

[1] Short Test of Functional Health Literacy for Adults

[2] Ejection fraction

[3] to reflect disease severity: serum creatinine, hemoglobin, B-type natriuretic peptide, and glycated hemoglobin; to reflect those usually associated with cognitive impairment: thyroid stimulating hormone and vitamin B-12

[4] Systolic blood pressure

[5] New York Heart Association functional class for HF severity

The data on the dependent variable, medication adherence, was obtained for each subject from the 30-day pill counts collected before and after the prior TARGET study intervention. To capture both overtaking and undertaking medication, a change score was determined for each prescribed medication by computing the absolute difference between the number of pills taken versus the prescribed number over the 30-day period. The change score values for each medication were summed for each individual subject, divided by the total number of pills prescribed, subtracted from 1, and finally multiplied by 100 to obtain an adherence score expressed as a percentage. Thus, a value of 100% indicated all pills were taken correctly. A value of 85% meant that 15% of prescribed pills were either not taken, or overtaken, or a combination of both. All currently prescribed medications were included in the pill counts except medications taken on an "as needed" (prn) basis, injectables, and inhaled medications. Over the counter medications were not included.

Data related to health literacy was based on participant's scores on the Short Test of Functional Health Literacy for Adults (S-TOFHLA). This instrument was derived from the longer Test of Functional Health Literacy for Adults (TOFHLA) that was designed to assess basic reading and numerical tasks encountered by patients in a healthcare setting (Parker, Baker, & Williams, 1995). The S-TOFHLA has been shown to be valid, reliable, and easily administered in a busy clinical setting (Bass, Wilson, & Griffith, 2003). It is a timed (seven minute) reading comprehension test using the modified Cloze procedure; the patient reads common medical instructions that have every 5^{th} to 7^{th} word in a passage omitted and is asked to select a word from 4 multiple-choice options to fill in the blank spaces (Bass, Wilson, & Griffith, 2003; Parker, Baker, & Williams, 1995). This

test has been administered to patients in the HF clinic as part of usual care since January 2011. In addition, there is a 17-item, timed (ten minute) subscale of the TOFHLA that tests the ability of patients to comprehend medication prescription labels, results of blood glucose tests, clinic appointment slips, and financial assistance for healthcare information. The numeracy subscale is scored in a weighted manner according to the test manual, to create a final score ranging from 0-50 (Parker, Baker, & Williams, 1995). The numeracy subscale had been administered to all TARGET participants as part of routine HF clinical care. All HL scores are recorded on HF clinic progress notes, which are maintained in the electronic medical record. There is no evidence in the literature that HL scores as assessed by S-TOFHLA change over time.

Statistical Analysis

Study data was entered into an Excel database, then transferred into the computer program, Statistical Package for the Social Sciences v. 20 (SPSS) (IBM Corporation), for analysis. A *p*-value of .05 or less was considered significant. Initially, frequency distributions for each variable were examined for normal distribution characteristics. Then descriptive and inferential statistical analysis were performed as appropriate.

Descriptive statistics including measures of central tendency and frequency were employed to address study aim 1: Describe the level of reading HL and numeracy HL in the study population. Study aim 2, that addressed the strength and direction of the relationships between reading HL and numeracy HL and selected clinical and demographic variables in the study population, was explored using bivariate correlational tests appropriate to the level of measurement (e.g. Spearman's rho for ordinal data and

Pearson's *r* for interval or ratio level data). To achieve aim 3: Determine the direct and indirect effects that HL and other key variables (including the intervention) had upon medication adherence in cognitively impaired veteran outpatients with HF based on prior data from an interventional study testing a pictorial medication sheet and alarmed pillbox to improve medication adherence, structural equation modeling (SEM) was utilized for analysis. This analysis was performed using *M*plus v.7 software (*M*plus, 2012), in consultation with a statistician experienced in SEM.

SEM was selected as the best method to estimate the causal relationships between HL, the intervention, other key variables and medication adherence. SEM offers an ideal method of analysis as models can be constructed to reduce measurement error and accommodate the complexity of the factors and relationships being studied. In addition, though not a panacea for problematic distributions or model misspecification, the bootstrapping option in *M*plus was considered to address the small sample size in the study population (Meyers, Gamst & Guarino, 2006).

Strengths and Limitations of Methods

There are important limitations to this research design. The sample size was small, drawn from a pilot feasibility study, and was selected as a convenience sample from the investigator's HF population of predominantly elderly Caucasian males veterans from an urban southern California VA medical center. The VA system offers ready access to prescription medication coverage. Therefore, the results may not be readily generalized to other populations. There is the recognized difficulty in objectively measuring actual medication adherence with the pill counting technique. There is no data

available to know if HL scores obtained from the S-TOFHLA instrument would change over time.

Strengths of the design actually mirror some of the limitations. The study sample is homogeneous, and all have ready access to prescription medication coverage.

HEART & LUNG

Cognitive impairment and medication adherence in outpatients with heart failure

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ARTICLE INFO

Article history:
Received 7 November 2011
Revised 23 May 2012
Accepted 5 June 2012
Online ■ ■ ■

Keywords:
Cognitive dysfunction
Cognitive screening
Heart failure
Medication nonadherence
Veterans

ABSTRACT

Objectives: The study objectives were (a) to describe the prevalence and severity of cognitive impairment (CI) in an outpatient veteran population with heart failure (HF), (b) to describe the cognitive domains affected in those subjects found to have CI, (c) to examine clinical and demographic variables that may be associated with CI, and (d) to determine the relationship between CI and medication adherence (MA). We hypothesized that CI is a prevalent condition in veterans with HF and is associated with poorer MA. Adherence to therapy is essential for successful outcomes. CI may affect adherence; little is known about CI in veterans with HF or the effect of CI on MA.

Methods: We enrolled 251 veteran outpatients with HF. Subjects were screened for CI; adherence was determined by pill counts. Subjects with CI underwent further neuropsychologic testing.

Results: Unrecognized CI was found in 58% of subjects. Verbal learning, immediate memory, and delayed verbal memory were most impaired. CI was significantly associated with poorer MA. Variables associated with CI included age, African-American race, depression, use of alcohol, and nonparticipation in pill count.

Conclusion: Unrecognized CI was prevalent and associated with poorer MA. We propose routine screening for CI in patients with HF.

Cite this article: Hawkins, L. A., Kilian, S., Firek, A., Kashner, T. M., Firek, C. J., & Silvet, H. (2012, ■/■). Cognitive impairment and medication adherence in outpatients with heart failure. Heart & Lung, ■(■), 1-11. http://dx.doi.org/10.1016/j.hrtlng.2012.06.001.

Heart failure (HF) is a prevalent, complex, and chronic medical condition that currently affects 5.8 million people in the United States, contributing significantly to increased mortality, morbidity, and healthcare expenditures, and decreased quality of life.[1,2] The negative impact of HF on patient outcomes and healthcare costs is projected to escalate as the American population ages and is of particular importance to the Veterans Affairs (VA) health care system, the largest integrated healthcare system in the United States.[3,4] Outpatient encounters for HF in the VA system have increased from 550,000 in 2002 to 900,000 in 2009 and represent not only the

Funding: Veterans Affairs Chronic Heart Failure Quality Enhancement Research Initiative Pilot Grant RRP-09-166.
Authors have no disclosures to report.

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http://dx.doi.org/10.1016/j.hrtlng.2012.06.001

increasing numbers of veterans with HF but also the increasing intensity of care these patients require.[4]

Large clinical trials have demonstrated the success of pharmacologic and lifestyle strategies in improving patient outcomes and have resulted in the development of consensus guidelines.[1] However, patients with HF tend to be older and to have multiple comorbidities, and may find it difficult to follow these often complex regimens, thereby losing the benefits of evidence-based care.[4,5] One particularly important manifestation of poor HF outcomes is the frequency of admissions. In the VA system, 20% of patients with HF are readmitted within 30 days.[4] Nonadherence to medication has been shown to be responsible for the majority of readmissions for HF in the United States.[5-10] Of even more concern, a recent trial linked medication nonadherence, defined as < 80% adherence to HF medications, to all-cause mortality.[11] Thus, identification and intervention for key factors contributing to poor medication adherence (MA) have become primary goals for clinicians and healthcare policymakers.[4]

Pharmaceutical trials have generally defined taking 80% of study medication as "adherent," although the rationale for this cutoff is not well defined.[12] In persons with HF, a minimum MA of 88% has been shown to predict improved event-free survival.[13] Population-based studies have shown MA to be as low as 40% to 50%, highlighting the importance of focusing on adherence to improve patient outcomes.[5,12-15]

Adherence is a complex issue and depends on multiple patient and healthcare-related factors. Nonadherence is usually thought of as missing medication doses; however, it may manifest in various ways, including underdosing, overdosing, taking self-imposed drug holidays, and taking medication that is not prescribed—all by the same patient.[16] The World Health Organization's Multidimensional Adherence Model classifies predictors of poor adherence into 5 broad domains: socioeconomic status, type of healthcare system, prescribed therapy, condition being treated, and individual patient-related factors.[17] However, this model explained less than 20% of poor adherence in patients with HF, emphasizing the need to identify other contributors to nonadherence in this population.[18] One frequently overlooked factor that may influence all of these domains is the presence of cognitive impairment (CI).

CI may range from mild to severe (dementia), manifesting as problems with memory, attention, learning, recall, motor speed, reaction times, and higher level orders of reasoning (executive function).[19] It is clinically intuitive that impairment in any of these domains would negatively affect patients' abilities to correctly take their medications, yet assessment for CI remains rare in clinical practice.[20-22] Persons with HF have been shown in recent studies to have up to a 4-fold higher risk of developing CI compared with the general population, and the overall prevalence of CI in outpatients with HF has been shown to be as high as 50%.[19,23] A limitation of previous studies examining CI in HF is the selective inclusion of persons with low left ventricular ejection fraction (LVEF), despite the fact that > 50% of HF admissions in the United States are for patients with preserved systolic function.[1] In addition, these studies have not examined the direct relationship of CI to MA in a selected population.

It is unknown whether the increased occurrence of CI with HF is due to a direct causal association or if both conditions are associated with certain patient demographics, such as advanced age and comorbid disease states, including diabetes, anemia, sleep apnea, and stroke.[19,23] Previous studies suggest that low cardiac output and variations in blood pressure are associated with CI, particularly in patients with ischemic cardiomyopathy.[19,24,25] Depression is prevalent in persons with HF and associated with both CI and poorer overall outcomes.[15,26] Prior literature has also focused on the association of CI with biomarkers for disease severity, including increased B-type natriuretic peptide, serum creatinine, and glycated hemoglobin, as well as derangements in thyroid function, serum vitamin B_{12}, and thiamine levels.[27-29]

The older American veteran is at risk for many of these comorbid illnesses. For example, the majority of veterans with HF have ischemic heart disease and approximately one third have diabetes.[4] In addition, the effects of post-traumatic stress disorder and substance abuse in the veteran population on HF outcomes are not well understood. To date, there are no published studies on the prevalence of CI and its potential effect on MA and outcomes in the outpatient veteran population with HF.

There are several advantages to conducting this investigation in a veteran population. The VA system presents a large and relatively controlled environment of managed care, and data collection is facilitated by a well-established, comprehensive electronic medical record system. In addition, veterans have increased access to care compared with the general population, including assistance with transportation to clinic appointments. Most important, medications are provided from the VA formulary at no cost or for a low fixed co-pay. Yet despite this seemingly ideal system, HF outcomes remain problematic as evidenced by the excessively high readmission rate.[4]

The objectives of this study were (a) to describe the prevalence and severity of CI in an outpatient veteran population with HF, (b) to describe the cognitive domains affected in those subjects found to have CI, (c) to examine clinical and demographic variables that may be associated with CI, and (d) to determine the relationship between CI and MA. We hypothesized that CI is a prevalent condition in veterans with HF that is associated with poorer MA.

Materials and Methods

This study was designed as a prospective observational cohort study at a large metropolitan Veterans

Administration facility, which serves an urban population of 246,000 veterans in southern California. The institutional review board approved the study, and all subjects provided written informed consent before enrollment.

Study Population

Clinical providers and research coordinators screened all eligible patients for the study who presented to the outpatient HF and general medical clinics at a VA medical center between December 2009 and March 2011. Patients were eligible for enrollment if they had an established clinical diagnosis of HF. Recruitment was not based on specific limits of LVEF. Persons with a life expectancy of less than 6 months or documented dementia requiring a caregiver were excluded from the study. To participate in cognitive function testing, participants were required to speak English, follow simple directions, and be able to draw simple figures. Thus, patients with severe functional limitations, acutely decompensated HF, or severe mental illness, such as schizophrenia, were not included. No subjects had known CI before enrollment into the study.

Procedures

At the initial study visit, all subjects were screened for CI, depression, and propensity to adhere to their prescribed medication regimen. Selected clinical and demographic variables were collected by direct patient interview using standard questions and medical record review. Subjects were asked to return for a second and third study visit bringing in their regularly prescribed medications for a direct 30-day pill count to determine MA. Subjects who initially screened positive for CI were invited back for a fourth study visit to undergo a neuropsychologic test battery. Screening, interviewing, and data collection were conducted by 2 research coordinators under the supervision of the investigators. The study flowsheet is presented in Figure 1.

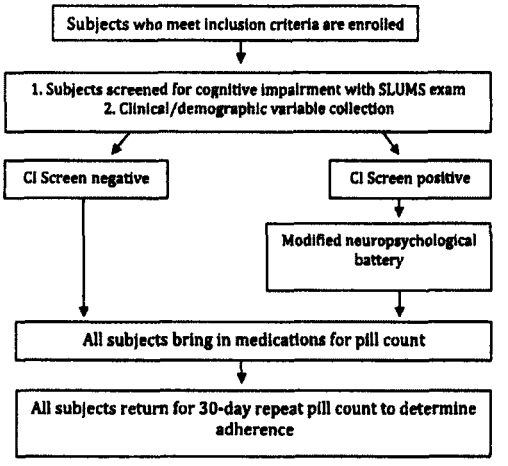


Figure 1 – Study flowsheet. CI, confidence interval; SLUMS, Saint Louis University Mental Status.

Variables and Measures

Screening for CI

Subjects were screened for CI using the Saint Louis University Mental Status (SLUMS) examination.[30] The SLUMS examination consists of a 30-point education adjusted, clinician-administered interview scale that classifies patient impairment as none, mild, or impairment consistent with dementia. Specifically, SLUMS screening is considered positive for mild CI if the score is < 27 in a person with a high school diploma or < 25 in a person who did not complete high school. SLUMS screening is considered positive for severe impairment consistent with dementia if the score is < 21 for persons with a high school diploma and < 20 for persons who did not complete high school.

The SLUMS examination contains 11 questions that incorporate tasks correlating with specific cognitive domains. These include immediate recall and orientation (day of week, year, and place); delayed recall with interference (subjects are asked to remember 5 objects and recall them after 2 intervening questions); numeric calculation and registration (a 2-part math story problem); semantic fluency (naming as many animals as possible within 1 minute); working memory (reciting numbers backward), visual spatial and executive function (clock-drawing test); visual spatial function (recognizing geometric figures); and contextual verbal memory (subject listens to a short story and answers 4 questions about the story's content).

The SLUMS examination was selected for our study for several reasons. The SLUMS examination contains empirically derived cutoff scores based on a study of 702 patients from an urban VA system with demographics similar to our sample of predominantly elderly Caucasian men.[31] This validation study indicated that the SLUMS examination had high sensitivity (98%-100%) and specificity (98%-100%) for detecting the presence of dementia. In addition, the SLUMS examination was shown to be more sensitive in detecting mild CI than the familiar Mini Mental Status Exam, with sensitivity of 93% versus 67% for patients with less than high school education, and 94% versus 67% for patients with a high school diploma or above.[31-33] The SLUMS examination includes a clock-drawing test, which is especially sensitive in detecting impaired executive function.[34] Finally, the SLUMS examination is quick to administer, taking approximately 7 minutes, and may be conveniently downloaded at no charge from the Internet.[35]

Neuropsychologic Testing

Our study was designed to further test those subjects who screened positive for CI to determine the cognitive

domains most affected. To be tolerable for older subjects with HF, a modified comprehensive battery of neuropsychologic testing was chosen that could be completed in one 2-hour session. In addition to brevity of administration, tests were selected on the basis of (a) sensitivity to the presence of CI including dementia, (b) available test norms with demographic adjustments, and (c) published research establishing good psychometric properties of each instrument. The domains tested included immediate and delayed verbal memory, delayed nonverbal memory, visuospatial/constructional ability, language, verbal learning, attention, information processing speed, executive functioning, motor dexterity, and premorbid intellectual functioning. The specific tests included Repeatable Battery of Assessment of Neuropsychological Status,[36] Trail Making Tests,[37] Wechsler Test of Adult Reading,[38] Grooved Pegboard Test,[39,40] phonemic and semantic verbal fluency tasks,[41,42] and Similarities, Matrix Reasoning, Letter Number Sequencing, and Digit Span subtests from the Wechsler Adult Intelligence Scale, 4th edition.[37,43] All examinations were conducted and scored by a single research coordinator trained in psychometric testing under the supervision of our neuropsychologist investigator.

Screening for Depression

The Geriatric Depression Scale (GDS) screens for depression in the elderly.[44] It is a widely used self-report consisting of 30 simple yes/no questions suitable for the ill or the mildly cognitively impaired person. The GDS has an acceptable reported internal consistency of .94 (Cronbach's alpha) and a split half reliability of .94.[44,45] Cutoff scores are as follows: 0 to 9 as normal, 10 to 19 as mildly depressed, and 20 to 30 as severely depressed.

Demographic and Clinical Variables

Demographic and clinical variables that might predict or influence the finding of CI in the study sample were selected on the basis of review of relevant literature as described in the introduction. These data were organized into 5 categories: demographic, health-related, HF-related, behavioral health-related, and clinic-related variables. Demographic data included age, gender, ethnicity, living arrangements, employment, educational level, and self-perceived financial distress. Health-related variables included systolic blood pressure, the presence of selected comorbidities (diabetes, hypertension, obstructive sleep apnea, stroke, and atrial fibrillation) and selected laboratory values (B-type natriuretic peptide, glycated hemoglobin, serum creatinine, thiamine, vitamin B_{12}, hemoglobin, and thyroid stimulating hormone levels). Venipuncture and blood specimen processing were conducted as part of routine medical care at the VA's clinical laboratory. HF-related variables included HF cause, HF duration, and LVEF as measured by echocardiogram. Behavioral health-related variables included documented history of depression, depression as measured by GDS, documented history of post-traumatic stress disorder, and self-reported use of tobacco, alcohol, marijuana, or illicit substances. Clinic-related variables included treatment provided by the specialized HF clinic versus general medical clinics, number of prescribing providers, and number of hospitalizations in the past year. The number and type of prescribed medications were collected during the pill counts on those subjects who returned for pill counts.

Screening for Propensity to Adhere to Medication

All subjects were screened for propensity to adhere using the Medication Adherence Estimator.[46] This 3-item instrument was designed to estimate a patient's propensity to adhere to medications prescribed for chronic disease and was validated in a large sample of elderly patients using pharmacy claims data over a 9-month period.[47] Respondents are scored as low, medium, or high risk for nonadherence.

Medication Adherence

Subjects were asked to bring their regularly taken prescription medications to be counted at the beginning of the study and again at 1 month to obtain a direct 30-day pill count. The pill count included all prescribed medications, not only those for HF, to reflect overall pill-taking behavior. Medications taken on an as-needed basis, injectables such as insulin, and inhaled medications were excluded from the pill count. Two research coordinators counted pills in the clinic in the presence of the subjects, both manually and with a Torbal DRX 300 NTEP (Fulcrum Inc., Clifton, NJ) certified pharmacy scale.

An MA score for each subject was computed from the 30-day pill counts. To capture both overtaking and undertaking medication, a "delta" was determined for each medication by computing the absolute difference between the number of pills taken and the number prescribed over the 30-day period. The delta values for each medication were summed for each individual subject, divided by the total number of pills prescribed, subtracted from 1, and finally multiplied by 100 to obtain an adherence score expressed as a percentage. Thus, a value of 100% indicated that all pills were taken correctly. A value of 85% meant that 15% of prescribed pills were not taken, overtaken, or a combination of both. Expressed mathematically, if the jth patient was prescribed p_{ji} and consumed c_{ji} of medication i, then MA can be computed for each jth patient:

$$MA_j = \left[1 - \left(\frac{\sum_i \left|c_{ji} - p_j\right|_i}{\sum_i p_{ji}}\right)\right] \times 100$$

Statistical Analysis

Data analysis was conducted using the Statistical Package for the Social Sciences version 19 (SPSS Inc,

Chicago, IL).[48] P values of .05 or less were deemed significant. Descriptive summaries included means and standard deviations for continuous variables and counts and percentages for categorical variables. To facilitate making semantically interpretable comparisons of relative effect sizes across variables, neuropsychologic test scores, age, and LVEF variables were transformed into z scores by subtracting the sample mean from the raw score and dividing the difference by the sample standard deviation.

To achieve study objective "a," SLUMS scores were obtained for each subject. The SLUMS scores calculate CI as a 3-item ordinal scale (none, mild, and impairment consistent with dementia). For the initial analysis, subjects were identified as "no CI" or "CI." For further analysis, subjects with CI were further grouped into 2 categories: mild or severe (impairment consistent with dementia).

To achieve study objective "b," neuropsychologic test scores were standardized on the basis of the individual test manual or published demographically adjusted test norms.[49]

To achieve study objective "c," unadjusted associations among clinical, demographic, and CI variables were assessed using Spearman's rho for ordinal variables or Pearson's tests for interval or ratio variables. Predictors of CI were computed from univariate generalized linear regressions with an ordinal multinomial link and robust standard errors. For categorical predictors (eg, race), effect sizes on CI were reported as simple odds ratios. For continuous predictors (eg, age), effect sizes on CI were reported as odds ratios representing the change in the likelihood of increasing CI by 1 level (eg, none to mild impairment, or mild to severe impairment) for a change in 1 standard deviation of the predictor variable.

To achieve study objective "d," unadjusted and adjusted associations between CI and MA were estimated using generalized linear regression. Estimates were adjusted for age, race (African-American), ethnicity (Hispanic), living arrangements (living alone), number of hospitalizations in the prior year, and tobacco use. These adjustment variables were selected to contain demographic and health-related factors identified by a literature review and the predictor's performance on this dataset to explain MA or CI.

Results

A total of 251 subjects were recruited. The ethnically mixed population served by the hospital (predominantly 60% Caucasian, 9% African-American, and 8% Hispanic) was fairly well reflected in the study sample of 72% Caucasian, 13.6% African-American, and 9.6% Hispanic subjects. Subjects were predominantly male (99%), with a mean age of 66 years (standard deviation ± 9.8; range, 33-93 years). Baseline characteristics for the cohort are shown in Table 1.

We found a high prevalence of unrecognized CI in our cohort; 58% (144/250) of patients had CI based on the SLUMS screening test; 41.6% of these had mild CI and 16% had severe impairment consistent with dementia (Table 2). All subjects who screened positive for CI during the initial study visit were invited back for further neuropsychologic testing. Despite vigorous efforts by the study team, only 61% (89/144) actually returned for further testing. Of the cognitive domains tested, verbal learning, immediate memory, and delayed verbal memory were found to be the most impaired based on a z score of <-1.5. Results of neuropsychologic tests are shown in Table 3.

Table 4 presents the results of bivariate analyses between study variables and CI. CI was positively associated with age, African-American race, depression as measured by the GDS, and use of alcohol. In addition, CI was associated with not returning for pill counts; however, this is not a variable that could easily be identified in a clinical setting.

Although all study subjects (both those with and without CI) initially agreed to return for the pill count, only 67% (168/250) of the enrolled subjects did so. Overall adherence in the cohort of patients who participated in the pill count was poor; subjects with no CI had adherence of 78%, those with mild CI had adherence of 70%, and those with severe CI had adherence of 73%. Specifically, compared with no CI, MA significantly worsened by 8 percentage points (78% to 70%, P = .017) for patients with mild CI, but did not continue to worsen for patients with severe CI in the dementia range. Similar findings were found between unadjusted and adjusted estimates (Table 5).

Our regression analyses revealed a robust association between the presence of CI and MA. Among the study variables listed in Table 4, only CI was found to have a statistically significant association with MA. We also found both overtaking and undertaking prescribed medications to be common in our study sample; however, no statistically significant patterns or trends were found.

Results from the Adherence Estimator survey revealed the majority of subjects intended to take their medications. Specifically, 52.2% (116/214) scored at low risk, 35% (75/214) scored at medium risk, and 10% (23/214) scored at high risk for potential nonadherence. However, these scores were not significantly correlated with actual MA found in the study population.

Discussion

Our study demonstrated 2 important findings: a high prevalence of previously unrecognized CI in veterans with HF and the association of CI with poorer MA. These findings have vital implications for the successful treatment of HF in the veteran population.

Table 1 Baseline characteristics of the study population (n = 251)	
Demographic variables	
Age (y) mean ± SD	66.4 ± 9.8
Male gender (n = 251)	247 (98.4%)
Race/ethnicity (n = 250)	
Caucasian	180 (72.0%)
African-American	34 (13.6%)
Hispanic	24 (9.6%)
Employment (n = 248)	
Employed	25 (10.1%)
On disability	61 (24.6%)
Retired	151 (60.9%)
Unemployed	11 (4.4%)
Living arrangements (n = 249)	
Live alone	68 (27.3%)
Live with spouse/partner	142 (57.0%)
Live with children	17 (6.8%)
Other	22 (8.8%)
Education (n = 248)	
Less than high school	25 (10.1%)
High school diploma	60 (24.2%)
Some college	103 (41.5%)
College degree or above	60 (24.2%)
Self-perceived financial status (n = 221)	
Does not affect ability to care for health	111 (50.2%)
Affects ability to care for health	110 (49.8%)
Health-related variables	
Diabetes (n = 251)	134 (53.4%)
Coronary artery disease (n = 251)	160 (63.7%)
Hypertension (n = 251)	193 (76.9%)
Obstructive sleep apnea (n = 251)	68 (27.1%)
History of stroke (n = 251)	26 (10.4%)
History of atrial fibrillation (n = 251)	82 (32.7%)
Systolic blood pressure mean ± SD (mm Hg)	125.8 ± 19.67
Thiamine level, mean ± SD (nmol/L)	169 ± 95.60
Vitamin B_{12} level, mean ± SD (pg/mL)	556.8 ± 298.26
Hemoglobin level, mean ± SD (g/dL)	13.6 ± 2.19
Serum creatinine level, mean ± SD (mg/dL)	1.59 ± 1.84
Thyroid-stimulating hormone, mean ± SD (uIU/mL)	2.99 ± 4.39
BNP ± SD (range) (pg/mL)	274.7 ± 497 (2-5000)
HgbA1c ± SD (range) (%)	6.8 ± 1.5 (4.2-15.4)
HF-related variables	
HF duration (n = 248)	
<1 y	22 (8.8%)
1-5 y	104 (41.8%)
>5 y	122 (49.2%)
HF cause* (n = 238)	
Ischemic	131 (55%)
Nonischemic	107 (45%)
LVEF (n = 249)	
>40%	85 (34.1%)
≤40%	164 (65.9%)
LVEF, mean ± SD	37.5 ± 16.90

(continued)

Table 1 (continued)	
Behavioral health-related variables	
History of depression (n = 250)	76 (30.3%)
GDS score, mean ± SD†	13.3 ± 3.80
PTSD (n = 251)	47 (18.7%)
Tobacco use (n = 248)	
Never smoked	47 (19.0%)
Former smoker	154 (62.1%)
Current smoker	47 (19.0%)
Alcohol use (n = 251)	
Never	80 (31.9%)
Former use	83 (33.1%)
Current use ≤ 3 drinks/wk	59 (23.5%)
Current use >3 drinks/wk	29 (11.6%)
Marijuana use (n = 248)	
Never	156 (62.9%)
Past use	78 (31.5%)
Current use	14 (5.6%)
Other illicit substance use (n = 248)	
Never	190 (76.6%)
Past use	57 (23.0%)
Current use	1 (.4%)
Clinic-related variables	
Treated in specialized HF clinic (n = 251)	143 (57.0%)
No. of prescribing providers, mean ± SD (range)	5.4 ± 2.4 (1-13)
No. of hospitalizations in past year, mean ± SD (range)	.58 ± 1.12 (0-7)
HF medications (n = 168)	
ACE inhibitor	128 (76%)
Angiotensin receptor blocker	52 (31%)
Beta-blocker	192 (114%)
Diuretic	176 (105%)‡
Digoxin	47 (28%)
Isosorbide/hydralazine	31 (19%)
Aldosterone antagonist	38 (23%)
No. of prescriptions (n = 168), mean ± SD (range)	7.83 ± 3.06 (1-17)

ACE, angiotensin-converting enzyme; BNP, B-type natriuretic peptide; GDS, Geriatric Depression Scale; HF, heart failure; HgbA1c, glycated hemoglobin; LVEF, left ventricular ejection fraction; PTSD, post-traumatic stress disorder; SD, standard deviation.
*Diagnosis based on chart review.
†Score 0-9 = normal, 10-19 = mild depression, 20-30 = severe depression.
‡May reflect combination diuretic therapy.

Table 2 Presence of cognitive impairment based on the Saint Louis University Mental Status examination (n = 250)	
CI	
None	106 (42.4%)
Mild impairment	104 (41.6%)
Severe impairment (dementia)	40 (16.0%)
SLUMS score, mean ± SD (range)	24.39 ± 4.0 (12-30)
SLUMS administration time in minutes, mean ± SD (range)	7.1 ± 1.4 (4-15)

CI, cognitive impairment; SLUMS, Saint Louis University Mental Status; SD, standard deviation.

Table 3 Results of neuropsychologic testing*

Cognitive domain	Tests	n	SD (range)	Mean standardized scores†
Estimate of premorbid IQ	WTAR	69	9.667 (81-119)	98.71
Attention	WAIS-IV digit span	84	.88 (−2.67 to 2.0)	−.60
	WAIS-IV letter-number sequencing age < 69 y	54	.68 (−3.00 to 1.33)	−.56
Information processing speed	Trails A	89	.99 (−3.80 to 1.40)	−.80
	RBANS coding	89	.87 (−3.81 to 4.3)	−1.196
Language	RBANS picture naming	89	1.24 (−9.33 to .90)	.2257
	Animals	88	1.17 (−3.20 to 2.10)	−.57
	RBANS semantic fluency	89	.88 (−2.85 to 1.74)	−.8645
Visuospatial abilities	RBANS figure copy	89	1.53 (−6.00 to 1.35)	−.6670
	RBANS line orientation	89	.85 (−2.28 to 1.29)	.1030
	WAIS-IV matrix reasoning	84	.98 (−2.33 to 2.00)	−.20
Verbal learning	RBANS list learning	89	.96 (−4.92 to .96)	−1.904*
	RBANS story memory	89	1.08 (−3.92 to 1.0)	−1.589*
Delayed verbal memory	RBANS list recall	89	.91 (−2.86 to .95)	−1.245
	RBANS list recall recognition	89	1.84 (−7.67 to .67)	−1.798*
	RBANS story recall	89	1.21 (−4.14 to .91)	−1.840*
Delayed nonverbal memory	RBANS recall figure	89	1.04 (−3.4 to 1.97)	−.3637
Executive functioning	COWAT	88	.90 (−3.0 to 1.30)	−.74
	Trails B	88	1.04 (−3.5 to 2.0)	−.73
	WAIS-IV similarities	84	.70 (−2.0 to 1.33)	−.17
Motor dexterity	Grooved pegboard Dominant hand	85	1.08 (−3.60 to 1.40)	−.70
	Grooved pegboard nondominant hand	83	1.12 (−3.5 to 1.80)	−.91

COWAT, Controlled Oral Word Association Test; IQ, intelligence quotient; RBANS, Repeatable Battery of Assessment of Neuropsychological Status; SD, standard deviation; WAIS-IV, Wechsler Adult Intelligence Scale, 4th edition; WTAR, Wechsler Test of Adult Reading.

* <−1.5 SD considered impaired.

† All standardized scores are presented in z scores with the exception of estimate of premorbid IQ (Wechsler Test of Adult Reading), which is presented in a standard score with a mean of 100 and SD of 15.

Previously unrecognized CI was found in 58% of our sample of veterans with HF. This prevalence, although unexpectedly high, is consistent with other studies conducted in nonveteran outpatients with HF.[19,23] In our veteran population, we found the expected positive association of CI with age. Other significant associations included African-American race, use of alcohol, depression as measured by the GDS, and increased likelihood of not returning for the pill count. Comorbidities shown in prior literature to be associated with CI in HF, including abnormalities in blood pressure, low LVEF, or ischemic cause of HF, were not found to be statistically significant in our study sample. This discrepancy may be explained by the heterogeneous population in our study that included outpatients with all-cause HF compared with prior studies that may have preferentially evaluated sicker patients.

The cognitively impaired subjects who completed further neuropsychologic testing demonstrated significant deficits in the domains of verbal learning, immediate memory, and delayed verbal memory. This effectively means that many cognitively impaired patients will not understand, or will forget, what the provider has just instructed them to do soon after leaving the clinic environment. By extension, interventions that rely on traditional models of patient education to improve adherence would likely fail in this patient group. The majority of subjects who failed to return for testing simply did not return multiple telephone messages or respond to written reminders to do so. It is unknown whether this reflects another aspect of poor adherence associated with CI or whether other factors, such as not wanting to spend the time or not clearly understanding what was expected of them, contributed to the low rate of return. This intriguing discovery deserves additional investigation in future studies because of the potential impact on actual adherence estimates.

Consistent with our original hypothesis, CI was the only factor studied that was found to be associated with poorer MA in our study population. The impact on adherence seemed to begin with mild CI and did not continue to worsen for patients with severe CI in the dementia range. This is particularly important to clinical practice because the presence of mild CI is easily missed; the patient, who may deny needing any assistance with medication administration, often hides memory loss.[8-10] We are uncertain as to why the more severely affected subjects did not have worsened MA. It is possible these subjects were actually receiving assistance from family members or others; however, living arrangements (alone or with others) were not significantly associated with MA in our study sample. Finally, it is unknown whether subjects were nonadherent before becoming cognitively impaired or whether prior nonadherence actually contributed to CI.

Table 4 Association between subjects' clinical and demographic factors and cognitive impairment

Variables	Unadjusted				Adjusted†			
	OR	95% CI	Chi-square (*df*)	P value	OR	95% CI	Chi-square (*df*)	P value
Demographic variables								
Age (z score)	1.41	1.03-1.92	4.66 (1)	.031	1.42	1.03-1.95	4.64 (1)	.031
African-American race	3.22	1.70-6.09	12.95 (1)	<.001	3.59	1.90-6.81	15.4 (1)	<.001
Hispanic race	2.17	1.02-4.60	4.09 (1)	.043	2.27	.971-5.30	3.58 (1)	.058
Lives alone	.811	.492-1.34	.679 (1)	.410	.817	.489-1.36	.600 (1)	.439
Health-related variables								
Diabetes	.960	.598-1.54	.029 (1)	.865	.931	.561-1.54	.076 (1)	.782
Thiamine (z score)	1.10	.942-1.29	1.48 (1)	.224	.982	.803-1.20	.032 (1)	.858
TSH (z score)	1.21	.865-1.68	1.22 (1)	.269	1.06	.741-1.51	.097 (1)	.756
Vitamin B_{12} (z score)	1.19	.950-1.48	2.28 (1)	.132	1.16	.903-1.48	1.32 (1)	.250
Hemoglobin (z score)	.735	.590-.917	7.48 (1)	.006	.789	.608-1.02	3.19 (1)	.074
Creatinine (z score)	1.35	1.01-1.81	3.98 (1)	.046	1.27	.960-1.68	2.80 (1)	.094
HF-related variables								
Duration of HF								
1-5 y	1.54	.583-4.04	.753 (1)	.385	1.50	.549-4.12	.630 (1)	.427
6-10 y	1.02	.380-.271	.001 (1)	.977	.833	.303-2.29	.126 (1)	.723
>10 y	.970	.343-2.74	.003 (1)	.954	.987	.327-2.97	.001 (1)	.981
Cause of HF								
Ischemic vs nonischemic	.894	.553-1.45	.208 (1)	.648	1.11	650-1.89	141 (1)	.707
LVEF (z score)	1.16	.936-1.44	1.85 (1)	.174	1.12	.893-1.41	.987 (1)	.321
Systolic BP (z score)	1.22	3.79-7.44	3.24 (1)	.072	1.14	.903-1.44	1.23 (1)	.268
Behavioral health-related variables								
Geriatric Depression Scale (z score)	1.38	1.09-1.74	7.11 (1)	.008	1.43	1.12-1.83	8.08 (1)	.004
Tobacco use								
Never or prior	.546	.295-1.01	3.72 (1)	.054	.591	.312-1.12	2.63 (1)	.105
Current smoker	.436	.209-.910	.489 (1)	.027	.545	.259-1.15	2.56 (1)	.109
Alcohol use								
Never	1.34	.736-2.43	.911 (1)	.340	1.47	.791-2.72	1.48 (1)	.224
Former use	1.67	.868-3.20	2.36 (1)	.124	2.13	1.06-4.31	4.47 (1)	.034
Current use 3 drinks/wk	.216	.46-1.01	3.79 (1)	.052	.236	.055-1.00	3.83 (1)	.050
Current use 4-7 drinks/wk	1.62	.379-6.93	.425 (1)	.514	1.82	.384-8.62	.568 (1)	.451
Current use >8 drinks/wk	1.62	.481-5.46	.608 (1)	.436	1.93	.505-7.39	.924 (1)	.336
Marijuana use								
Never or prior	.608	.368-1.01	3.77 (1)	.052	.913	.526-1.58	.106 (1)	.745
Current use	1.10	.607-1.98	.095 (1)	.758	1.75	.820-3.71	2.09 (1)	.148
Clinic-related variables								
HF clinic patient	.639	.395-1.04	3.31 (1)	.069	.745	.443-1.25	1.23 (1)	.267
Did not return for pill count	2.33	1.41-3.88	10.7 (1)	.001	2.03	1.20-3.45	6.85 (1)	.009
Hospitalized in past year	1.08	.935-1.25	1.10 (1)	.294	1.14	.960-1.35	2.21 (1)	.137

BP, blood pressure; CI, confidence interval; HF, heart failure; LVEF, left ventricular ejection fraction; OR, odds ratio; TSH, thyroid-stimulating hormone.
* Based on SLUMS screening.
† Adjusted for age, African-American race, Hispanic ethnicity, living alone, tobacco use, and number of prior hospitalizations in past year.

Implications for Practice

Overall MA was poor in our cohort, with subjects both overtaking and undertaking their medication. Overtaking medication has not received much attention in the literature but poses potentially serious patient safety issues. In a multimorbid population, this problem is compounded by polypharmacy prescribed by multiple providers. In our study, it was not uncommon to find patients with several bottles of the same medication and taking a tablet from each one. We found patients most often knew their medications by color and shape rather than by name or indication. This is particularly important in the VA system because generic medications are mailed to patients' homes from a centralized pharmacy. Changes in vendors used by the pharmacy frequently resulted in changes in tablet appearance; patients may not recognize that the new tablet is actually the same medication. Potentially harmful medication errors can be discovered by careful medication reconciliation during clinic visits. However, accurate medication reconciliation requires time and expertise and is neither routinely recognized as an important part of care nor reimbursed in the current model of healthcare delivery.[11,14]

Table 5 Cognitive impairment and medication adherence (n = 168)

CI	Unadjusted				Adjusted*			
	Adherence	95% CI	Chi-square (df)	P value	Adherence	95% CI	Chi-square (df)	P value
None	81.1%	77.1-85.0	Ref	Ref	78.1%	70.5-85.6	Ref	Ref
Mild	74.1%	69.6-78.5	5.22 (1)	.022	70.7%	63.0-78.4	5.68 (1)	.017
Dementia	74.0%	65.9-82.1	2.33 (1)	.127	73.3%	63.3-83.4	1.03 (1)	.310

CI, confidence interval.
*Adjusted for age, African-American race, Hispanic ethnicity, living alone, tobacco use, and number of admissions to the hospital in past year.

A large proportion of our study participants indicated on the Adherence Estimator questionnaire that they intended to adhere to their medication regimen, yet overall their actual MA was poor, and clearly the presence of CI contributed to worsening adherence. Unfortunately, current clinical practice guidelines do not recognize CI as a risk factor for poor adherence. Consideration should be given to screening all patients with HF for CI using a tool such as the SLUMS examination, which can be administered in less than 10 minutes by regular clinic staff.

In addition, the mean score on the GDS (13.3, standard deviation ± 3.80, n = 249) indicated that the average participant in the study was mildly depressed. However, the prevalence of previously diagnosed depression in the study sample based on medical record review was only 30.3% (n = 250). These findings confirm the comorbidity of depression in persons with HF and suggest it may be another easily missed diagnosis in this population. Depression is known to affect information processing and has been shown to be prevalent and associated with worsened outcomes in nonveterans with HF.[15,26] Therefore, screening for both CI and depression may be of particular importance in veterans with HF.

Implications for Further Research

HF is a chronic disease that disproportionately affects the elderly and presents with other conditions, such as diabetes or hypertension. Successful outcomes depend on adhering to treatment regimens that are often highly complex and require significant cognitive ability to comply. Our findings suggest that CI may be a key factor in clinical success or failure, and indeed a large portion of the outpatient population with HF may be affected by the impact of unrecognized CI on MA. Further research is needed to develop and test interventions to improve MA by specifically targeting underlying CI. Consideration should be given to interventions that specifically address potential problems with verbal learning, verbal memory, and delayed verbal memory.

Study Limitations

Our study had several important limitations. It was conducted in a predominantly male veteran population in an urban community in southern California, where patients have ready access to medications via prescription medication coverage; the results of our study may therefore not be readily generalized to other populations. There is the recognized difficulty in objectively measuring actual MA with the pill counting technique. We had a higher nonreturn rate for cognitively impaired patients for the pill count. However, we predict that these patients would have had at least as poor, if not worse, adherence compared with the other subjects with CI who did follow up; thus, our data may overestimate actual MA. There was also a high nonreturn rate for cognitively impaired subjects to return for further neuropsychologic testing. Although the SLUMS examination has been validated in a veteran population as a sensitive screening tool, any brief screening is not considered adequate to make quantitative conclusions about CI. In addition, the association of CI with African-American race, although significant, was based on a small segment of the overall study population and therefore should be interpreted with caution. Finally, we did not include health literacy as part of the study design; impaired health literacy may further affect patients' abilities to understand and carry out self-care and medication regimens.

Conclusions

On the basis of our clinical experience and previous studies, we hypothesized that veterans with HF would have a high prevalence of CI and that the presence of CI would negatively affect MA. Our study found that unrecognized CI was highly prevalent and associated with poorer adherence to medication in our sample of older outpatient veterans with HF. Verbal learning, immediate memory, and delayed verbal memory were the cognitive domains most affected. Our findings suggest that CI may be a key factor in clinical success or failure in this challenging population. Consideration should be given to screening all veterans with HF for CI to identify those who will need additional help with adherence. Further research developing interventions to improve MA by targeting underlying problems with CI is urgently needed.

Acknowledgments

The authors thank Kelli McSwan, PhD, for contributing to the study design, and Elena V. Perez, for contributing to data collection.

References

1. Heart Failure Society of America; Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. J Card Fail 2010;16:e1-194.
2. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Heart disease and stroke statistics-2010 update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2010;121:e1-170.
3. Population Resource Center. Aging of America. Available at: http://prcdc.org/300million/The_Aging_of_America/. Accessed June 12, 2012.
4. Heidenreich P. CHF QUERI 2011 Strategic Plan. 2011. Available at: http://www.queri.research.va.gov/about/strategic_plans/chf.pdf. Accessed June 12, 2012.
5. Heidenreich PA. Patient adherence: the next frontier in quality improvement. Am J Med 2004;117:130-2.
6. Murray MD, Morrow DG, Weiner M, Clark DG, Tu W, Deer MM, et al. A conceptual framework to study medication adherence in older adults. Am J Geriatr Pharmacother 2004;2:36-43.
7. Esposito D, Bagchi AD, Verdier JM, Bencio DS, Kim MS. Medicaid beneficiaries with congestive heart failure: association of medication adherence with healthcare use and costs. Am J Manag Care 2009;15:437-45.
8. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. Circulation 2009;119:3028-35.
9. Munger MA, Van Tassell BW, LaFleur J. Medication nonadherence: an unrecognized cardiovascular risk factor. MedGenMed 2007;9:58.
10. Murray MD, Tu W, Wu J, Morrow D, Smith F, Brater DC. Factors associated with exacerbation of heart failure include treatment adherence and health literacy skills. Clin Pharmacol Ther 2009;85:651-8.
11. Fitzgerald AA, Powers JD, Ho PM, Maddox TM, Peterson PN, Allen LA, et al. Impact of medication nonadherence on hospitalizations and mortality in heart failure. J Card Fail 2011;17:664-9.
12. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-97.
13. Wu JR, Moser DK, De Jong MJ, Rayens MK, Chung ML, Riegel B, et al. Defining an evidence-based cutpoint for medication adherence in heart failure. Am Heart J 2009;157:285-91.
14. Cutler DM, Everett W. Thinking outside the pillbox–medication adherence as a priority for health care reform. N Engl J Med 2010;362:1553-5.
15. Riegel B, Moser DK, Anker SD, Appel LJ, Dunbar SB, Grady KL, et al. State of the science: promoting self-care in persons with heart failure: a scientific statement from the American Heart Association. Circulation 2009;120:1141-63.
16. van der Wal MH, Jaarsma T. Adherence in heart failure in the elderly: problem and possible solutions. Int J Cardiol 2008;125:203-8.
17. Sabate E. Adherence to Long-term Therapies: Evidence for Action. Geneva: WHO: World Health Organization; 2003.
18. Wu JR, Moser DK, Chung ML, Lennie TA. Predictors of medication adherence using a multidimensional adherence model in patients with heart failure. J Card Fail 2008;14:603-14.
19. Sauve MJ, Lewis WR, Blankenbiller M, Rickabaugh B, Pressler SJ. Cognitive impairments in chronic heart failure: a case controlled study. J Card Fail 2009;15:1-10.
20. Arlt S, Lindner R, Rosler A, von Renteln-Kruse W. Adherence to medication in patients with dementia: predictors and strategies for improvement. Drugs Aging 2008;25:1033-47.
21. Cameron J, Worrall-Carter L, Page K, Riegel B, Lo SK, Stewart S. Does cognitive impairment predict poor self-care in patients with heart failure? Eur J Heart Fail 2010;12:508-15.
22. Hayes TL, Larimer N, Adami A, Kaye JA. Medication adherence in healthy elders: small cognitive changes make a big difference. J Aging Health 2009;21:567-80.
23. Pressler SJ, Subramanian U, Kareken D, Perkins SM, Gradus-Pizlo I, Sauvé MJ, et al. Cognitive deficits in chronic heart failure. Nurs Res 2010;59:127-39.
24. Kennelly SP, Lawlor BA, Kenny RA. Blood pressure and the risk for dementia: a double edged sword. Ageing Res Rev 2009;8:61-70.
25. Woo MA, Kumar R, Macey PM, Fonarow GC, Harper RM. Brain injury in autonomic, emotional, and cognitive regulatory areas in patients with heart failure. J Card Fail 2009;15:214-23.
26. Rutledge T, Reis V, Linke SE, Greenberg BH. Depression in heart failure: a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Card 2006;48:1527-37.
27. van den Hurk K, Reijmer YD, van den Berg E, Alssema M, Nijpels G, Kostense PJ, et al. Heart failure and cognitive function in the general population: the Hoorn study. Eur J Heart Fail 2011;13:1362-9.
28. Ceresini G, Lauretani F, Maggio M, Ceda GP, Morganti S, Usberti E, et al. Thyroid function abnormalities and cognitive impairment in elderly people: results of the Invechiare in Chianti study. J Am Geriatr Soc 2009;57:89-93.
29. U.S. National Library of Medicine, Dementia due to metabolic causes. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001703/. Accessed June 12, 2012.
30. Morley JE. Saint Louis University Mental Status Examination (SLUMS). Aging Successfully 2002; XII(Issue No. 1).
31. Tariq SH, Tumosa N, Chibnall JT, Perry MH 3rd, Morley JE. Comparison of the Saint Louis University mental status examination and the mini-mental state examination for detecting dementia and mild neurocognitive disorder–a pilot study. Am J Geriatr Psychiatry 2006;14:900-10.
32. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189-98.
33. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 2000.
34. Juby A, Tench S, Baker V. The value of clock drawing in identifying executive cognitive dysfunction in people with a normal Mini-Mental State Examination score. CMAJ 2002;167:859-64.

35. Saint Louis University Mental Status Examination. Available at: http://www.stlouis.va.gov/GRECC/SLUMS_English.pdf. Accessed June 12, 2012.
36. Randolph C. Repeatable Battery for the assessment of neuropsychological status (RBANS). San Antonio, TX: Psychological Corporation; 1998.
37. Lezak MD. Neuropsychological Assessment. 3rd ed. New York, NY: Oxford University Press; 1995.
38. The Psychological Corporation. Wechsler Test of Adult Reading. San Antonio, TX: Harcourt Assessment; 2001.
39. Haaland KY, Delaney HD. Motor deficits after left or right hemisphere damage due to stroke or tumor. Neuropsychologia 1981;19:17-27.
40. Putzke JD, Williams MA, Daniel FJ, Foley BA, Kirklin JK, Boll TJ. Neuropsychological functioning among heart transplant candidates: a case control study. J Clin Exp Neuropsychol 2000;22:95-103.
41. Heun R, Papassotiropoulos A, Jennssen F. The validity of psychometric instruments for detection of dementia in the elderly general population. Int J Geriatr Psychiatry 1998;13:368-80.
42. Tierney MC, Moineddin R, McDowell I. Prediction of all-cause dementia using neuropsychological tests within 10 and 5 years of diagnosis in a community based sample. J Alzheimers Dis 2010;22:1231-40.
43. Strauss E, Sherman EMS, Spreen O. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. 3rd ed. New York, NY: Oxford University Press; 2006.
44. Brink TL, Yesavage JA, Lum O, Heersema PH, Adey M, Rose TS. Screening tests for geriatric depression. Clin Gerontol 1982;1:37-43.
45. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;17:37-49.
46. McHorney CA. The Adherence Estimator: a brief, proximal screener for patient propensity to adhere to prescription medications for chronic disease. Curr Med Res Opin 2009;25:215-38.
47. McHorney CA, Victor Spain C, Alexander CM, Simmons J. Validity of the adherence estimator in the prediction of 9-month persistence with medications prescribed for chronic diseases: a prospective analysis of data from pharmacy claims. Clin Ther 2009;31:2584-607.
48. IBM Corporation. Statistical Package for the Social Sciences. Available at: http://www-01.ibm.com/software/analytics/spss/. Accessed June 12, 2012.
49. Heaton RK, Miller SW, Taylor MJ, Grant I. Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults. Lutz, FL: Psychological Assessment Resources; 2004.

Department of Veterans Affairs
Chronic Heart Failure Quality Enhancement Research Initiative (CHF-QUERI)
Pilot Grant RRP-12-198

Title: Targeted Intervention to Improve Medication Adherence in Cognitively Impaired Patients with Heart Failure

Merit Review Application submitted to:
Veteran's Affairs Health Services Research and Development (HSR&D) cost center 8134
Primary Research Program Area: Quality Enhancement Research Initiative (QUERI)
Primary Research Specialty Area: Internal Medicine, Cardiovascular Disease

Approved December 2011 and funded April 2012.
Total grant funding received: $99,780 for twelve month study period.

A. Background

A.1. Heart failure is a significant burden in the VA health care system.

Heart failure **[HF]** is a prevalent, costly, chronic, and complex condition that impacts an increasingly larger number of people as the population ages. In the VA system, hospitalizations and encounters for HF are on the rise, reflecting the growing number of veterans who are impacted by this chronic condition that drastically impacts quality of life **[QOL]**, morbidity and mortality, and greatly increases expenditures for VA health care. In 2009, over 96,000 hospitalizations in the VA system listed HF as a diagnosis, a 30% increase from 2002.[1] The CHF QUERI 2009 Strategic Plan lists reducing hospitalization rates, increasing use of care known to prolong survival and improve QOL, and empowering the patient for self-management as their top goals.[1]

A.2. HF outcomes are related to adherence.

Evidence-based medication and lifestyle strategies have shown to decrease mortality and hospitalizations for HF and improve QOL, and are included in the current published guidelines that summarize recommended clinical regimens.[2,3] However, the successful implementation of these published guidelines in clinical practice remains challenging.[2-4] HF patients tend to be older, with multiple comorbidities, and can find it difficult to follow complex management regimens, resulting in poor adherence and the loss of the proven benefits of guideline-based care. In fact, not adhering to medication regimens has been shown to be the most common cause of HF exacerbations and subsequent hospital readmissions; a recent trial linked poor adherence (defined as <80% adherence to HF medications) to all cause mortality.[5-14]

A.3. Adherence is multifactorial.

Adherence depends on complex patient and healthcare factors.[5,9,15,16] Specifically, medication adherence **[MA]** refers to both compliance (the extent to which behavior coincides with health advice; e.g. patients take their medication as prescribed, such as twice daily), and persistence (following treatment recommendations over time).[9,17] The World Health Organization's Multidimensional Adherence Model classifies predictors of poor adherence into five domains: socio-economic, health care system, therapy, condition, and patient-related domains.[18] However, the factors outlined in this model explain less than 20% of poor adherence in HF patients, highlighting the need to identify other important drivers of non-adherence in this population.[19,20] One relatively overlooked factor that may influence all of these domains is the presence of cognitive impairment **[CI]**.

A.4. CI has been associated with adherence in non-HF populations in prior studies.

Prior studies in the elderly have shown that even mild cognitive dysfunction interferes with the patient's ability to adhere to self-care and medication regimens, yet assessment for CI remains rare in clinical practice.[21-23] CI manifests as problems with memory, attention, learning, motor speed, reaction times and executive functioning (i.e., higher-order capacities such as cognitive flexibility, concept formation, initiation, inhibition, selective attention, planning, and problem-solving).[24] It is clinically intuitive that CI would directly lead to poor MA based on the tasks commonly confronting HF patients such as learning what pill to take, remembering to take it, and having the dexterity and sequencing skills to open pill bottles and count tablets. Unfortunately, while the cognitive processes needed to manage and take medications often decline with aging, the number of prescription and nonprescription medications consumed is likely to increase. Although the relationship between patient's cognition and MA appears intuitive, prior studies evaluating the prevalence of CI in HF have not evaluated the link between CI and patient outcomes, including MA.

A.5. CI is common in patients with HF.

Previous studies evaluating CI in HF patients have documented a high rate of CI, ranging from 30-50%.[25-32] Most of these prior studies were limited to small samples of hospitalized patients, such as those awaiting heart transplant, and thus not applicable to the patients seen in everyday clinical practice. However, two recent outpatient studies also demonstrated increased incidence of CI in patients with HF compared to matched community controls, consistent with the results found in patients with end-stage HF.[24,33] No studies have evaluated CI in the outpatient veterans with HF, or the association to MA. Our recently completed CHF QUERI funded pilot study *Cognitive Impairment as a Risk for the Admission-Readmission Cycle seen in Veterans with Heart Failure: Closing the Adherence Gap* [34], examined both the prevalence of CI in outpatient veterans with HF and the association of CI with MA.

A.6. Our CHF QUERI funded study provides the basis for an intervention study to improve MA.

Our study recruited 251 outpatients with HF at VA Loma Linda Healthcare System **[VALLHCS]**; data collected included screening scores for CI, 9-item demographic survey, 17-item health survey, 10-item chart review, 7 lab results, 25 neuropsychology tests, a 9-item medication management survey, and a 3-item medication adherence attitude survey. All subjects were asked to bring in all regularly prescribed medications for a direct 30-day pill count. Subjects were predominantly male (99%), with a mean age of 66 years. Sixty-six percent of subjects had left ventricular ejection fraction of $\leq$ 40%, with the mean of 37.5% (SD $\pm$16.90, range 10-85). Average number of total prescriptions per subject was 7.83 (SD $\pm$ 3.06, range 1-17).

We found a strikingly high prevalence of undiagnosed CI in our cohort: 58% (144/250) of patients had CI based on the Saint Louis University Mental Status **[SLUMS]** screening test; 41.6% scored in the mild CI range and 16% in the dementia range. Of the cognitive domains tested, verbal learning, immediate memory, and delayed verbal memory were found to be the most impaired.

Although all study subjects (both with and without CI) initially agreed to return for the pill count, only 67% (168/250) of the enrolled subjects did so. Returning for pill count was in itself associated with CI (OR 2.03, 95% CI 1.20-3.45, χ^2 =6.85, p=0.009). In the sample participating in the pill count, we found a robust and significant association between the presence of CI and MA. MA (calculated to reflect both overtaking and under-taking regularly prescribed medications) significantly worsened with mild CI, but interestingly did not continue to worsen as CI increased in severity to the dementia range. Overall, adherence in the entire cohort was poor: subjects with no CI had MA of 81%, those with mild CI had MA of 74% (95% CI 69.6-78.5, χ^2 5.22, p=0.022), and those with severe CI (dementia) had MA of 74% (95% CI 65.9-82.1, χ^2 2.33, p=0.127). These results suggest three clinically important findings: CI is highly prevalent, mild CI is sufficient to impair MA, and overtaking medications has an important role in nonadherence.

A.7. Different measurements have been used to estimate medication adherence.

MA, as estimated in clinical trials, overestimates the true adherence in the environment of usual clinical practice; population-based studies have shown actual adherence to medications to be as low as 40-50%.[4,35,36] Medication non-adherence may take multiple forms, including underdosing, overdosing, self-imposed drug holidays and taking medication that is not prescribed—all in the same patient. Currently, there is no gold standard used to measure MA though multiple methods are available, and include patient adherence questionnaires/diaries, assessing direct or indirect clinical response, performing pill counts, ascertaining rates of refilled prescriptions, and using electronic medication monitors.[37-42] Pill counts are relatively easy to perform, have been correlated

with electronic monitors, and have been frequently used in randomized, controlled clinical trials.[43-50] Recent clinical trials have used electronic devices, such as the Medication Event Monitoring System, which register the date and time when caps of medication bottles are removed.[14,44,51-53] Such devices have been shown to be valid instruments in measuring adherence in research settings, but are impractical to use when measuring adherence with multiple medications.[14,20,54]

A.8. Prior studies designed to improve adherence due to patient-dependent factors have not had a sustained effect in patients with HF.

Multiple interventions have been tested to improve MA; however, a systematic review by Haynes et al. found that most interventions studied in patients with HF did not have a large or sustained effect, and the ones that had any effect at all were complex and involved multiple disciplines.[16] Intervention trials in patients with HF have used counseling by a pharmacist, home nursing interventions, and extensive education programs.[50,53,55-66] Many of these interventions have shown improved MA, but the effect typically disappeared once the intervention was over.

A.9. Targeted interventions are more likely to be efficient and cost effective.

The existing studies have approached interventions to improve MA based on stratification on existing primary diagnosis (for example, HF, coronary disease or hypertension) rather than targeting specific determinants of non-adherence such as CI. In fact, many of the interventions tested in HF populations in prior studies were patient-action driven and therefore likely to fail in patients who have CI. The high prevalence of CI demonstrated in our recent study suggests that this may be an important contributing factor in MA in patients with HF. Unfortunately, there are few if any studies providing guidance on how to effectively improve MA in this vulnerable population. Traditional interventional strategies are not effective, or do not have a sustained effect, suggesting that new innovative methods are needed to improve outcomes.

We propose that interventions designed to improve MA by addressing underlying problems posed by CI are likely to be more effective and less costly as specific populations would be targeted to receive the appropriate level of intervention. An ideal intervention to improve MA in patients with CI would be technology-driven, easy to implement, sustainable in the long-term, and cost-effective. It would also be targeted at the specific cognitive domains affected in patients with HF such as learning and memory.

Based on Wu criteria for optimal adherence (the cutoff of adherence predicting event-free survival in outpatients with HF was 88%),[14] our findings suggest that the 74% adherence found in our patients with mild CI offers a rich target for intervention to improve outcomes to directly meet the CHF QUERI goals of reducing hospitalization rates, increasing use of care known to prolong survival and QOL, and empowering the patient for self-management.

B. Automated Medication Dispensing Device [AMDD].

One novel and promising technology is based on the use of the AMDD.[61,67] This device is designed to improve MA and target several cognitive domains of memory, attention (reminding the patient to take medications on time), fine motor skills, sequencing, processing speed (selecting and manipulating medication bottles) and executive functioning (helping patients to decide which pills they should take). This device is able to hold up to 60 doses of medications in pre-filled cups, to be programmed as needed based on the frequency of dosing. It is equipped with an alarm mechanism that alerts the patient to take the medications; when the patient pushes the button on the device, it will dispense the medications. If medications are not dispensed at the appropriate interval (within 90 minutes of the pre-set time), the patient and the study staff will receive an

automated phone call from a centralized monitoring center. The monitoring center will continue to ring the telephone until a dedicated button is pushed on the phone, indicating the call was received. The study staff will attempt to telephone the subject to remind them to take their medication; and to problem-solve as needed.

The AMDD will be set up in the subject's home, and training will be provided to the subject and family by study staff. The medication dispenser will be pre-filled with the subject's prescribed cardiac medications by a home health nurse once a month (home health nurse will be hired on a contract basis from the agency currently providing home care to patients at VALLHCS).

This device was selected for several reasons: 1) it targets the cognitive domains of memory, attention, sequencing, fine motor skills, processing speed, and executive functioning; 2) the locking mechanism promotes medication safety and prevents patient "overtaking" their medications (which was found to be a significant problem in our current study); 3) it provides means whereby patients with CI may be empowered to remain independently in their home; 4) the centralized monitoring system will add another aspect to the collectable adherence data (when and how many times the phone calls were prompted by missed doses); 5) it is programmable to prompt patients to take medications with food, to check their blood glucose level, use their inhaler, etc.; 6) it has an early-dispense feature to allow for planned doses if the subject is away from home; 7) it is in alignment with the VA's philosophy of utilizing commercially available, off-the-shelf technology; 8) it has the potential for future device modification to allow expanded use, such as collecting physical parameters (blood glucose, weight, blood pressure) and to tie in with the VA's commitment to health informatics, disease management, and care coordination/home telehealth so the veteran maintains independence.[68]

C.Specific Aims.

AIM 1. Feasibility.

Our purpose is to assess the feasibility of using the AMDD in veterans with HF and CI.

We powered the study to detect the "success rate" of the AMDD, defined as both patient acceptance and a clinical response to the AMDD. Clinical response is defined as a 9% increase in patient-level adherence and, alternatively, a 7% increase in medication-level adherence. The 9% and 7% represent, respectively, the adjusted mean differences in patient-level and medication-level adherence rates between patients with no CI and mild CI in our finished study.

Our specific aims will therefore be the following:

Aim 1A. Measure the percentage of patients with diagnosed HF who qualify for the AMDD based on our study inclusion/exclusion criteria (qualifying rate).

Aim 1B. Measure the percentage of qualified patients who agree to participate (consent rate).

Aim 1C. Measure the percentage of enrolled and consenting patients able to place the AMDD in their homes and use it appropriately (user rate).

Aim 1D (1). Measure the percentage of patients using the AMDD who have a positive clinical response to the AMDD over a one-month period (patient-level response rate).

Aim 1D (2). Measure the likelihood that the patient using the AMDD responds to the AMDD for a given medication over a one-month period (medication-level response rate).

Aim 1E. Measure the percentage of patients who both accept and respond to the AMDD (success rate).

AIM 2. Medication Adherence (exploratory analytical aim).

We will calculate the improvement of MA in patients with HF and CI who use the AMDD, based on a 30-day pill count following the introduction of the AMDD.

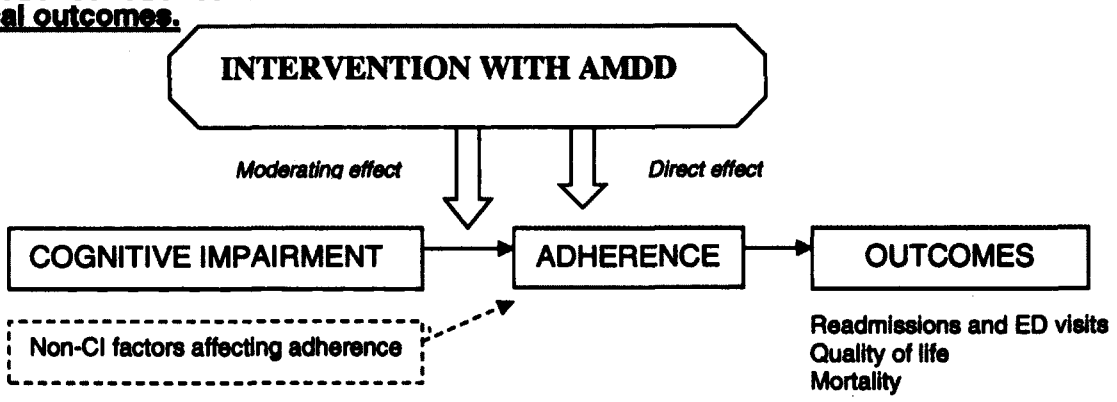
AIM 3. Medication Adherence (qualitative aim).

Aim 3A. Describe the reasons why enrolled patients were not able to use the AMDD.
Aim 3B. Describe patient satisfaction with the AMDD.
Aim 3C. Quantitatively describe the time spent to set up and fill the AMDD.

AIM 4. Clinical outcomes (exploratory aim).

Clinical outcomes, including readmissions for HF, are going to be important in any larger interventional study; we therefore included measurements of these outcomes in our pilot study for exploratory reasons.
Aim 4A. Measure changes in physical parameters, such as blood pressure, heart rate, and weight.
Aim 4B. Measure changes in clinical/functional outcomes, such as New York Heart Association (NYHA) functional class, serum B-type natriuretic peptide (BNP) levels, and diuretic usage.
Aim 4C. Measure changes in utilization (emergency department visits and hospitalizations).
The conceptual basis for our study is explained by the model presented below. This model shows CI as one of the factors associated with adherence, with adherence predicting clinical outcomes for HF such as readmissions, QOL, morbidity and mortality. We propose that an intervention with the AMDD in patients with CI and HF will target adherence directly, and also indirectly by having a moderating effect on the link between CI and adherence. This pilot study will measure a total effect and will not distinguish between moderating and direct effect.

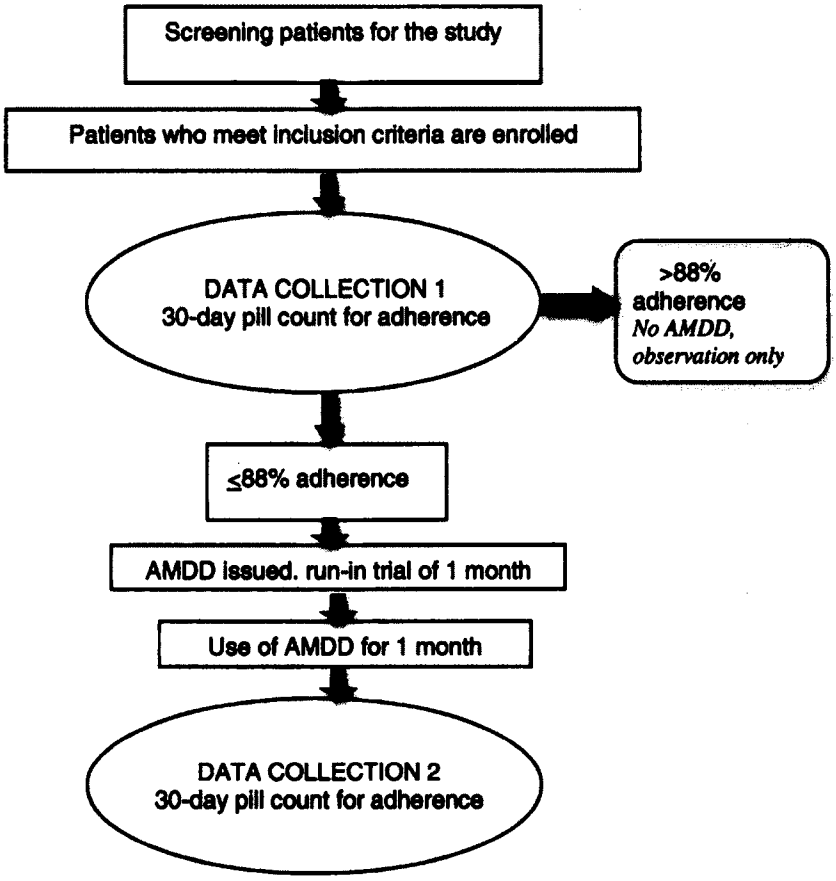
Figure 1. Model showing proposed levels of AMDD effect on adherence and clinical outcomes.



D. Research Design and Methods.

D.1. Study Design.
This study is designed as a feasibility study testing an intervention, with the subjects serving as their own controls. Figure 2 outlines the flowsheet describing the study design.
D.2. Study Setting.
The study will be conducted at the VALLHCS, Loma Linda, CA, which serves a population of 246,000 veterans. This is an urban setting with an ethnically mixed population.

Figure 2. Study flowsheet.



D.3. Study Population.

This study will enroll patients with HF and CI from outpatient HF clinic. If inclusion and exclusion criteria are satisfied, patients will be invited to participate, informed consent will be obtained, and patients will be enrolled.

Inclusion/Exclusion Criteria:

1. Outpatients with a diagnosis of HF supported by established criteria.
2. CI as measured by SLUMS and defined as a score of <27 in a person with high school education of <25 in a person with less than high school education.
3. English-speaking.
4. Age 18 or older.
5. Able to provide consent.
6. Able to provide a stable home environment for at least 90 days that will enable the use of the AMDD (i.e. electricity, stable surface to place the dispenser on, and telephone access).
7. Able to be trained on the use of the AMDD.
8. Stable on at least two standard HF medications for at least one month.

Exclusion Criteria:

1. Life expectancy < 6 months.
2. Patients whose medications are already administered by family members or a caregiver.

Projected enrollment is 5-6 subjects a month over nine months, for a total of 50 subjects.

Figure 2. Study flowsheet.

D.4. Data Collection.

D.4.a. Screening for CI.

SLUMS will be used to screen for CI and will be administered by HF clinic staff. The SLUMS exam is a brief screening measure to assess cognition.[69,70] This 30-point, 11-item clinician-administered interview scale was developed by researchers at the St. Louis VAMC and normed in a veteran population. It contains norms adjusted for patient education levels, and quantifies the level of impairment as none, mild, or impairment consistent with dementia, with the score of <27 considered to be consistent with CI in a person with high school education or <25 in a person with less than high school

education. A comparison study of the SLUMS exam with the well-known Mini-Mental Status Examination **[MMSE]** in veterans suggested that the SLUMS exam was superior to MMSE in detecting mild CI and impairment in executive functioning.[71-74]
Trained research staff administered the SLUMS exam to 250 subjects in our prior study; all subjects were able to complete the test with an average time of completion of 7.1 minutes (range 4-15). Similar to the MMSE, the SLUMS exam can also be administered by front-line clinicians. To demonstrate feasibility of screening using SLUMS in a busy clinic setting with a wide range of patients, we asked the RN and LVN staff in our clinic to use this tool to screen patients for CI during the check-in process. The staff was trained in a brief 15-minute inservice on how to accurately administer and score the SLUMS. The opportunity to administer the SLUMS exam was well received by the nursing staff; they noted that the time used to administer the SLUMS exam was equivalent to obtaining an accurate set of vital signs and checking VA clinical reminders. This exam was administered by the clinic nurses to 28 patients in an average of 7.2 minutes over the course of one week.

D.4.b. Other data collection.

During the initial interview, we will collect basic **demographic** data, such as the patient's gender, age, education level, living arrangement, and social support. **Physical parameters** collected at baseline and after the use of the AMDD include blood pressure (as measured by a standard manual cuff), heart rate (as measured by direct auscultation of the heart with a stethoscope), and weight (as measured by the same scale routinely used in the HF clinic). **Clinical/functional** data collected at baseline and after the use of the AMDD include NYHA class (as determined by a health care practitioner from patient interview),[2] BNP (standard lab test), and change in diuretic usage (determined by chart review).

D4.c. Quantitative data collection for feasibility.

As outlined in Aim 1, to test feasibility, we will measure the percentage of patients qualifying for the AMDD (qualifying rate), consenting to participate (consent rate), able to place the AMDD in their homes and use it appropriately based on the instructions (user rate).

D.4.d. Qualitative data collection for feasibility.

Patient, family member and home health nurse interviews will be used to describe the reasons for not being able to use the AMDD, and patient satisfaction with the AMDD. These interviews will be qualitative in nature and conducted by the investigators using an interview guide designed to capture participant decision-making and identify barriers to use of the AMDD. The interview guide questions will cover four topics based on the MacCat-CR Interview format: understanding, appreciation, reasoning, and expressing a choice. Interview results will be analyzed using open and axial coding.[75] We will also collect data on time spent to set up and fill the AMDD (average time per patient per month spent by the home health nurse).

D.5. Targeted intervention.

D.5.1. Baseline medication adherence.

Baseline MA to prescribed cardiac medications will be measured by a 30-day pill count. On study day one, subjects will bring in their medications for the initial pill count. They will continue with usual care, and return on study day 30 +/- 3 days for the baseline 30-day pill count.

D.5.2. Intervention with AMDD.

Only patients with MA $\leq$88% will continue with the AMDD part of the study, with the goal of 50 patients recruited to test AMDD. Based on data from our completed study, we estimate that we will need to recruit 80 subjects for the first pill count in order to arrive at

the goal of 50 subjects with MA of ≤88%. We chose to test the AMDD only in subjects with baseline impaired MA in order to ensure the effect of the intervention in a population that is most likely to benefit. Subjects selected to continue will be assigned the device to use for 60 days (one month to familiarize the study subjects with the device, one month to collect outcome data). The 30-day pill count will be repeated on study day 90.

D.6. Statistical Analysis.

Descriptive statistics include means, frequencies, variance, and simple correlations. To determine patients' response to the AMDD, we will define patient-level and medication-level adherence rates by taking the absolute difference between the amount of pills prescribed and amount of pills taken, as shown:

$$MA_{ij} = \left(\frac{|P_{ij} - T_{ij}|}{P_{ij}} \right), \qquad MA_i = \left(\frac{\sum_{j=1}^{n_i} |P_{ij} - T_{ij}|}{\sum_{j=1}^{n_i} P_{ij}} \right),$$

with MA_i as patient-level adherence for patient i over all cardiac medications, and MA_{ij} as medication-level adherence for subject i and cardiac medication $j=1, \ldots, n_i$, with $P_{ij} > 0$ pills prescribed and $T_{ij} \geq 0$ pills taken. This approach penalizes success whenever subjects either over-, or under-took a prescription. All rates (qualifying, consent, user rates and "success" rates will be computed and tested for significance based on a binomial distribution, and by bootstrapping 10,000 samples. Mean AMDD response rates will be captured from the constant term to Generalized Linear Models (patient-level) and Generalized Estimating Equations (medication-level) with robust standard errors and logit linking function to account for repeated medication-level nesting within patient. For exploratory analyses, mean centered covariates may be added to adjust rates to account for differences in medication class, patient demographic (age, ethnicity/race), and clinical factors (CI severity, illness duration).

Phone bank data from the centralized monitoring system will be used to establish and describe patterns of nonadherence (how many times did the patient need reminder calls; did the reminder calls have an identifiable pattern).

D.7. Power calculation.

Sample size power for n=50 was computed at 95% and 99% confidence intervals based on our pilot data (n=251) for three anticipated patient- and medication-level success rates and an estimated IntraClass Correlation = .414 with CI 95%[.368, .457], F(1315,1315) = 2.410, p<.001, and mean 5.23 cardiac meds/patient (SD=1.808). Estimates were computed from 100,000 parametric bootstrapped samples simulating study condition for 50 completed subjects, as reported below in Table 1. In summary, we can detect a 20% clinically relevant success rate in patient-level adherence with a two-tailed test at an alpha=.05 with 99% power.

Table 1. Expected Confidence Intervals for Anticipated Success Rate for 50 Subjects.

	20% Success Rate		*50% Success Rate*		*80% Success Rate*	
Medication-level adherence						
95% Confidence Interval	12.5%	28.1%	39.6%	60.4%	71.9%	87.5%

99% Confidence interval	10.4%	31.3%	36.5%	63.5%	68.8%	89.6%
Patient-level adherence						
95% Confidence Interval	10.0%	32.0%	36.0%	64.0%	68.0%	90.0%
99% Confidence Interval	6.0%	36.0%	32.0%	68.0%	64.0%	94.0%

D.8. Data Management.

All data will be double entered and checked for consistency, with inconsistencies resolved by the study coordinator and principal investigator [PI]. Data are entered into secure electronic password-protected files residing in the VA in a locked office, accessible only to approved study investigators and the study coordinator. To maintain patient privacy and confidentiality, data will be de-identified prior to statistical analysis by assigning subjects a study number. A linkage log relating subject name and last four digits of their social security number to the study number will be kept in a secure location in the HF clinic. After validation, de-identified data will be transferred to an SPSS format Research Ready file using our 3-part data accounting system designed to ensure data safety and security, ease of access, information integrity, efficiency of use, and accuracy and consistency of data interpretation.[76] All data will be processed on VA site, OI&T approved facilities through the VALLHCS Center for Advanced Statistics in Education.

D.9. Limitations.

The results of this study may not be generalizable to all patient groups with HF, specifically, nonveteran patients, women, or patients with clinically less severe HF who were not referred to HF clinic. Our study is limited by single center location, which may give rise to selection bias.

E. Research Context/Implementation Plan.

Contributing to the body of implementation science is an objective of the CHF QUERI's strategic plan, and in keeping with that objective, our research is designed to directly facilitate the implementation of evidence-based strategies known to improve outcomes in patients with HF. By addressing underlying CI, the AMDD could produce reliable and persistent improvements in MA in a population where traditional strategies have fallen short. This commercially available 'off the shelf' device, if found feasible, could be readily implemented into clinical practice to meet the immediate needs of the VA. However, in order for any novel intervention to be widely implemented by clinicians, effective case-finding to identify the population at risk is essential to improve outcomes and control costs. In order to identify cognitively impaired veterans more at risk for poor MA, a simple yet reliable screening tool for CI that can be used in clinical setting is of critical importance. We have shown that the SLUMS exam, which was developed by VA clinician/researchers and validated in a veteran population, may be quickly and accurately administered by front-line staff in a busy clinic setting. In addition, SLUMS provides a cut-off score to identify mild CI, which was shown to be sufficient to negatively impact MA in our pilot study.

The next goal will be to utilize results of this research to inform future studies examining whether early identification of, and intervention for, CI in patients with HF will result in improved adherence and outcomes. The future trial would test implementation of a range of multidisciplinary interventions, including the AMDD for select populations. The study design would include methods to identify which patients are more likely to benefit from which intervention since the adherence may be moderated by presence of factors other than CI. If future efforts show that targeted interventions are effective in improving

outcomes in HF patients with CI, it will provide impetus to implement screening for CI in HF management guidelines, and potentially change the current standard of practice. Finally, this approach to patients with CI is likely not unique to populations of patients with HF, and may be generalized to populations with other chronic illnesses, such as diabetes or hypertension. Thus we envision that the results from our studies examining patients with CI and HF can be used in the future in other large veteran populations.

F. Barriers and Facilitators.

As a feasibility study, our proposed research aims are designed to identify, both quantitatively and qualitatively, the practical issues that will need to be addressed during clinical implementation of the AMDD outside a research context. Health care barriers in implementing the intervention with AMDD include cost of the device, time spent by clinical staff and the availability of home health nursing. Patient barriers include living situation, social and cultural issues, willingness to use the device, and lack of family support. Formal evaluation of these barriers is built into our study design. Future barriers in implementing the screening for CI include time spent in clinic for screening, clinician awareness and clinician "buy-in" (whether the clinician is convinced that screening for CI will change the outcomes).

Formal analysis of direct and direct costs would be integral to future, larger trials; this pilot study will provide preliminary data about the costs of the intervention, as well as unforeseen barriers.

Possible facilitators to overcome barriers include seeking support of local and national VA administrators, enlisting local opinion leaders in raising clinicians' awareness of the problem, and familiarizing the clinicians with the data as outlined in the dissemination plan.

G. Evaluation plan/Dissemination.

We will evaluate the results of this study in light of published data prior to dissemination. Rogers' Diffusion of Innovation Theory suggests that new ideas are spread by individuals, largely by imitation.[1,77] We will utilize local opinion leaders at our facility as well as the CHF QUERI network to disseminate results of this pilot study. The results of this pilot trial will be presented at national cardiology meetings and published on the QUERI website. We also expect to publish a manuscript with the findings in a peer-reviewed cardiology journal to ensure wider dissemination of the data.

H. Project Management Plan.

H.1. Study Timeline.

Table 2. Gantt Chart for study timeline.

Activity	Month 1	Month 2-7	Month 8-10	Month 11-12
Preparation and submission of documents to IRB	------			
Hire/train study coordinator	------			
Preparation of study documents and database	------			
Enrollment of subjects		----------	----------	
Data collection		----------	----------	------
Data analysis				--------
Data presentation				--------
Write manuscripts				-----
Write final report				---

H.2. Resources Required.

This is a single center study and will be conducted at VALLHCS, utilizing existing space in the cardiology and research sections. The PI and co-PIs will have access to statistical resources and the library at the VALLHCS and at Loma Linda University.

The Philips medication dispenser will be contracted at the regular market rate of $85.00 for installation, and $75.00 per month for monitoring. We will not enter into any special financial arrangement with the Philips company to avoid financial conflict of interest, and to allow us to retain ownership of all data collected.

H.3. Research Team.

The project team is multidisciplinary and includes:

Principal Investigator (Name removed) MD, MPH is currently working as a staff cardiologist at VALLHCS. (Name removed) has been active in cardiology outcomes research with special interest in patients with atrial fibrillation and HF. As PI, she will be responsible for the study and will coordinate the work among the co-investigators and the study coordinator. She will oversee all the aspects of the study, including the regulatory aspects, patient recruitment, and adherence to the proper consent process, data collection and data management. She will be responsible for analyzing and interpreting the results of the study with the project team.

Co-Investigator Lee Ann Hawkins, RN, MSN, FNP is the HF Clinic nurse practitioner at the VALLHCS. She is pursuing her PhD and is active in HF research. As co-investigator, she will be responsible for the day-to-day aspects of the study, training the study coordinator and working closely with him or her to ensure that operations are performed according to schedule and according to study protocol. She will also fill in for the PI responsibilities when the PI is on vacation or not available.

Co-Investigator and Senior Research Consultant (Name removed), PhD is a Research Professor of Medicine at the Loma Linda University School of Medicine and Director of the Center for Advanced Statistics in Education at the VALLHCS. He is a well-published senior HSRD career scientist who will be involved in the design and analysis part of the study. As co-investigator, he will serve in an advisory capacity, based on his prior experience in multivariable analysis in numerous HSR&D research projects.

Co-Investigator and Senior Research Consultant (Name removed), MD, MS is currently the director of Diabetes Services at the VALLHCS. He has been PI or co-PI on numerous research projects. As co-investigator, he will serve in an advisory capacity, based on his prior experience in chronic diseases outcomes research.

Co-investigator (Name removed), PhD is a Neuropsychologist who conducts neuropsychological assessments for a variety of patients with cognitive disorders at VALLHCS and has prior research experience in the area of CI. She will serve in an advisory capacity to help interpret the results of this study and design future studies.

Study Staff, (Name removed), PharmD is currently working as the Research Pharmacist and Infectious Disease Clinical Pharmacist at the VALLHCS. He will serve in an advisory capacity in collecting and interpreting the pill count data.

The study coordinator will be hired prior to the start of the study. He or she will be responsible for screening potentially eligible patients for the study, collecting study data, coordinating the setup of the AMDD with the Philips company and with the home health nurse, coordinating and conducting appointments for labwork and performing pill counts. The study coordinator will receive alerted telephone calls from the Philips central monitoring station, and initiate calls to the subjects as appropriate. The study coordinator will also perform chart review with the supervision of the PI and co-PIs, assist with

preparation and maintenance of all regulatory documentation, and enter all clinical data to Excel database.

1. Heidenreich P. CHF QUERI Strategic Plan. 2009; http://www.queri.research.va.gov/about/strategic_plans/chf.pdf.
2. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol.* Apr 14 2009;53(15):e1-e90.
3. Lindenfeld J, Albert NM, Boehmer JP, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *J Card Fail.* Jun;16(6):e1-194.
4. Heidenreich PA. Patient adherence: the next frontier in quality improvement. *Am J Med.* Jul 15 2004;117(2):130-132.
5. DiMatteo MR, Giordani PJ, Lepper HS, Croghan TW. Patient Adherence and Medical Treatment Outcomes: A Meta-Analysis. *Medical Care.* 2002;40(9):794-811.
6. Esposito D, Bagchi AD, Verdier JM, Bencio DS, Kim MS. Medicaid beneficiaries with congestive heart failure: association of medication adherence with healthcare use and costs. *Am J Manag Care.* Jul 2009;15(7):437-445.
7. Fitzgerald AA, Powers JD, Ho PM, et al. Impact of medication nonadherence on hospitalizations and mortality in heart failure. *J Card Fail.* Aug;17(8):664-669.
8. Heisler M, Choi H, Rosen AB, et al. Hospitalizations and deaths among adults with cardiovascular disease who underuse medications because of cost: a longitudinal analysis. *Med Care.* Feb;48(2):87-94.
9. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation.* Jun 16 2009;119(23):3028-3035.
10. Hope CJ, Wu J, Tu W, Young J, Murray MD. Association of medication adherence, knowledge, and skills with emergency department visits by adults 50 years or older with congestive heart failure. *Am J Health Syst Pharm.* Oct 1 2004;61(19):2043-2049.
11. Mockler M, O'Loughlin C, Murphy N, et al. Causes and consequences of nonpersistence with heart failure medication. *Am J Cardiol.* Mar 15 2009;103(6):834-838.
12. Munger MA, Van Tassell BW, LaFleur J. Medication nonadherence: an unrecognized cardiovascular risk factor. *MedGenMed.* 2007;9(3):58.
13. Murray MD, Tu W, Wu J, Morrow D, Smith F, Brater DC. Factors associated with exacerbation of heart failure include treatment adherence and health literacy skills. *Clin Pharmacol Ther.* Jun 2009;85(6):651-658.
14. Wu JR, Moser DK, Chung ML, Lennie TA. Objectively measured, but not self-reported, medication adherence independently predicts event-free survival in patients with heart failure. *J Card Fail.* Apr 2008;14(3):203-210.
15. Delamater. Improving Patient Adherence. *Clinical Daibetes.* 2006 2006;23(2):71-71, 75-77.
16. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev.* 2008(2):CD000011.
17. George J, Elliott RA, Stewart DC. A systematic review of interventions to improve medication taking in elderly patients prescribed multiple medications. *Drugs Aging.* 2008;25(4):307-324.
18. Sabate E. Adherence to long-term therapies: evidence for action. *Geneva: WHO: World Health Organization.* 2003.

19. van der Wal MH, Jaarsma T. Adherence in heart failure in the elderly: problem and possible solutions. *Int J Cardiol.* Apr 10 2008;125(2):203-208.
20. Wu JR, Moser DK, Chung ML, Lennie TA. Predictors of medication adherence using a multidimensional adherence model in patients with heart failure. *J Card Fail.* Sep 2008;14(7):603-614.
21. Arlt S, Lindner R, Rosler A, von Renteln-Kruse W. Adherence to medication in patients with dementia: predictors and strategies for improvement. *Drugs Aging.* 2008;25(12):1033-1047.
22. Cotrell V, Wild K, Bader T. Medication management and adherence among cognitively impaired older adults. *J Gerontol Soc Work.* 2006;47(3-4):31-46.
23. Hayes TL, Larimer N, Adami A, Kaye JA. Medication adherence in healthy elders: small cognitive changes make a big difference. *J Aging Health.* Jun 2009;21(4):567-580.
24. Sauve MJ, Lewis WR, Blankenbiller M, Rickabaugh B, Pressler SJ. Cognitive impairments in chronic heart failure: a case controlled study. *J Card Fail.* Feb 2009;15(1):1-10.
25. Bennett SJ, Sauve MJ. Cognitive deficits in patients with heart failure: a review of the literature. *J Cardiovasc Nurs.* Jul-Aug 2003;18(3):219-242.
26. Clark AP, McDougall G. Cognitive impairment in heart failure. *Dimens Crit Care Nurs.* May-Jun 2006;25(3):93-100; quiz 101-102.
27. Cohen MB, Mather PJ. A review of the association between congestive heart failure and cognitive impairment. *Am J Geriatr Cardiol.* May-Jun 2007;16(3):171-174.
28. Lackey J. Cognitive impairment and congestive heart failure. *Nurs Stand.* Jul 14-20 2004;18(44):33-36.
29. Pressler SJ. Cognitive functioning and chronic heart failure: a review of the literature (2002-July 2007). *J Cardiovasc Nurs.* May-Jun 2008;23(3):239-249.
30. Pullicino PM, Wadley VG, McClure LA, et al. Factors contributing to global cognitive impairment in heart failure: results from a population-based cohort. *J Card Fail.* May 2008;14(4):290-295.
31. Vogels RL, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: a systematic review of the literature. *Eur J Heart Fail.* May 2007;9(5):440-449.
32. Zuccala G, Cattel C, Manes-Gravina E, Di Niro MG, Cocchi A, Bernabei R. Left ventricular dysfunction: a clue to cognitive impairment in older patients with heart failure. *J Neurol Neurosurg Psychiatry.* Oct 1997;63(4):509-512.
33. Pressler SJ, Subramanian U, Kareken D, et al. Cognitive deficits in chronic heart failure. *Nurs Res.* Mar-Apr 2010;59(2):127-139.
34. Silvet H HL. Cognitive Impairment as a Risk for the Admission-Readmission Cycle seen in Veterans with Heart Failure. 2010.
35. Cutler DM, Everett W. Thinking outside the pillbox--medication adherence as a priority for health care reform. *N Engl J Med.* Apr 29 2010;362(17):1553-1555.
36. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med.* Aug 2005;353(5):487-497.
37. Christensen DB, Williams B, Goldberg HI, Martin DP, Engelberg R, LoGerfo JP. Assessing compliance to antihypertensive medications using computer-based pharmacy records. *Med Care.* Nov 1997;35(11):1164-1170.
38. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther.* Jun 1999;21(6):1074-1090; discussion 1073.
39. Gehi AK, Ali S, Na B, Whooley MA. Self-reported medication adherence and cardiovascular events in patients with stable coronary heart disease: the heart and soul study. *Arch Intern Med.* Sep 10 2007;167(16):1798-1803.
40. Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. *J Clin Epidemiol.* May 1997;50(5):619-625.

41. Smith H, Hankins M, Hodson A, George C. Measuring the adherence to medication of elderly patients with heart failure: Is there a gold standard? *Int J Cardiol.* Jul 15 2009.
42. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol.* Jan 1997;50(1):105-116.
43. Botelho RJ, Dudrak R, 2nd. Home assessment of adherence to long-term medication in the elderly. *J Fam Pract.* Jul 1992;35(1):61-65.
44. Choo PW, Rand CS, Inui TS, et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Med Care.* Sep 1999;37(9):846-857.
45. Friedman RH, Kazis LE, Jette A, et al. A telecommunications system for monitoring and counseling patients with hypertension. Impact on medication adherence and blood pressure control. *Am J Hypertens.* Apr 1996;9(4 Pt 1):285-292.
46. Grymonpre RE, Didur CD, Montgomery PR, Sitar DS. Pill count, self-report, and pharmacy claims data to measure medication adherence in the elderly. *Ann Pharmacother.* Jul-Aug 1998;32(7-8):749-754.
47. Laporte S, Quenet S, Buchmuller-Cordier A, et al. Compliance and stability of INR of two oral anticoagulants with different half-lives: a randomised trial. *Thromb Haemost.* Mar 2003;89(3):458-467.
48. Lee JK. How should we measure medication adherence in clinical trials and practice? *Ther clin risk manag.* Aug 2007;3(4):685-690.
49. Marquez-Contreras E, Martell-Claros N, Gil-Guillen V, et al. Efficacy of a home blood pressure monitoring programme on therapeutic compliance in hypertension: the EAPACUM-HTA study. *J Hypertens.* Jan 2006;24(1):169-175.
50. Rich MW, Gray DB, Beckham V, Wittenberg C, Luther P. Effect of a multidisciplinary intervention on medication compliance in elderly patients with congestive heart failure. *Am J Med.* Sep 1996;101(3):270-276.
51. Cramer JA. Microelectronic systems for monitoring and enhancing patient compliance with medication regimens. *Drugs.* Mar 1995;49(3):321-327.
52. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. *JAMA.* Jun 9 1989;261(22):3273-3277.
53. Murray MD, Young J, Hoke S, et al. Pharmacist intervention to improve medication adherence in heart failure: a randomized trial. *Ann Intern Med.* May 15 2007;146(10):714-725.
54. Wu JR, Moser DK, De Jong MJ, et al. Defining an evidence-based cutpoint for medication adherence in heart failure. *Am Heart J.* Feb 2009;157(2):285-291.
55. Naylor MD, Brooten D, Campbell R, et al. Comprehensive discharge planning and home follow-up of hospitalized elders: a randomized clinical trial. *JAMA.* Feb 17 1999;281(7):613-620.
56. Naylor MD, Brooten DA, Campbell RL, Maislin G, McCauley KM, Schwartz JS. Transitional care of older adults hospitalized with heart failure: a randomized, controlled trial. *J Am Geriatr Soc.* May 2004;52(5):675-684.
57. Schnipper JL, Roumie CL, Cawthon C, et al. Rationale and design of the Pharmacist Intervention for Low Literacy in Cardiovascular Disease (PILL-CVD) study. *Circ Cardiovasc Qual Outcomes.* Mar;3(2):212-219.
58. Anderson C, Deepak BV, Amoateng-Adjepong Y, Zarich S. Benefits of comprehensive inpatient education and discharge planning combined with outpatient support in elderly patients with congestive heart failure. *Congest Heart Fail.* Nov-Dec 2005;11(6):315-321.
59. Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *N Engl J Med.* Nov 2 1995;333(18):1190-1195.
60. Coleman EA, Parry C, Chalmers S, Min SJ. The care transitions intervention: results of a randomized controlled trial. *Arch Intern Med.* Sep 25 2006;166(17):1822-1828.

61. Coleman EA, Smith JD, Frank JC, Min SJ, Parry C, Kramer AM. Preparing patients and caregivers to participate in care delivered across settings: the Care Transitions Intervention. *J Am Geriatr Soc.* Nov 2004;52(11):1817-1825.
62. Hansen RA, Dusetzina SB, Song L, Gaynes BN, Tu W, Murray MD. Depression affects adherence measurement but not the effectiveness of an adherence intervention in heart failure patients. *J Am Pharm Assoc (2003).* Nov-Dec 2009;49(6):760-768.
63. Laramee AS, Levinsky SK, Sargent J, Ross R, Callas P. Case management in a heterogeneous congestive heart failure population: a randomized controlled trial. *Arch Intern Med.* Apr 14 2003;163(7):809-817.
64. Peters-Klimm F, Muller-Tasch T, Schellberg D, et al. Rationale, design and conduct of a randomised controlled trial evaluating a primary care-based complex intervention to improve the quality of life of heart failure patients: HICMan (Heidelberg Integrated Case Management). *BMC Cardiovasc Disord.* 2007;7:25.
65. Powell LH, Calvin JE, Jr., Mendes de Leon CF, et al. The Heart Failure Adherence and Retention Trial (HART): design and rationale. *Am Heart J.* Sep 2008;156(3):452-460.
66. Rondinini L, Coceani M, Borelli G, et al. Survival and hospitalization in a nurse-led domiciliary intervention for elderly heart failure patients. *J Cardiovasc Med (Hagerstown).* May 2008;9(5):470-475.
67. Philips. Phillips Automated Medication Dispenser Website. [Web Page]. 2010; http://www.managemypills.com/content/How_PMD_Works.
68. Darkins A, Ryan P, Kobb R, et al. Care Coordination/Home Telehealth: the systematic implementation of health informatics, home telehealth, and disease management to support the care of veteran patients with chronic conditions. *Telemed J E Health.* Dec 2008;14(10):1118-1126.
69. Banks WA, Morley JE. Memories are made of this: recent advances in understanding cognitive impairments and dementia. *J Gerontol A Biol Sci Med Sci.* Apr 2003;58(4):314-321.
70. Morley JE TN. Saint Louis University Mental Status Examination (SLUMS). *Aging Successfully.* 2002;XII.
71. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* Nov 1975;12(3):189-198.
72. Juby A, Tench S, Baker V. The value of clock drawing in identifying executive cognitive dysfunction in people with a normal Mini-Mental State Examination score. *CMAJ.* Oct 15 2002;167(8):859-864.
73. Shulman KI. Clock-drawing: is it the ideal cognitive screening test? *Int J Geriatr Psychiatry.* Jun 2000;15(6):548-561.
74. Tariq SH, Tumosa N, Chibnall JT, Perry MH, 3rd, Morley JE. Comparison of the Saint Louis University mental status examination and the mini-mental state examination for detecting dementia and mild neurocognitive disorder--a pilot study. *Am J Geriatr Psychiatry.* Nov 2006;14(11):900-910.
75. Appelbaum PS G, T. *MacCAT-CR: MacArthur Competence Assessment Tool for Clinical Research.* Sarasota, FL: Professional Resource Press; 2001.
76. Kashner TM, Hinson R, Holland GJ, et al. A data accounting system for clinical investigators. *J Am Med Inform Assoc.* Jul-Aug 2007;14(4):394-396.
77. Rogers E. *Diffusion of Innovations.* New York: Free Press; 2004.

Title Page

Title: Health literacy and use of a pictorial medication sheet to improve adherence.

Short title: Health Literacy and Medication Adherence

Article Type: Research Paper

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Submission includes:
Abstract: 207 words
Keywords: 5
Abbreviation list
Text: 15 pages
3 Tables
2 Figures
38 References

Disclosures: No disclosures

Funding support: VA CHF QUERI pilot grant: RRP 12-198

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Abstract

Background: Interventions to increase medication adherence are needed to improve heart failure (HF) outcomes. A recently completed study tested a pictorial medication sheet to improve adherence in veterans with HF and cognitive impairment. While health literacy (HL) scores were not collected as part of that study, they were part of the patient medical records. This new data-based study examines potential mediating effects of HL on observed medication adherence in that study.

Objectives: (a) describe the level of HL, (b) determine relationships between HL and selected clinical and demographic variables, and (c) estimate the relationships between HL, key variables, and medication adherence in the study sample.

Methods: In a secondary analysis, HL scores from medical records were analyzed with data from the original pilot study using conventional statistics and structural equation modeling.

Results: 27 subjects with a mean age of 65.3 years (SD 8.2, range 45-80) had evaluable data. HL was less than adequate in 19% of the sample. HL scores were strongly correlated with cognition. HL did not significantly affect relationships between study covariates (cognition scores, depression, number of medications) and medication adherence.

Conclusions: HL scores are associated with cognitive function scores. More research is needed to evaluate the prevalence and effect of poor HL on medication adherence in veterans with HF.

Key Words: Medication non-adherence, cognitive dysfunction, veterans, heart failure, health literacy

Abbreviations:

CI: Cognitive Impairment
HF: Heart Failure
HL: Health Literacy
IRB: Institutional Review Board
NYHA: New York Heart Association
RMSEA: Root Mean Square Error of Approximation
SEM: Structural equation modeling
SLUMS exam: Saint Louis University Mental Status examination
VA: Veteran's Health Care Administration

Introduction

Heart failure (HF) is an epidemic confronting the American healthcare system; currently 5.8 million people in the United States have HF, and this number is projected to grow as the population ages.[1-3] HF presents as a complex chronic disease characterized by frequent exacerbations often resulting in emergency department visits and hospital readmissions. This excessive admission-readmission cycle is costly in terms of poor patient outcomes as well as healthcare expenditures, particularly within the Veterans' Health Care System (VA), the largest integrated healthcare system in the United States. Within the VA, 20% of HF patients are readmitted within 30 days, contributing to the total annual cost estimates of over $37 billion for HF care in the United States.[4] The majority of HF readmissions are related to medication non-adherence and are therefore preventable.[5-9] Thus identification of and intervention for factors contributing to poor medication adherence is key to reducing readmissions and improving outcomes.[10, 11]

Factors related to poor medication adherence

Adherence is a complex issue and may be conceptualized as one of the dynamic and multidimensional activities that comprise self-care. Self-care is particularly important in a chronic illness such as HF that is primarily managed at home by the patient him or herself. Conceptual frameworks and theoretical models describe HF self-care as an iterative process requiring a series of thoughtful decisions on the part of the patient.[12, 13] Factors that affect decision making such as difficulty in understanding and remembering directions, or the presence of depression, impair the patient's ability to engage in successful self-care.[12, 13] The capability to make appropriate decisions is especially critical in negotiating the complex medication regimen HF patients are often required to follow. Because HF is primarily a disease of the elderly and presents with co-morbid illnesses, this complexity is compounded by polypharmacy prescribed by multiple providers, and the fact medications are subject to change with each hospital readmission. [8-12]

One important, yet clinically under-recognized factor affecting a patient's ability to correctly take medication is the presence of cognitive impairment (CI). It is clinically intuitive that impairment in cognitive domains such as memory, verbal fluency, attention, motor speed, and executive functioning (e.g. higher-order capacities such as planning and problem-solving) would negatively affect a person's ability to correctly obtain and take medications.[14, 15] CI has been shown to be a prevalent co-morbid condition in outpatients with HF, who may have a four-fold risk of developing CI compared to the general population.[15-17] A recent study of outpatient veterans with HF demonstrated a high prevalence (58%, n=251) of clinically unrecognized CI that was significantly associated with poorer medication adherence.[14]

Another factor commonly associated with non-adherence to medication is poor health literacy (HL), broadly defined as the degree to which individuals obtain and understand basic information in order to make appropriate decisions and negotiate the healthcare system to manage their well-being.[18] In America, low HL is considered to be a prevalent and clinically under-recognized problem in the general population; up to 57% of patients with HF may have poor HL.[18-21] One study assessed HL in 1,786 veterans and reported a lower prevalence of poor HL than is generally described in the civilian population; specifically 8.3% of subjects had inadequate and 11.8% had marginal HL skills.[22] However, little is known about the prevalence of poor HL in veterans with HF, or the effect of HL on medication adherence in cognitively impaired veterans with HF.

Depression is yet another condition that has been associated with less than adequate self-care, and worsened outcomes such as hospital readmissions and mortality, in persons with HF.[23, 24] Studies have shown depression to be common in persons with HF, with prevalence rates conservatively estimated at about 26%, or 2 to 3 times higher than in the general population. [24] Although examining the effect of depression on HF outcomes has received increasing attention in the literature, this condition often remains clinically under-recognized. [23, 24] For example, in a study of 250 veterans with HF, the average subject was found to be mildly depressed, yet only 30% of the sample had been formally diagnosed.[14]

Interventions to Improve Adherence

Unfortunately there remains a general lack of awareness on the part of providers, as well as no incentive in the current model of healthcare, to screen elderly HF patients at risk for poor medication adherence at clinic visits.[25, 26] Interventions to improve adherence that rely on traditional models of patient education are likely to fail in this population. There is a paucity of tested interventions designed to improve outcomes by targeting key determinants of poor adherence such as CI and poor HL.[25, 27] Interventions that have shown improvement in adherence to date were complex and did not result in sustainable outcomes.[28-30]

Cognitive impairments such as impaired memory and verbal fluency are associated with poor HL and are commonly found in elderly persons with HF. [31] Indeed, the close association of poor HL with CI has received increased attention in the literature; a recent study proposed that current measures of HL are actually rudimentary assessments of cognition.[32] Hence, interventions to improve adherence in patients with low HL should also reduce demands on cognitive abilities. The commonly accepted view that simply utilizing 8th-grade language and a few illustrations for health information will not help low-literacy patients if the pictures must be mentally integrated to be understood.[19, 28]

As a first step to address this gap, a pilot study (TARGET) was designed to target CI as an underlying cause of medication non-adherence. The TARGET study enrolled 36 subjects with known CI from an outpatient veteran HF clinic and tested the effectiveness of a customized pictorial medication sheet along with an optional alarmed pillbox to improve medication adherence.[33] The primary outcome, medication adherence, was measured from sequential direct 30-day pill counts, using subjects as their own controls.

Secondary outcomes included feasibility and tolerability determined by qualitative interviews.

A major limitation in the TARGET study was that no information on HL was collected as part of the study itself. HL may actually have mediated the relationship between key independent variables (including the intervention) and the outcome measure of medication adherence.

Therefore the purpose of this study was to estimate the relationships between participant's HL scores (obtained from the medical record), and key variables, including the outcome, medication adherence, using data obtained from the TARGET study. The specific aims of this study included:

Aim 1. Describe the level of HL in the study population.

Aim 2. Determine the strength and direction of relationships between HL and selected clinical and demographic variables in the study population.

Aim 3. Determine the direct and indirect effects that HL and other key variables (including the intervention) on post intervention medication adherence in cognitively impaired veteran outpatients with HF.

Methods

The study employed a retrospective, correlational, cross-sectional design using data from the completed TARGET pilot study and the participants' medical records. Approval was obtained from the institutional review board (IRB) prior to data collection. The data were de-identified prior to analysis. The TARGET study was conducted at a large metropolitan Veteran's Administration facility that serves an urban population of 246,000 veterans in southern California.

Sampling Procedure

The sample included subjects (n=36) from the TARGET pilot study. These subjects were originally recruited as a convenience sample from an outpatient VA medical center HF clinic between November 2011 and June 2012. All were 18 years old or older, had an established clinical diagnosis of HF, and had screened positive for CI using the Saint Louis University Mental Status (SLUMS) exam [34] prior to entrance into the study. SLUMS is an education-adjusted, 30-point clinician-administered screen for CI that has been validated in a veteran population and shown to be more sensitive to detecting mild CI than the more familiar MMSE. [35,36]

In order to participate in testing the pictorial medication sheet and alarmed pillbox, participants were required to speak and read English, follow simple directions, be able to see, and have the manual dexterity to take their own medications. Thus, persons with severe functional limitations, acutely decompensated HF, dementia requiring a caregiver, or severe mental illness, such as active schizophrenia, were excluded. Subjects were also excluded if they had a life expectancy of less than six months. The TARGET study was designed as a pilot study to test feasibility and effectiveness of the intervention. Thus, no power analysis was conducted.

Data Collection Procedures

For this current study, subject's data were retrospectively obtained from the TARGET study data and the electronic medical record, and placed into a database with all personal identifiers removed. This database was compiled by the investigator and audited for completeness and veracity by another researcher. The new database included HL scores from the subject's medical record and medication adherence scores,

demographic, and clinical data from the TARGET study. Demographic data included age, gender, race, living arrangements (alone or with others), and educational level. Clinical data included the presence of comorbid depression, participant's SLUMS score, and number of prescribed medications. These demographic and clinical data were selected as having potential influence on medication adherence in the study sample, based on review of relevant literature. Subject ID numbers were assigned sequentially, and all data was subsequently de-identified.

Details of the TARGET study have been reported elsewhere, but are summarized here for relevance to the current investigation.[33] The TARGET study consisted of four study visits. Subjects were enrolled during a routine visit to the investigator's clinic. At study visit one, subjects were asked to bring in all their regularly prescribed medications for a pill count. Subjects returned in approximately 30 days for visit two. At visit two, a repeat pill count was performed to determine baseline adherence. During this visit the subject received a customized pictorial medication sheet consisting of images of their current medications in full color and dose range (i.e. the image showed two and one-half tablets if they were to take two and one-half tablets) in columns for morning, noon, and evening. Brief descriptions of the medication name, indication and dose were also included. A sample medication sheet is displayed in Figure 1. Subjects were also offered an optional CADEX Pocket Pill Box (ePill LLC) with 4 vibrating daily alarms. Subjects returned for repeat 30-day pill counts at visit three (giving them a month to adjust to the intervention), and visit four, to determine their post-intervention adherence. At each visit the subject had a brief physical exam and New York Heart Association (NYHA) functional class determined by the investigator. Qualitative data regarding the feasibility

and acceptability of the intervention were collected in patient interviews at each visit using standardized questions.

Measures

In the current study, data related to HL were derived from participants' scores on the Short Test of Functional Health Literacy for Adults (S-TOFHLA) documented in the medical record.[37] This instrument was derived from the longer Test of Functional Health Literacy for Adults (TOFHLA) designed to assess the ability to perform basic reading and numerical tasks in a healthcare setting.[38] The S-TOFHLA has been shown to be valid, reliable, and easily administered in a clinical setting.[37] The S-TOFHLA includes a timed (7 minute) reading comprehension test using the modified Cloze procedure; the patient reads common medical instructions that have every 5th to 7th word in a passage omitted and is asked to select a word from 4 multiple-choice options to fill in the blank spaces. Possible scores range from 0-36, with 0-16 scored as "inadequate", 17-22 "marginal" and 22-36 "adequate" health literacy [37, 38] In addition, the S-TOFHLA includes a 17-item, timed (10 minute) numeracy subscale that tests the practical ability of patients to comprehend medication prescription labels, results of blood glucose tests, clinic appointment slips, and financial assistance for healthcare information. The numeracy subscale is scored in a weighted manner according to the test manual to create a final score ranging from 0-50.[38] These HL measures had been administered to patients in the HF clinic as part of usual care since January 2011, and scores recorded on progress notes maintained in the VA electronic medical record. There is no evidence in the literature that HL scores as assessed by S-TOFHLA change over time.

As background, the data on the dependent variable for this study, medication adherence score, was obtained for each prior study subject from their post-intervention 30-day pill count collected as part of the prior TARGET study. The TARGET study medication adherence scores were determined in the following manner: to capture both overtaking and undertaking medication, a delta was determined for each prescribed medication by computing the absolute difference between the number of pills taken versus the prescribed number over the 30-day period for each pill count. The delta values for each medication were summed for each individual subject, divided by the total number of pills prescribed, subtracted from 1, and finally multiplied by 100 to obtain an adherence score expressed as a percentage. Thus, a value of 100% indicated all pills were taken correctly. A value of 85% meant that 15% of prescribed pills were either not taken, or overtaken, or a combination of both. All currently prescribed medications were included in the pill counts, except medications taken on an "as needed" (prn) basis, injectables, and inhaled medications. Over-the-counter medications were also excluded.

Statistical Analysis

Data analysis was performed using Statistical Package for the Social Sciences v. 20 (SPSS) (IBM Corporation) and *M*plus v.7 software (*M*plus, 2012). A *p*-value of .05 or less was determined as significant. Frequency distributions for each variable were examined for normal distribution characteristics, missing data, and outliers.

Descriptive statistics, including measures of central tendency and frequency, were employed to address study aim one. Study aim two was explored using bivariate correlational tests appropriate to the level of measurement (e.g. Spearman's rho for ordinal data and Pearson's *r* for interval or ratio level data). To achieve aim three,

structural equation modeling (SEM), specifically a path mediation model, was utilized for analysis.

Results

Study characteristics. Thirty-six (36) subjects were enrolled in the TARGET study. Of these, two subjects died before completing the study; one subject was hospitalized for a prolonged period and was not able to return in a timely manner for study visits; one subject dropped out due to transportation issues; three subjects had unusable adherence data (they attended all study visits but did not bring in medication consistently enough to be counted); and two simply did not return for scheduled study visits despite repeated telephone and written messages asking them to do so. Thus, 27 subjects completed the study with usable data; 26 (96%) were male, with an average age of 65.3 years (SD 8.2, range 45-80). Baseline characteristics of the study sample are presented in Table 1.

Prevalence of poor HL. The mean reading HL (S-TOFHLA) score for the sample was 29.92 (n=26, SD 7.27, range: 15-36) and the mean numeracy HL score was 43.40 (n=27, SD 9.36, range 15-50). Specifically, 19.2% of the entire sample had less than adequate HL (S-TOFHLA score <23). Only one subject did not complete the reading HL instrument and therefore this was treated as missing data with no imputations for the analysis.

Correlational analysis. The strength and direction of relationships between reading HL, numeracy HL, and demographic and clinical variables were explored as shown in Table 2. Few significant relationships were found in this study. Specifically, age was negatively associated to both reading HL ($r = -.407$, $p < .05$) and numeracy HL

($r = -.499, p < .05$). This suggests a moderate contribution of age to the variability in HL scores (r^2 values of .16 and .25, respectively). SLUMS exam scores were strongly associated with both reading HL ($r = .804, p < .01$) and numeracy HL ($r = .545, p < .01$). This suggests a moderate to strong contribution of cognition to the variability of health literacy scores (r^2 values of .65 and .30, respectively).

Structural equation model. A path mediation model was constructed after a set of preliminary analyses including descriptive data examination for outliers, missing data and non-normality were conducted. Three exogenous covariates chosen for the model were based on review of relevant literature and included SLUMS score, number of prescribed medications, and history of depression. Reading and numeracy HL scores were hypothesized to mediate the effects of the covariates on the dependent endogenous variable, medication adherence.

Analysis of post-intervention data using the path model revealed that path coefficients were in the hypothesized direction. SLUMS score was associated with reading HL (standardized coefficient 4.995, $p = 0.000$) and numeracy HL (standardized coefficient 3.842, $p = 0.000$); history of depression was negatively associated with numeracy HL (standardized coefficient -2.513, $p = 0.012$); and the number of prescribed medications had a direct, negative association with medication adherence (standardized coefficient -2.515, $p = 0.012$). Model fit was evaluated and found to be acceptable by Chi-square (0.755, df 1, $p = 0.385$) and a Root Mean Square Error of Approximation (RMSEA) estimate of 0.000, 90% CI 0.000 -0.473, and probability of RMSEA <= .05: 0.430. The path model is presented in Figure 2.

An attractive aspect of path modeling is the ability to estimate indirect, or mediating, effects as well as direct and total effects among variables. In relation to study aim number three, Table 3 presents the estimated indirect effects of HL scores for the covariates on post-intervention medication adherence. Neither reading nor numeracy HL scores reached statistical significance as mediating the effects of SLUMS score (p = 0.459 and 0.604, respectively), history of depression (p = 0.862 and 0.608, respectively), or number of medications (p = 0.575 and 0.716, respectively) on medication adherence.

Discussion

This study had three important findings: (1) The prevalence of poor HL in the study sample was lower than generally described in the civilian population, (2) cognitive function was strongly correlated with measures of HL, and (3) HL did not mediate the outcome of medication adherence in the interventional TARGET pilot study.

We found HL to be less than adequate in 19% of our study sample, which is strikingly similar to the 20% reported by Griffin in a study of over 1700 veterans (not limited to those with HF). [22] Poor HL in the general population with HF has been reported to be as high as 57%.[21] Further study is warranted to better understand the prevalence of poor HL in veterans with HF.

Our finding that the subjects' cognitive scores strongly correlated with HL scores is supported by current trends in the literature. For example, the cognitive domains of memory and verbal fluency were related to HL in a study of 414 older community-dwelling adults. [31] Intriguingly, these two domains were found to be the most affected in a study of veterans with HF and CI.[14] In the LitCog study (n=882), associations between poor HL and performance of healthcare tasks diminished once cognitive ability was

controlled for, and the authors concluded that measures of HL actually identified differences in cognition.[32] This study is one of the first to examine the effect of HL on an intervention to improve adherence that was modified to address patient's cognitive limitations.

The finding that HL did not mediate the effect of the covariates CI, depression, and number of medications, on medication adherence in the TARGET study is not surprising for several reasons. Foremost, the TARGET interventional medication sheet was not specifically designed to address poor HL, although it does incorporate medication images with simple text. Next, the low prevalence of poor HL in the study sample may have affected the outcome. Finally, there may be covariates other than the three chosen for analysis that may have had a stronger interaction with poor HL.

Implications for Practice

It is important for clinicians to identify those patients at risk for poor medication adherence so that extra resources may be allocated to help them. This risk profile will need to be tailored to individual patient populations, and include screening for prevalent conditions that have been shown to contribute to poor adherence in that particular population. For the busy clinician screening HF patients for CI and depression may have better yield than trying to screen for poor HL. The design of future interventions to improve adherence should take into account all the cognitive demands placed on the patient rather than simply skills in reading and numeracy.

Strengths and Limitations of Methods

There are important limitations to this research design. The sample size is small, drawn from a pilot feasibility study, and was selected as a convenience sample from the

investigator's HF population of predominantly elderly Caucasian male veterans from an urban southern California VA medical center. The VA system offers ready access to prescription medication coverage. Therefore, the results may not be readily generalized to other populations. There is no data available to know if HL scores obtained from the S-TOFHLA instrument and recorded in the past medical record would change over time. Finally, the study sample size was theoretically inadequate for full SEM analysis. Although not a panacea for low sample size, the bootstrapping option (as was done in this study) may be employed for exploratory analysis. Indeed, we did run our path analysis with an additional 500 bootstrapping sample iterations, and did not find substantial differences in the significance testing.

Conclusions

Consistent with the current literature, the prevalence of poor HL in our sample population of veterans with HF and CI was lower than generally found in the civilian population; and HL scores were found to be strongly associated with cognitive function scores. HL did not mediate the effect of key variables on the outcome, medication adherence. More research is needed to evaluate the prevalence and effect of poor HL upon adherence in veterans with HF and CI.

References

1. Lindenfeld J, Albert NM, Boehmer JP, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *J Card Fail* 2010;16:e1-194.

2. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics-2010 update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2010;121:e1-e170.

3. Population Resource Center. *Aging of America.* Available at: http://prcdc.org/300million/The_Aging_of_America/

4. Heidenreich P. CHF QUERI 2011 Strategic Plan. 2011. Available at: http://www.queri.research.va.gov/about/strategic_plans/chf.pdf

5. Albert NM. Improving medication adherence in chronic cardiovascular disease. *Crit Care Nurse* 2008; 5:54-64.

6. Esposito D, Bagchi AD, Verdier JM, Bencio DS, Kim MS. Medicaid beneficiaries with congestive heart failure: association of medication adherence with healthcare use and costs. *Am J Manag Care* 2009;15:437-445.

7. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation* 2009;119:3028-3035.

8. Munger MA, Van Tassell BW, LaFleur J. Medication nonadherence: an unrecognized cardiovascular risk factor. *MedGenMed* 2007;9:58.

9. Murray MD, Tu W, Wu J, Morrow D, Smith F, Brater DC. Factors associated with exacerbation of heart failure include treatment adherence and health literacy skills. *Clin Pharmacol Ther* 2009;85:651-658.

10. Fitzgerald AA, Powers JD, Ho PM, et al. Impact of medication nonadherence on hospitalizations and mortality in heart failure. *J Card Fail* 2011;17:664-669.

11. Heidenreich PA. Patient adherence: the next frontier in quality improvement. *Am J Med* 2004;117:130-132.

12. Moser DK, Watkins JF. Conceptualizing self-care in heart failure: A life course model of patient characteristics. *J Cardiovasc Nurs* 2008;23:205-218.

13. Riegel B, Dickson VV. A situation-specific theory of heart failure self-care. *J Cardiovasc Nurs* 2008; 23:190-196

14. Hawkins LA, Kilian S, Firek A, Kashner TM, Firek, CJ, Silvet H. (in press). Cognitive impairment and medication adherence in outpatients with heart failure. *Heart & Lung*. Retrieved from http://doi.org/10.1016/j.hrtlng.2012.06.001.

15. Sauve MJ, Lewis WR, Blankenbiller M, Rickabaugh B, Pressler SJ. Cognitive impairments in chronic heart failure: a case controlled study. *J Card Fail* 2009;15:1-10.

16. Pressler SJ, Subramanian U, Kareken D, et al. Cognitive deficits in chronic heart failure. *Nurs Res* 2010;59:127-139.

17. Gure TR, Blaum CS, Giordani B, Koelling TM, Galecki A, Pressler SJ et al. Prevalence of cognitive impairment in older adults with heart failure. *J AmGeriatr Soc* 2012; *60*:1724–1729.

18. Nielsen-Bohlman LT, Panzer AM, Kindig DA. Institute of Medicine. Health literacy: A prescription to end confusion. Washington, DC: National Academic Press:2004.

19. Morrow D, Clark D, Tu W, Wu J, Weiner M, Steinley D et al. Correlates of health literacy in patients with chronic heart failure. *Gerontologist* 2006; 46:669-676.

20. DeWalt DA, Berkman ND, Sheridan S, Lohr KN, Pegnone MP. Literacy and health outcomes: A systematic review of the literature. *J Gen Intern Med* 2004; 12:1228-1239.

21. Evangelista LS, Rasmusson KD, Laramee AS, Barr J, Ammon SE, Dunbar S et al. Health literacy and the patient with heart failure-implications for patient care and research: A consensus statement of the Heart Failure Society of America. *J Card Fail* 2010; 16:9-16.

22. Griffin JM, Partin MR, Noorbaloochi S, Grill JP, Saha S, Snyder A et al. Variation in estimates of limited health literacy by assessment instruments and non-response bias. *J Gen Intern Med* 2010; 25: 675-681.

23. Riegel B, Moser DK, Anker SD, Appel LJ, Dunbar SB, Grady KL, et al. State of the science: promoting self-care in persons with heart failure: a scientific statement from the American Heart Association. *Circulation* 2009;120:1141-1163.

24. Rutledge T, Reis V, Linke SE, Greenberg BH. Depression in heart failure: a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Card* 2006;48:1527-1537.

25. Cutler DM, Everett W. Thinking outside the pillbox—medication adherence as a priority for health care reform. *N Engl J Med* 2010; 362:1553-1555.

26. Cameron J, Worrall-Carter L, Page K, Riegel B, Lo SK, Stewart S. Does cognitive impairment predict poor self-care in patients with heart failure? *Eur J Heart Fail* 2010;12:508-515.

27. Wu, JR, Corley, DJ, Lennie, TA, & Moser, DK. Effect of a medication-taking behavior feedback theory-based intervention on outcomes in patients with heart failure. *J Card Fail* 2012;18:1-9.

28. Kripalani S. Schmotzer B, Jacobson TA. Improving medication adherence through graphically enhanced interventions in coronary heart disease (IMAGE_CHF): A randomized controlled trial. *J Gen Intern Med* 2012; published online Jul 13, 2012;PMID 22790614

29. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2008; 2:CD000011.

30. Murray MD, Young J, Hoke S, Tu W, Weiner M. Morrow D et al. Pharmacist intervention to improve medication adherence in heart failure: a randomized trial. *Ann Intern Med*2007; 146:714-725.

31. Federman AD, Sano M, Wolf MS, Siu AL, Halm EA. Health literacy and cognitive performance in older adults. *J Am Geriatr Soc* 2009; 57:1475-1480.

32. Wolf MS, Curtis LM, Wilson EA, Revelle W, Waite KR, Smith SG et al. Literacy, cognitive function, and health: Results of the LitCog study. *J Gen Intern Med* pub online 08 May 2012; DOI:10.1007/s11606-012-2079-4.

33. Hawkins LA, Firek CJ, Silvet H. Targeted intervention to improve medication adherence in veterans with heart failure and cognitive impairment. Manuscript in preparation.

34. Saint Louis University Mental Status Examination. Available at: http://medschool.slu.edu/agingsuccessfully/pdfsurveys/slumsexam_05.pdf

35. Tariq SH, Tumosa N, Chibnall JT, Perry MH3rd, Morley JE. Comparison of the Saint Louis University mental status examination and the mini-mental state examination for detecting dementia and mild neurocognitive disorder—a pilot study. *Am J Geriatr Psychiatry* 2006; 14:900-910.

36. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12:189-198.

37. Bass PF 3rd, Wilson JF, Griffith CH. A shortened instrument for literacy screening. *J Gen Intern Med* 2006;18:1036-1038.

38. Parker RM, Baker DW, Williams MV, Nurss J R. The test of functional health literacy in adults: a new instrument for measuring patients' literacy skills. *J Gen Intern Med* 1995; 10:537-541.

Table 1. Characteristics of the Study Sample.

Variable	Subjects n=27
Age (y) mean ± SD (range)	65.3 ± 8.2 (45-80)
Male gender	26 (96.3%)
Race:	
African American	3 (11.1%)
Caucasian	20 (74.1%)
Hispanic	4 (14.8%)
Educational level:	
Less than high school	4 (14.8%)
High school diploma	9 (33.3%)
College or above	14 (51.9%)
Living arrangements:	
Alone	11 (40.7%)
With others	16 (59.3%)
History of depression	13 (48.1%)
SLUMS score[1] mean ± SD (range)	22.90 ± 2.93 (13-26)
Number of prescribed med.[4] mean ± SD (range)	14.44 ± 5.93 (5-27)

Med: medication, SD: standard deviation, SLUMS: Saint Louis University Mental Status exam, S-TOFHLA: Short form test of functional health literacy for adults.

[1] SLUMS screening is positive for mild cognitive impairment for score < 27 in persons with high school diploma or <25 in persons who did not complete high school. Screen is considered positive for severe impairment consistent with dementia for score <21 for persons with high school diploma or <20 for persons who did not complete high school.

[2] S-TOFHLA is scored from 0-36, with 0-16 considered inadequate, 17-22 marginal, and 22-36 adequate health literacy.

[3] Numeracy is scored from 0-50.

[4] Prescribed medications for the participant at the start of study, obtained from chart review.

Table 2.
Direction and Strength of Relationship of HL to Selected Variables

	Reading HL n=26	Numeracy HL n=27
Age		
Pearson Correlation	-.407	-.499
Sig. (2-tailed)	.039	.008
Race		
Spearman's Rank Order	-.255	-.386
Sig. (2-tailed)	.209	.047
Educational Level		
Spearman's Rank Order	.159	.315
Sig. (2-tailed)	.437	.109
SLUMS Score[1]		
Pearson Correlation	.804	.545
Sig. (2-tailed)	.000	.003
Depression		
Point-biserial	-.106	-.218
Sig. (2-tailed)	.607	.276
# Medications[2]		
Pearson Correlation	.205	.007
Sig. (2-tailed)	.127	.971
Adherence Pre[3]		
Pearson Correlation	-.210	.070
Sig. (2-tailed)	.303	.730
Adherence Post[4]		
Pearson Correlation	-.046	.085
Sig. (2-tailed)	.825	.674

[1] Saint Louis University Mental Status exam
[2] Number of prescribed medications for each subject
[3] Medication adherence pre-intervention in TARGET pilot study
[4] Medication adherence post-intervention in TARGET pilot study

Table 3.

Indirect Effects of HL Scores on Medication Adherence

HL did not mediate the effect of cognitive impairment, depression, or number of medications on medication adherence after exposure of the subjects to the intervention.

Reading HL Score	Indirect effect post-intervention[1,2]	Two-tailed P-value
SLUMS score	-0.121	0.459
History of depression	0.005	0.862
Number of medications	-0.022	0.575
Numeracy HL Score		
SLUMS score	0.065	0.604
History of depression	-0.046	0.608
Number of medications	0.009	0.716

[1] Estimated regression coefficient for indirect effect
[2] Standardized (Z-score)

Figure 1. Interventional Pictorial Medication Sheet

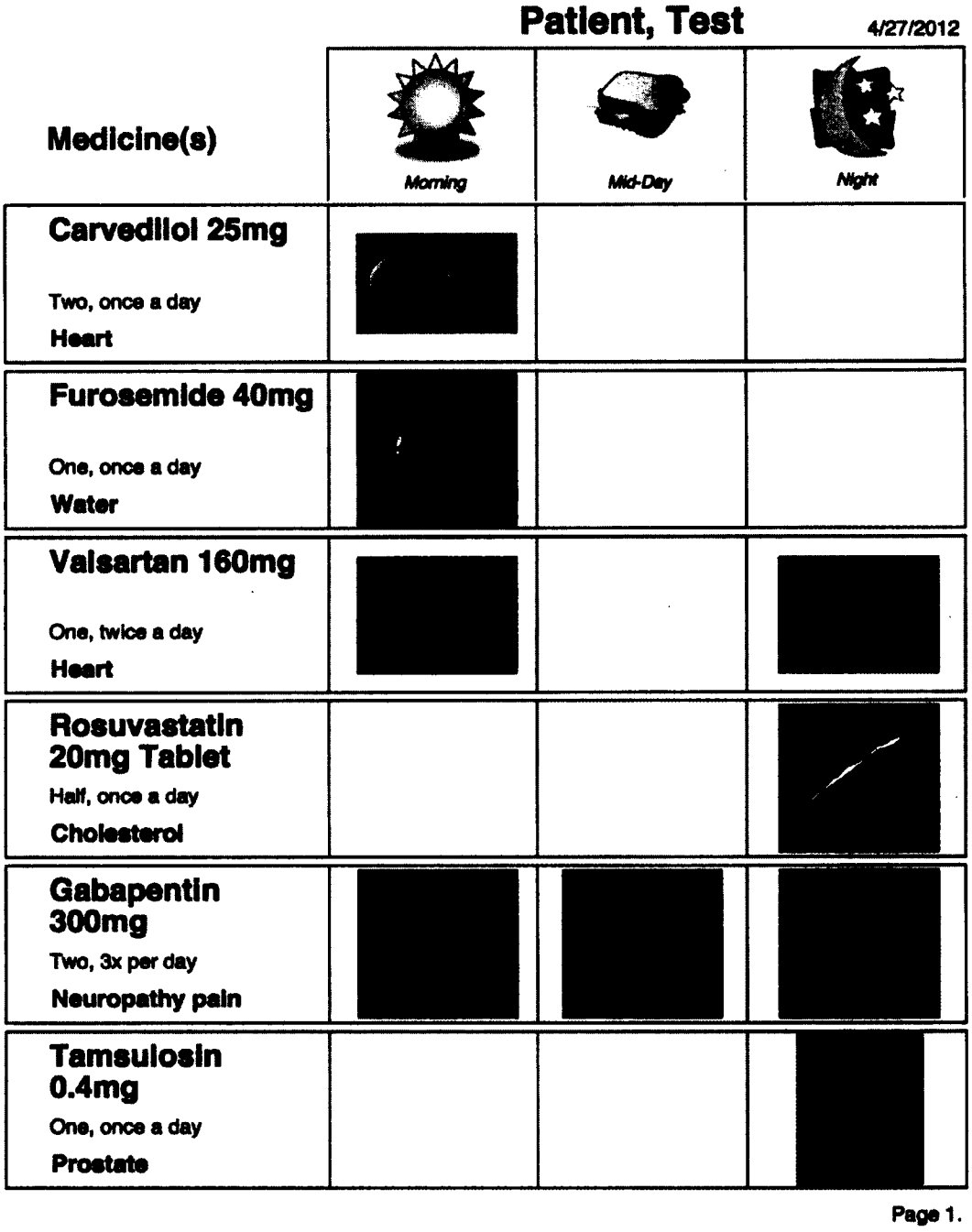
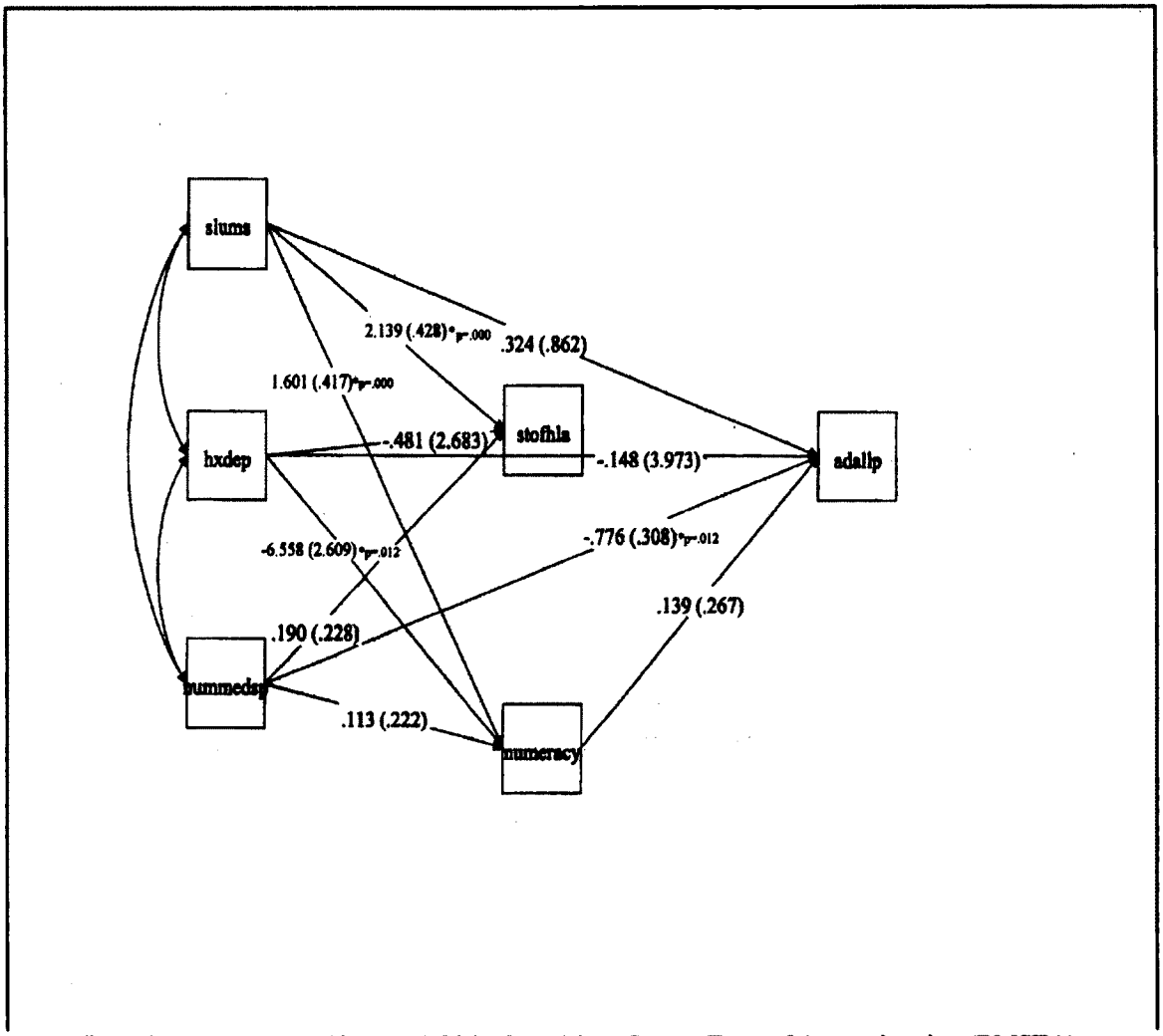


Figure 2. Path mediation model



Model fit: Chi-square (0.755, df 1, $p = 0.385$); Root Mean Square Error of Approximation (RMSEA) estimate of 0.000, 90% CI 0.000 -0.473, and probability of RMSEA <= .05: 0.430.

Figure 1. Three exogenous covariates are shown in the boxes on the left: slums = Saint Louis University Mental Status Exam (cognitive scores); hxdep =history of depression as determined by chart review; nummedsp =number of medications prescribed for each subject at the start of the study. Health literacy scores are shown as the mediating variables in the boxes in the middle of the model: stofhla =Short Test of Functional Health Literacy for Adults (reading HL), and Numeracy (numeracy HL). The endogenous dependent variable is shown in the box to the far right: adallp =post-intervention medication adherence. The numbers on the paths represent unstandardized regression coefficients with standard errors in parenthesis.

Dissertation Summary and Conclusion

This dissertation presented elements of my program of research in the field of medication adherence, cognition, and health literacy in persons with heart failure (HF). The overarching goal of this research is to improve HF outcomes by effecting change in the current model of care by ensuring patients at risk for poor medication adherence are identified and given extra support and assistance.

The background, review of the current literature, and theoretical framework relative to this research was included in Chapters 1 and 2. Chapter 3 presented the methodology for the study protocol that was proposed and conducted as the focus of this dissertation.

The three research papers contained in this dissertation represent the natural flow of a developing program of research. Initially, based on a problem noted in clinical practice, research was conducted that revealed unrecognized cognitive impairment that significantly worsened medication adherence in a sample of veterans with HF. This is reported in the first manuscript, Cognitive Impairment (CI) and Medication Adherence in Outpatients with Heart Failure, which has been accepted for publication (Hawkins, 2012). The results of that research informed the next two papers. The second document is a grant proposal: Targeted Intervention of Improve Medication Adherence in Cognitively Impaired Patients with Heart Failure. This is a project to test the feasibility and effectiveness of an automated medication-dispensing device to help patients with HF and CI take their medications correctly at home. The grant was funded and enrollment began November 2012. The final paper presents the results in manuscript form of the protocol

described in Chapter 3: Health Literacy and Use of a Pictorial Medication Sheet to Improve Adherence.

These research efforts have added to the body of existing nursing knowledge, and will provide a foundation for a continuing program of research. The Veterans Administration has compiled a library of 30,000 medication images, however the use of a pictorial medication sheet has not been tested in the veteran population (Echt, McConnell & Trettin, 2012). This dissertation research is one of the first to examine the effect of HL on a pictorial intervention to improve adherence in veterans with HF and CI. In addition, testing an intervention targeted towards underlying CI and poor HL operationalizes the Self-Care of HF model (Riegel, 2008) in a unique way.

Conclusion

It is important for clinicians to identify those patients at risk for poor medication adherence so that extra resources may be allocated to help them. This risk profile will need to be tailored to individual patient populations, and include screening for prevalent conditions that have been shown to contribute to poor adherence in that particular population. For the busy clinician screening HF patients for CI and depression may have better yield than trying to screen for poor HL. The design of future interventions to improve adherence should take into account all the cognitive demands placed on the patient, as well as other key determinants of poor adherence, rather than simply skills in reading and numeracy.

References

Adherence Research Network. (2010). US Department of Health and Human Services, Adherence Research Network. Retrieved from: http://obssr.od.nih.gov/scientific_areas/health_behaviour/adherence/adherenceresearchnetwork.aspx

Albert, N. M. (2008). Improving medication adherence in chronic cardiovascular disease. *Critical Care Nurse, 12,* 54-64.

Aranda, J. M., Johnson, J. W., & Conti, J. B. (2009). Current trends in heart failure readmission rates: Analysis of Medicare data. *Clinical Cardiology, 32(1),* 47-52.

Aronson, J. K. (2007). Compliance, concordance, and adherence. *British Journal of Clinical Pharmacology, 63,* 383-384.

Bass, P. F. 3rd, Wilson, J. F., & Griffith, C. H. (2003). A shortened instrument for literacy screening. *Journal of General Internal Medicine, 18,* 1036-8.

Bennett, S. J., & Sauve, M. J. (2003). Cognitive deficits in patients with heart failure: A review of the literature. *Journal of Cardiovascular Nursing. 18,* 219-242.

Cacciatore, F., Abete, P., Ferrara, N., Calabrese, C. Napoli, C., Maggi, S., . . .& Rengo, F. (1998) Congestive heart failure and cognitive impairment in an older population. Osservatorio Geriatrico Campano Study Group. *Journal of the American Geriatrics Society, 46,* 1343-1348.

Cameron, J., Worrall-Carter, L., Page, K., Riegel, B., Lo, S. K., & Stewart, S. (2010). Does cognitive impairment predict poor self-care in patients with heart failure? *Euoropean Journal of Heart Failure, 12*, 508-515. doi: 10.1093/eurjhf/hfq042

Carpenter, R. (2005). Perceived threat in compliance and adherence research. *Nursing Inquiry, 12*, 192-199.

Cutler, D. M., & Everett, W. (2010). Thinking outside the pillbox medication adherence as a priority for healthcare reform. *New England Journal of Medicine, 362,*1553-1555. doi: 10.1056/NEJMp1002305

Davis, T. C., Wolf, M. S., Bass, P. F., 3rd, Thompson, J. A., Tilson, H. H., Neuberger, M. & Parker, R. M. (2006). Literacy and misunderstanding prescription drug labels. *Annals of Internal Medicine, 145,* 887-894.

Echt, K., McConnell M., Trettin, E. (2012). Medication Use Crisis. Retreived from: http://www.health.mil/Libraries/PSP_Calendar_Docs/Adherence_Preferences_Literacy_May_8.pdf

Edwards, M., Davies, M., & Edwards, A. (2009). What are the external influences on information exchange and shared decision-making in healthcare consultations: a meta-synthesis of the literature. *Patient Education and Counseling, 75*, 37-52.

Esposito, D., Bagchi, A. D., Verdier, J. M., Bencio, D. S., & Kim, M. S. (2009). Medicaid beneficiaries with congestive heart failure: Association of medication adherence with healthcare use and costs. *American Journal of Managed Care, 15*, 437-445.

Evangelista, L. S., Rasmusson, K. D., Laramee, A. S., Barr, J., Ammon, S. E., Dunbar, S., . . . Yancy, C. W. (2010). Health literacy and the patient with heart failure--Implications for patient care and research: A consensus statement of the Heart Failure Society of America. *Journal of Cardiac Failure, 16(1)*, 9-16. doi: 10.1016/j.cardfail.2009.10.026

Federman, A. D., Sano, M., Wolf, M. S., Siu, A. L., & Halm, E. A. (2009). Health literacy and cognitive performance in older adults. *Journal of the American Geriatrics Society, 57,* 1475-1480. doi: 10.1111/j.1532-5415.2009.02347.x

Fitzgerald, A. A., Powers, J. D., Ho, P. M., Maddox, T. M., Peterson, P. N., Allen, L. A., . . . Havranek, E. P. (2011). Impact of medication nonadherence on hospitalizations and mortality in heart failure. *Journal of Cardiac Failure. 17,* 664-669. doi: 10.1016/j.cardfail.2011.04.011

Gould, E., & Mitty, E. (2010). Medication adherence is a partnership, medication compliance is not. *Geriatric Nursing, 31*, 290-298.

Griffin, J. M., Partin, M. R., Noorbaloochi, S., Grill, J. P., Saha, S., Snyder, A., . . .van Ryn, M. (2010). Variation in estimates of limited health literacy by assessment instruments and non-response bias. *J Gen Intern Med. 25,* 675–681. doi: 10.10007/s11606-010-1304-2

Hawkins, L.A., Firek, A., Kilian, S., Firek, C.J., Kashner, M. & Silvet, H. (2012). Cognitive Impairment and Medication Adherence in Outpatients with Heart Failure. *Heart & Lung*. Advance online publication. Retrieved from http://doi.org/10.1016/j.hrtlng.2012.06.001

Hawkins, L.A., Firek, C.J., & Silvet, H. (2012). Targeted intervention to improve medication adherence in patients with heart failure and cognitive impairment. Unpublished manuscript.

Haynes, R. B., Ackloo, E., Sahota, N., McDonald, H. P, & Yao, X. (2008). Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews,* 2.Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/18425859

Heidenreich, P. A. (2004). Patient adherence: The next frontier in quality improvement. *American Journal of Medicine, 117*, 130-132. doi: 10.1016/j.amjmed.2004.03.007

Heidenreich, P. A. (2011). CHF QUERI 2011 Strategic Plan. Retrieved from http://www.queri.research.va.gov/about/strategic_plans/chf.pdf

Ho, P. M., Bryson, C. L., & Rumsfeld, J. S. (2009). Medication adherence: Its importance in cardiovascular outcomes. *Circulation, 119*, 3028-3035. doi: 10.1161/ CIRCULATIONAHA.108.768986

IBM Corporation. Statistical Package for the Social Sciences. (2012). Retrieved from http://www-01.ibm.com/software/analytics/spss/

Keller, D., Wright, J. & Pace, H. A. (2008). Impact of health literacy on health outcomes in ambulatory care patients: A systematic review. *Annals of Pharmacotherapy, 42*,1272-1281. doi:10.1345/aph.1L093

Kennelly S.P., Lawlor B.A., & Kenny R.A. (2009). Blood pressure and the risk for dementia: A double edged sword. *Ageing Research Reviews ,8* ,61-70. doi:10.1016/j.arr.2008.11.001

Lee, J. K. (2007). How should we measure medication adherence in clinical trials and practice? *Therapeutics and Clinical Risk Management, 3*,685-690.

Levinthal, B. R., Morrow, D. G., Tu, W., Wu, J., & Murray, M.D. (2008). Cognition and health literacy in patients with hypertension. *Journal of General Internal Medicine, 23*,1171-1176. doi: 10.1007/s11606-008-0612-2

Lindenfeld, J., Albert, N. M., Boehmer, J. P., Collins, S. P., Ezekowitz, J. A., Givertz, M. M., . . . Walsh, M. N. (2010). HFSA 2010 Comprehensive Heart Failure Practice Guideline. *Journal of Cardiac Failure, 16*, e1-194. doi:10.1016/j.cardfail.2010.04.004

Lloyd-Jones, D., Adams, R.J., Brown, T.M., Carnethon, M., Dai. S., De Simone, G., . . . Wylie-Rosett, J. (2010). Heart disease and stroke statistics-2010 update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*, 121, e1-e170.

*M*plus. (2012). Retrieved from http://www.statmodel.com/glance.shtml

Meyers, L. S., Gamst, G. & Guarino, A. J. (2006). Applied Multivariate Research: Design and Interpretation. Thousand Oaks, CA: Sage Publications.

Morrow, D., Clark, D., Tu, W., Wu, J., Weiner, M., & Steinley, D. (2006). Correlates of health literacy in patients with chronic heart failure. *Gerontologist, 46*, 669-676. doi:10.1093/geront/46.5.669

Moser, D. K., & Watkins, J. F. (2008). Conceptualizing self-care in heart failure: A life course model of patient characteristics. *Journal of Cardiovascular Nursing, 23*, 205-218. doi: 10.1097/01.JCN.0000305097.09710.a5

Munger, M. A., Van Tassell, B. W., & LaFleur, J. (2007). Medication nonadherence: An unrecognized cardiovascular risk factor. *Medscape General Medicine, 9(3)*, 58.

Murray, M.D., Tu, W., Wu, J., Morrow, D., Smith, F, & Brater, D.C. (2009). Factors associated with exacerbation of heart failure include treatment adherence and health literacy skills. *Clinical Pharmacology and Therapeutics,* 85, 651-658. doi: 10.1038/clpt.2009.7

Murray, M. D., Young, J., Hoke, S., Tu, W., Weiner, M., & Morrow, D. (2007). Pharmacist intervention to improve medication adherence in heart failure: a randomized trial. *Annals of Internal Medicine, 146*(10), 714-725.

National Center for Educational Statistics. (2012). National assessment of adult literacy (NAAL). Retrieved from: http://nces.ed.gov/naal/kf_demographics.asp

Nielsen-Bohlman L.T., Panzer A.M., & Kindig D.A. (2004). Health literacy: A prescription to end confusion. Institute of Medicine.Washington, DC: National Academic Press.

Osterberg, L., & Blaschke, T. (2005). Adherence to medication. *New England Journal of Medicine, 353*, 487-497.

Parikh, N. S., Parker, R. M., Nurss, J. R., Baker, D. W., & Williams, M. V. (1996). Shame and health literacy: The unspoken connection. *Patient Education and Counseling, 27,* 33-39.

Parker, R. M., Baker, D. W., Williams, M. V., & Nurss, J. R. (1995). The test of functional health literacy in adults: A new instrument for measuring patients' literacy skills. *Journal of Generao Internal Medicine, 10,* 537-41.

Polit, D. F., & Beck, C. T. (2012). *Nursing research: Generating and assessing evidence for nursing practice.* Philadelphia. Wolters Kluwer Health/Lippincott Williams & Wilkins.

Population Resource Center. (2011). *Aging of America.* Retrieved from http://prcdc.org/300million/The_Aging_of_America/

Pressler, S. J. (2008). Cognitive functioning and chronic heart failure: A review of the literature (2002-July 2007). *Journal of Cardiovascular Nursing, 23,* 239-249.

Pressler, S.J., Subramanian, U., & Kareken, D. (2010). Cognitive deficits in chronic heart failure. *Nursing Research, 59,* 127-139. doi:10.1097/NNR.0b013e3181d1a747

Riegel, B., & Dickson, V. V. (2008). A situation-specific theory of heart failure self-care. *Journal of Cardiovascular Nursing, 23,*190-196.

Riegel, B., Moser, D. K., Anker, S. D., Appel, L. J., Dunbar, S. B., Grady, K. L,. . .Whelan, D. J. (2009). Promoting self-care in persons with heart failure: A scientific statement from the American Heart Association. *Circulation, 120,* 1141-1163. doi:10.1161/CIRCULATIONAHA.109.192628

Rutledge, T., Reis, V., Linke, S.E., & Greenberg, B.H. (2006). Depression in heart failure: A meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *Journal of the American College of Cardiology, 48,* 1527-37. doi:10.1016/j.jacc.2006.06.055

Sabate, E. (2003). Adherence to long-term therapies: Evidence for action. Geneva, Switzerland: World Health Organization.

Sauve, M. J., Lewis, W. R., Blankenbiller, M., Rickabaugh, B., & Pressler, S. J. (2009). Cognitive impairments in chronic heart failure: a case controlled study. *Journal of Cardiac Failure, 15(1)*, 1-10. doi: 10.1016/j.cardfail.2008.08.007

Smith, H., Hankins, M., Hodson, A, & George, C. (2010). Measuring the adherence to medication of elderly patients with heart failure: Is there a gold standard? *International Journal of Cardiology, 145 (1),*122-123. doi:10.1016/j.ijcard.2009.06.031

Tariq, S.H., Tumosa, N., Chibnall, J.T., Perry, M.H. 3rd, & Morley, J. E. (2006). Comparison of the Saint Louis University mental status examination and the mini-mental state examination for detecting dementia and mild neurocognitive disorder--a pilot study. *Amerian Journal of Geriatric Psychiatry,14,* 900-910. doi:10.1097/01.JGP.0000221510.33817.86

U.S. Department of Health and Human Services. (2012). Administration on Aging. Retrieved from: http://www.aoa.gov/AoARoot/index.aspx

U.S. National Library of Medicine. (2012). Dementia due to metabolic causes. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001703/

van der Wal, M.H. & Jaarsma, T. (2008). Adherence in heart failure in the elderly: Problem and possible solutions. *International Journal of Cardiology,125*, 203-208. doi:10.1016/j.ijcard.2007.10.011

Vogels, R. L., Scheltens, P., Schroeder-Tanka, J. M., Weinstein, H. C. (2007). Cognitive impairment in heart failure: A systematic review of the literature. *European Journal of Heart Failure*, 9, 440-449. doi:10.1016/j.ejheart.2006.11.001

Wolf, M. S., Gazmararian, J. A., & Baker, D. W. (2005). Health literacy and functional health status among older adults. *Archives of Internal Medicine, 165,*1946-1952.

Woo, M.A., Kumar, R., Macey, P.M., Fonarow, G.C., & Harper, R.M. (2009). Brain injury in autonomic, emotional, and cognitive regulatory areas in patients with heart failure. *Journal of Cardiac Failure,15(3),* 214-223. doi.org/10.1016/j.cardfail.2008.10.020

Wu, J. R., Corley, D. J., Lennie, T. A., & Moser, D. K. (2012). Effect of a medication-taking behavior feedback theory-based intervention on outcomes in patients with heart failure. *Journal of Cardiac Failure,18 (1),*1-9. doi:10.1016/j.cardfail.2011.09.006

Wu, J.R., Moser, D.K., Chung, M.L., & Lennie, T.A. (2008). Predictors of medication adherence using a multidimensional adherence model in patients with heart failure. *Journal of Cardiac Failure, 14(7),*603-614. doi.org/10.1016/j.cardfail.2008.02.011

Wu, J. R., Moser, D. K., & De Jong, M. J. (2009). Defining an evidence-based cutpoint for medication adherence in heart failure. *Amerian Heart Journal, 157*, 285-291. doi: 10.1016/j.ahj.2008.10.001

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