Validation of Psychosocial Factors as Predictors of Medication Adherence among Veterans following Hospitalization for Acute Coronary Syndrome

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Abstract of Dissertation

Validation of Psychosocial Factors as Predictors of Medication Adherence among Veterans following Hospitalization for Acute Coronary Syndrome

The current study was an analysis of a randomized clinical trial of a multifaceted intervention to improve adherence to cardiac medications. This study sought to validate selected psychosocial factors as predictors of medication adherence among veterans hospitalized for an Acute Coronary Syndrome event. The participants in this study were recruited from four Veterans Administration medical centers in the United States. This study was grounded in the Social Cognitive Theory as the basis for exploring the role of medication-taking self-efficacy as a predictor of medication adherence behaviors. The primary psychosocial variables of interest included self-efficacy, depression, cognitive functioning and health literacy. The outcome variable in this study was patient's overall medication adherence to cardioprotective medications prescribed at hospital discharge. This study was guided by a conceptual framework that examined how the separate but interrelated and reciprocally influencing variables of cognitive function, health literacy and depression, impacted self-efficacy which, in turn, was predicted act as a determinant of medication adherence. In this study, self-efficacy was found to be a significant independent predictor of medication adherence. Patients with high self-efficacy had higher odds of being adherent than patients with lower self-efficacy, after controlling for the other predictor variables in the model. Health literacy, depression and cognitive functioning were not found to predict medication adherence in this study. However, considering the prevalence of depression and cognitive impairment within this sample of

veterans, future research should examine these psychosocial factors in a larger veteran population and, perhaps, in the population at large. With the knowledge that medication adherence is a multi-dimensional problem, future interventions to improve medication-taking behaviors should integrate existing health behavior models that can provide a framework for isolating recognized triggers of behavior and applying strategies to deal with them in an effort to drive and sustain behavior change. Improving general awareness and enhanced evaluation of patients' personal, behavioral, and environmental factors will enable healthcare providers to make appropriate treatment recommendations that take into consideration based on the specific needs of their patients.

Table of Contents

List of Figures

List of Tables

Glossary of Terms

ACS: Acute coronary syndromes

AMI: Acute myocardial infarction

CABG: Coronary artery bypass grafting

CAD: Coronary artery disease

CVD: Cardiovascular disease

DSM-IV: Diagnostic and Statistical Manual Fourth Edition

IVR: Interactive voice response

MDD: Major depressive disorder

MPR: Medication possession ratio

NAAL: National Assessment of Adult Literacy

NSTEMI: Non-ST segment elevation myocardial infarction

PCI: Percutaneous coronary intervention

PDC: Proportion of days covered

PHQ-9: Patient Health Questionnaire

PTSD: Posttraumatic stress disorder

REALM-R: Rapid Estimate of Adult Literacy in Medicine, Revised

SCT: Social cognitive theory

SEAMS: Self-efficacy for Appropriate Medication Use Scale

SLUMS: Saint Louis University Mental Status Examination

STEMI: ST-segment elevation myocardial infarction

TBI: Traumatic brain injury

UA: Unstable angina

VHA: Veterans Health Administration

CHAPTER 1: INTRODUCTION

In order for patients to derive optimal benefit from medications, they must not only be prescribed the appropriate medication but also adhere to their prescribed treatments. Poor adherence to medications has been clearly associated with various adverse health outcomes, including increased ambulatory care visits, emergency department visits and hospitalizations (Lee, Grace, & Taylor, 2006). In the United States, poor medication adherence accounts for substantial worsening of disease, death and increased health care costs (Mcdonnell & Jacobs, 2006; Senst et al., 2001; Osterberg & Blaschke, 2005).

Cardiovascular disease is the most common cause of death in the United States and has an annual health care cost of approximately $475 billion (Heindenreich et al., 2011). Among patients with cardiovascular diseases, non-adherence to medication is linked to increased mortality risk and re-hospitalization (Munger, Van Tassell, & LaFleur, 2007; Ho et al., 2006). At the time of hospital discharge, patients are commonly prescribed a variety of medications, such as β-blockers, statins, clopidogrel, Angiotensin-converting enzyme (ACE) inhibitors, and/or aspirin, which have been consistently shown in multiple randomized controlled clinical trials to reduce morbidity and/or mortality. These medications are all class I indicated medications which is the highest level of support as defined in the American Cardiology of College (ACC) and American Heart Association (AHA) guidelines (Anderson et al., 2007; American College of Cardiology/American Heart Association Task Force on Practice Guidelines, 2008; Smith et al., 2011). Despite the known benefits of these medications, non-adherence in the first year following Acute Coronary Syndrome (ACS) discharge is common, ranging from 10-40% (Spertus et al., 2006; Ho et al., 2008). Thus, not surprisingly, patients who do not take their medications as prescribed are at increased risk of adverse outcomes in the short-term (e.g., stent thrombosis due to premature clopidogrel discontinuation) and in the long-term (e.g., recurrent myocardial infarction (MI), mortality).

The World Health Organization has suggested that medication non-adherence is a common problem that leads to serious economic consequences in terms of years of life lost as a result of premature death, higher costs and uncontrolled disease (World Health Organization [WHO], 2003). Non-adherence to cardiac medications has been associated with higher disease-related medical costs (Sokol, McGuigan, Verbrugge, & Epstein, 2005; Choudhry, Patrick, Antman, Avorn, & Shrank, 2008). Comparisons of all-cause healthcare costs over one year among adherent versus non-adherent patients have demonstrated the total economic burden of medication non-adherence (Musbeck, Brixner, Benedict, Keskinaslan, & Khan, 2008). Musbeck (2006) reported that high adherence among patients with hypercholesterolemia was associated with significantly lower non-drug related medical spending when compared to patients with poor adherence ($4,780 vs $5,509-$9,849).

1.1 Significance of the Problem

Cardiovascular medications are estimated to be responsible for half of the 50% reduction in mortality from cardiovascular disease over the past 20 years (Ford et al., 2007). Therefore, changing an individual's medication adherence behavior holds both a theoretical and practical potential to decrease morbidity and mortality associated with non-adherence to cardioprotective medications. This underscores the need and importance to seriously take into account and address the issue of behavior change. Most research on medication adherence has been focused on minimizing the practical and logistical barriers to adherence. However, several individual factors appear to significantly influence adherence behaviors. Ongoing research continues to identify correlates and predictors of poor medication adherence. However, to date, research on the determinants of medication adherence has been hampered, in part, by the lack of applied theories and models of behavior change that can be used to predict and explain patients' adherence behaviors. These behavior change theories hinge on personal, environmental, and behavioral characteristics as the major factors in determining individuals' behavior and actions. Yet, to better understand the specifics of treatment adherence, further research must be undertaken that examines the interplay of health behavior constructs and the relationship between specific attributes of these constructs and an individual's personal and environmental factors and the potential impact on behavior. While these factors are common in many segments of the population, this study will specifically examine the role of self-efficacy, health literacy, cognitive functioning, and depression as predictors of medication adherence within the veteran population.

In general, intervention strategies addressing behavioral risk factors most closely associated with leading causes of death have the potential to produce significant improvements in an individual's health and possibly in the population at large. Before attempting to modify an individual's health behavior, it is necessary to understand why people behave the way they do despite the obvious detrimental effects that the individuals at risk may be already aware of. The underlying theoretical basis of this study is centered on Bandura's Social Cognitive Theory (SCT) which calls attention to the construct of self-efficacy as a determinant of individual behavior (Bandura, 1977a). Self-efficacy refers to an individual's belief in his or her capacity to carry out behaviors or actions necessary to produce a desired performance outcome. According to the SCT, self-efficacy beliefs are influenced by personal and environmental circumstances surrounding behavior. Self-efficacy reflects an individual's confidence in their own ability to exercise control over these personal, environmental and behavioral circumstances. As a result, this perceived self-efficacy has an effect on the likelihood of expending energy toward achieving a desired goal. In this study, the construct of medication-taking self-efficacy is a reflection of an individual's confidence in their ability to adhere to their prescribed cardioprotective medications and is examined as a predictor of overall medication adherence.

In addition to self-efficacy, this study will examine several other determinants of poor medication adherence. Among these, an emerging and important factor contributing to poor medication adherence is low health literacy. In *Healthy People, 2010*, the U.S. Department of Health defines health literacy as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions" (U.S. Department of Health and Human Services [U.S. DHHS], 2000). To have an adequate degree of health literacy is important because there is concrete evidence showing that, compared to patients with adequate health literacy, patients with poor understanding of medication and prescribed drug therapies are more likely to have adherence problems (Gazmararian et al., 2006). Limited health literacy skills are associated with an increase in preventable hospital visits, higher rates of hospitalization and use of emergency services (Baker et al., 2002; Baker, Parker, Williams, & Clark, 1998; Baker, Parker, Williams, Clark, & Nurss, 1997). Individuals with limited health literacy also have a higher prevalence and severity for chronic diseases, poorer global measures of health, and lower utilization of screening and preventive services (U.S. DHHS, 2000). The role of health literacy in medication adherence, particularly among patients with cardiovascular disease, is an especially important problem. Considering that nearly 90 million people in the U.S. have less than adequate health literacy skills and over 70 million Americans suffer from cardiovascular diseases, the impact of health literacy on cardiovascular disease is certain to be felt by every physician's practice (Safeer, Cooke, & Keenan, 2006).

Depression has also been recognized as a risk factor for recurrent events in patients with established cardiovascular disease and is common following ACS, occurring in as many as 45% of patients while hospitalized for an ACS event (Kronish et al., 2006). Persistently depressed patients are less likely than non-depressed patients to adhere to prevention behaviors following an ACS (McGee, Doyle, Conroy, La Harpe, & Shelley, 2006). Several causes have been suggested as potential mediators of the link between depression and cardiovascular disease, including medication non-adherence.

The risk of cognitive impairment increases with age and specifically among the aging veteran population, traumatic brain injuries (TBI) put individuals at an even greater risk for disturbances in cognitive function (Vincent, Roebuck-Spencer, & Cernich, 2014). Impaired cognitive functioning has been shown to have a strong connection with cardiovascular risk factors including high cholesterol, hypertension and metabolic syndrome (Yaffe, Hoang, Byers, Barnes & Friedl, 2014). In addition, patients with cognitive impairments are hindered by their inability to carry out specific self-care activities such as understanding and adhering to medication regimens that are common in chronic diseases (Campbell et al., 2012). Considering the estimated growth of the aging population and the resulting increase in age-related cognitive dysfunction and cardiovascular risk factors, this study will examine the role of cognitive function on patients' medication adherence behaviors.

Medication non-adherence is an issue health care providers have been facing for some time. Several interventions have been designed to improve adherence and many studies have examined the effect of these interventions, yet no one method has been shown to be the most effective strategy. While studies of adherence interventions appear to be promising, they include one or more of the following limitations which may limit their effectiveness among the veteran population: 1) they did not include veterans who often have multiple co-morbid conditions and are prescribed many medications; 2) they did not focus on the post-ACS hospital discharge period; 3) they were of short duration and did not address the continuing problem of non-adherence longer term after hospital discharge; and 4) they did not examine factors related to any of the theoretical underpinnings of individuals' health behavior.

1.2 Purpose of the Study

In Fiscal Year 2013, there were 8.92 million enrollees in the VA Health Care System and approximately 695,000 inpatient admissions (U.S. Department of Veterans Affairs, 2012). In order to receive VA health care benefits, most veterans must enroll. When veterans enroll, they are placed in priority groups or categories that help the VA manage health care services within budgetary constraints and ensure quality care for those enrolled.

Among veterans, ACS is one of the leading causes of hospitalization. There are no known studies that have specifically examined medication-taking self-efficacy in the veteran population. The goal of this study aims to identify specific individual psychosocial risk factors and understand how they relate to medication adherence among veterans hospitalized for an ACS event. Individuals' psychosocial factors, including self-efficacy, health literacy, depression and cognitive function are assumed to be important interdependent factors that contribute to medication non-adherence. Each of these factors will be examined in the context of a larger theoretical framework to examine whether these factors influence medication adherence behaviors. Understanding how these psychosocial factors impact medication adherence is necessary for developing future interventions to decrease the excess morbidity and mortality and health service utilization in patients with cardiovascular disease. The outcomes of this study could generate significant new benefits to improve population health. In fact, the more that is understood about the specific underlying influences and determinants of an individual's health risk behavior, the greater the likelihood that selective behavior change strategies and interventions aimed at targeting and transforming the risk factors responsible for the development and progression of disease can be successfully applied.

Multiple factors influence an individual's behavioral choices and actions, and that even within one topic, such as adherence, considerable variability may exist among these factors. This study will identify and quantify self-efficacy, functional health literacy, depression and cognitive functioning among veterans hospitalized for ACS and examine the relationship between these factors and resulting adherence to prescribed cardioprotective medications. The variables in this study have been selected based on their ability to represent key constructs found in the Social Cognitive Theory to better understand and address the underlying influences and determinants of medication adherence. Examining the relationship between key variables (e.g. self-efficacy, health literacy, depression and cognitive functioning) and developing statistical models to assess the impact of these predictors on medication adherence may lead to insight into the underlying relationships that exist between these psychosocial factors and medication adherence behavior.

It is not within the scope of this study to improve individuals' health literacy or self-efficacy per se; however, the results of this study may lead to an increased understanding of the factors that are thought to influence adherence behaviors and may yield new insight that may be useful in the development of future medication adherence intervention strategies for patients across a variety of chronic diseases.

1.3 Specific Aims & Hypotheses

The primary objective of this study is to examine the relationship between self-efficacy, health literacy, depression and cognitive functioning in an effort to understand and improve medication adherence behaviors.

This study will conduct a secondary analysis using data from the MEDICATION study (Multi-FacetED Intervention to Improve Cardiac Medication Adherence and Secondary PrevenTION Measures), funded by the Department of Veterans Affairs and the Veteran's Health Administration. By examining a hypothesized predictive model and mediation model of medication adherence, this study will address the following specific aims:

1. Assess functional health literacy levels among veterans who have been hospitalized for an ACS event.
2. Determine the association of high versus low self-efficacy and medication adherence behaviors among veterans who have been hospitalized for an ACS event.
3. Examine the relationship between the selected psychosocial variables of self-efficacy, depression, cognitive functioning and health literacy and medication adherence.
4. Explore whether veterans have different patient- and condition-related factors that make them more or less susceptible to poorer medication adherence behaviors compared to the general population.

The 4 aims of this study will be used to guide and test the following hypotheses:

1. Among veterans hospitalized for an ACS event, rates of functional health literacy levels will approximate rates of health literacy within the general U.S. population.
2. Among veterans, there will be a positive association between functional health literacy and self-efficacy.
3. The effects of health literacy, depression and cognitive functioning on medication adherence will be partially mediated through self-efficacy.
4. Among veterans hospitalized for an ACS event, individuals with low self-efficacy will have worse medication adherence compared to veterans with high levels of self-efficacy.

CHAPTER 2: LITERATURE REVIEW

2.1 Theoretical Framework

An individual's health behavior is rooted in biological, psychological, social, and environmental factors. Addressing each of these factors individually or the complex interplay among them is challenging, which makes the task of changing behavior to improve health far from a straightforward undertaking. In general, the most effective interventions are those that address each distinct undesirable behavior individually and sequentially.

Many health behavior theories and models have been developed to understand the multifaceted components of individual behavior and to explain why individuals are either successful in carrying out health-promoting practices while others fail to do so (Glanz, Rimer, & Lewis, 2002). Health behavior theories were created based on the need to explain human behavior and further comprehend an individual's personal processes of understanding, contemplating, adopting, modifying, and maintaining healthy behavior.

The principles of social learning that suggest that individuals learn from each other by observing, imitating and modeling behavior were first applied by Albert Bandura to explain human behavior in the context of the Social Cognitive Theory. Bandura's Social Learning Theory proposes that individuals learn through observation of the behaviors of others and the rewards that others receive as result of their actions (Bandura, 1977a). It also emphasizes that cognitive processes that develop out of social learning regulate an individual's behavior so that individuals do not simply respond to stimuli unconsciously. Instead, individuals think about and interpret stimuli. Insight into how an individual processes and reflects on personal, environmental and social factors helps predict how those factors will shape his or her behavior. The concept of reciprocal determinism, which stresses the interconnection of an individual's personal factors, environment and behavior in influencing behavior, was later introduced to the Social Cognitive Theory to illustrate how individual behavior is largely determined by the reciprocal interaction of personal, environmental and behavioral factors (Bandura, 1978).

2.1.1 Self-Efficacy and Outcome Expectancies

The constructs of self-efficacy and outcome expectancies play a significant role in influencing and explaining human behavior and within Bandura's framework, self-efficacy and outcome expectancies are distinguished (Bandura, 1977b). Self-efficacy is likely the most well-known and widely-used concept to stem from the Social Cognitive Theory (Bandura, 1986). Apart from a person's own cognitive processes, cognitive events are stimulated and modified by an individual's experiences and, in turn, these experiences can alter the person's expectations of self-efficacy (Bandura, 1977a). Self-efficacy is the confidence that an individual has in his or her ability to successfully carry out certain behavior(s) in order to produce a desired outcome. Individuals with high levels of self-efficacy are typically more likely to persevere in the face of challenges, whereas individuals with low levels of self-efficacy are more likely to be easily discouraged and accept an early defeat. The perception of high self-efficacy also increases the likelihood that individual will attempt a particular behavior. Individuals who perceive themselves as capable of carrying out a specific action to achieve a specific goal will be more likely to succeed than those who do not believe themselves capable of performing that action. This self-belief has a powerful effect on behavior. Individuals will generally choose to engage in behaviors or take on activities that they are confident that they can successfully accomplish and are inclined to steer clear of activities that they believe exceed their potential.

Outcome expectancy is defined as an individual's belief that a certain behavior will produce certain outcome. Outcome expectancy is important in that an individual who perceives that a particular course of action will result in a successful outcome, will more likely view that action as a positive one and engage in that action, in contrast to an individual who perceives that the behavior will have a negative or unsuccessful outcome and thus becomes less willing to attempt that behavior. Whether performance-based or symbolic, an individual's mental process can alter expectations of self-efficacy. In contrast, an efficacy expectation is the confidence that an individual has that he/she can successfully carry out the actions required to produce the desired outcome (Figure 1). In addition, an individual can believe that certain actions will produce certain outcomes (outcome expectancy), but may still question whether he or she can successfully implement the necessary actions.

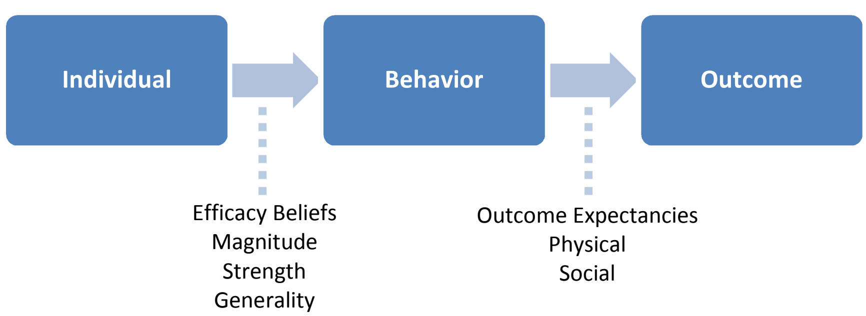


Figure 1. Relationship between efficacy beliefs and outcome expectancies

Bandura strongly believed that an individual's belief in their ability to appropriately handle situations has a very powerful effect on behavior (Bandura, 1989). Perceived self-efficacy determines how much energy an individual will use and how long they will persevere in the face of difficulties to achieve the desired goal. In essence, individuals with a stronger sense of self-efficacy are more intense and persistent in their efforts, are more motivated to apply considerable effort to take on activities, and are more likely to devote their attention and cognitive resources to conquering a problem.

The basis for an individual's expectation of self-efficacy is based on four major sources of information that influence behavior change in different ways: performance accomplishments, vicarious experiences, verbal persuasion and emotional arousal (Table 1) (Bandura, 1977b).

Table 1: Sources of efficacy expectations

SOURCE	MODE OF INFLUENCE
Performance Accomplishment	Participant Modeling Performance Desensitization Performance Exposure Self-Instructed Performance
Vicarious Experiences	Live Modeling Symbolic Modeling
Verbal Persuasion	Suggestion Exhortation Self-Instruction Interpretive Treatments
Emotional Arousal	Attribution Relaxation, Biofeedback Symbolic Desensitization Symbolic Exposure

Performance accomplishment provides the steadiest source of efficacy expectations through an individual's personal successes and failures. The influence of self-evaluative and self-efficacy mechanisms on performance motivation has been studied under varying conditions of performance feedback and self-reactive influences (Bandura & Cervone, 1983). When both factors are present, self-evaluative and self-efficacy influences have been shown to predict the magnitude of motivation enhancement. The higher the self-dissatisfaction with a sub-standard performance and the greater the perceived self-efficacy for goal-attainment, the more intense the subjects' efforts were in subsequent sessions.

Through *vicarious experiences*, individuals can persuade themselves that if others are able to perform certain activities without adverse consequences, they too will eventually succeed if they persist in their efforts. *Verbal persuasion* leads individuals into believing they can handle activities that appear undoable or have been overwhelming in the past. However, verbal persuasion is considered to be less effective because the expectations it produces are not derived from an individual's own experiences. Lastly, *emotional arousal* can influence self-efficacy under stressful circumstances via an individual's anticipation that success is more likely when they are prepared, confident and ready.

Efficacy expectations vary on several dimensions including magnitude, strength and generality, and will differ among individuals when activities are arranged according to their magnitude of difficulty. The generalizability of self-efficacy depends on the extent to which an experience can broaden an individual's sense of efficacy to situations beyond the current situation. Lastly, expectations differ in their strength so that the intensity of an individual's perception of self-efficacy will determine the degree of his or her effort to take on and accomplish a specific goal-oriented task.

2.1.2 Reciprocal Determinism

A central principle in Bandura's Social Cognitive Theory is the concept of reciprocal determinism, which stresses the interdependence of an individual's personal factors, environment and conduct in influencing behavior (Figure 2) (Bandura, 1978).

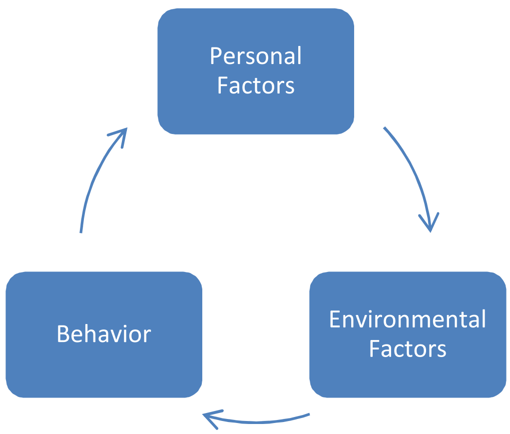


Figure 2. Reciprocal Determinism

In reciprocal determinism, each factor possesses an inherent potential to influence behavior, yet the potential of that influence is only realized when activated by the proper actions. For example, an individual's behavior can determine which environmental factors will become relevant, and those environmental factors, in turn, will activate the actions required to perform the desired action. An individual's reality is thus formed by the interaction of their environment and their cognitions. The term *determinism* is used to signify the production of effects by events, as opposed to the notion that actions are completely determined by a prior sequence of causes independent of the individual (Bandura, 1978). According to Bandura, when an individual interacts with the environment, that individual does not simply react to external stimuli. In reality, most stimuli affect behavior through intermediary cognitive process that determine which external events are observed, how they will be perceived, whether they will have lasting effects, what valence and efficacy they have, and how the information they convey will be organized for future use. Through their choices and actions, individuals alter their environment and produce the conditions that reciprocally affect their behavior. Personal factors (e.g., knowledge, conceptions, beliefs, self-perceptions) and behavior also function as reciprocal determinants of each other. For example, an individual's self-efficacy and outcome expectancies influence behavior and the environmental effects created by the individual's actions alter expectations. In reciprocal determinism, the influence of environment, personal factors and behavior will vary among individuals and under a variety of circumstances.

Patients with chronic diseases are often given disease-specific knowledge to be applied to and utilized for self-care behaviors. Lack of knowledge may also affect an individual's confidence in their ability to carry out self-care activities, negatively impacting their self-efficacy. Most research on medication adherence has been focused on minimizing practical and logistical barriers to adherence that patients frequently encounter. However, several individual factors appear to significantly influence adherence including patients' confidence in their ability to follow recommended behaviors (Miller, Hill, Kottke, Ockene, 1997). Few studies have examined the relationship between self-efficacy beliefs and medication adherence and fewer still have been focused specifically on patients with ACS. However, studies examining the role of personal factors, such as self-efficacy, within the context of medication adherence have been conducted in patients with other chronic illnesses such as HIV. Evidence from these studies shows that medication-taking self-efficacy beliefs predict adherence to highly active antiretroviral therapy (HAART). Cha, Erlen, Kim Sereika, & Caruthers (2008) examined the impact of perceived social support, depressive symptoms and medication-taking self-efficacy on self-reported medication adherence in persons with HIV. Their study proposed three models to examine the mediating roles of medication-taking self-efficacy and depressive symptoms: *Model 1* hypothesized that medication-taking self-efficacy mediates the negative relationship between depressive symptoms and self-reported medication adherence; *Model 2* hypothesized that medication-taking self-efficacy mediates the positive relationship between perceived social support and self-reported medication adherence; and *Model 3* hypothesized that depression mediates the positive relationship between perceived social support and medication-taking self-efficacy. A comprehensive model with the combined three hypotheses showed a good fit. The prediction of self-reported medication adherence through social support and depressive symptoms was fully mediated by self-efficacy. This study confirmed Bandura's self-efficacy theory that self-efficacy beliefs were affected by perceived social support and depressive symptoms. In *Model 1*, participants with greater depressive symptoms had lower medication-taking self-efficacy while participants with higher self-efficacy had higher rates of self-reported medication adherence. In *Model 2*, participants with higher medication-taking self-efficacy had higher self-reported medication adherence and perceived social support was found to indirectly impact medication adherence through self-efficacy. Lastly, in *Model 3*, participants with fewer depressive symptoms had higher medication-taking self-efficacy. The mediating role of depressive symptoms between perceived social support and medication-taking self-efficacy was partially supported.

Unni & Farris (2011) developed a conceptual framework to understand the determinants of medication non-adherence in both cholesterol-lowering and asthma maintenance medications. Their model demonstrated that self-efficacy was a significant predictor of all types of non-adherence for both types of medications. The predisposing factors of non-adherence for cholesterol-lowering medications included beliefs in medications and convenience; the factors for non-adherence for asthma medications included disease severity and perception of illness.

In a cross-sectional study of 1,024 patients with coronary disease, Sarkar, Ali & Whooley (2007) administered a validated measure of cardiac self-efficacy to examine the relationship between cardiac self-efficacy and health status outcomes. Cardiac self-efficacy was defined as participants' confidence in their ability to carry out daily life functions. An evaluation of the extent to which psychosocial factors mediated the relationship between self-efficacy and health status found that self-efficacy was significantly affected by depressive symptoms and depressive symptoms were predictive of worse health status. Patient self-efficacy was strongly predictive of health status including symptom burden, physical functioning and quality of life.

Self-efficacy has also been associated with self-management behaviors in various chronic conditions. Aljasem, Peyrot, Wissow & Rubin (2001) examined the relationship between diabetes management and self-efficacy associated with self-care behaviors. Self-care behaviors included exercise, diet, blood glucose testing and skipping medication. In this study, greater self-efficacy predicted less frequent skipping of medication in addition to carrying out other self-care behaviors more frequently. In another study, Chen et al. (2014) tested a model to explain the relationships between self-efficacy, health literacy, heart failure knowledge and adherence to self-care recommendations. Patients' self-efficacy, self-care maintenance and management adherence were evaluated by the Self-Care Heart Failure Index. The study found that self-efficacy was independently associated with self-care (p = .016), underscoring the importance of patient self-efficacy on implementation of self-care behaviors.

Self-efficacy has also been proposed as a mediating factor between educational attainment and health behaviors. Wolf et al. (2007) sought to examine the proximal relationships between health literacy, HIV medication adherence, while estimating the mediating role of treatment knowledge and self-efficacy. In this study, patients' self-efficacy, but not knowledge, mediated the impact of low health literacy on medication adherence (AOR 7.4, 95% CI = 2.7, 12.5). In their mediational analyses, the effect of literacy on adherence was reduced by 40% after knowledge and self-efficacy were included in the model. Medication self-efficacy was a significant mediating factor that independently predicted missed doses in patients' medication regimens.

2.1.3 Assessing Self-Efficacy in Clinical Settings

Until recently, reliable and valid tools to assess patients' self-efficacy for understanding and using prescribed medications have not been routinely used in clinical settings. Different scales have been developed to measure disease-specific self-efficacy or patients' confidence in their ability to take their medications correctly.

Cameron et al. (2010a) developed an assessment tool to assess patients' understanding of how medication is to be taken – specifically, patients' self-efficacy related to concepts of both understanding and using prescription medications. The Medication Understanding and Use Self-Efficacy Medication Understanding and Use Self-Efficacy (MUSE) scale assesses patients' learning about their medications and adherence to prescribed medication regimens. Moreover, the MUSE performs similarly well across literacy levels and can be used in a wide variety of contexts among various patient populations.

Based on the premise that self-efficacy is an important determinant of medication adherence, Risser, Jacobson, & Kripalani (2007) developed the Self-efficacy for Appropriate Medication Use Scale (SEAMS) to fulfill the need for a reliable and valid tool for measuring this construct. Its psychometric properties were evaluated among 436 patients with coronary heart disease and other comorbid conditions. This self-efficacy scale for medication adherence can be used in chronic disease management and in patients with a broad range of health literacy skills.

As a system for explaining health behavior in the context of the reciprocal relationship between the environment, individual factors and behavior, the Social Cognitive Theory serves as an effective model for examining the relationship between personal factors and medication adherence. The current study incorporates the specific construct of self-efficacy in an attempt to understand the relationship between individuals' self-efficacy and medication adherence behavior. Interventions to lower risky health behaviors are most effective when the knowledge of what motivates health behavior change and the understanding of the process through which it occurs are integrated into behavior change strategies. In order to develop effective interventions aimed at reducing medication non-adherence, it is essential that interventions be based on applicable theoretical models that can properly explain and predict negative behavior.

2.2 Acute Coronary Syndrome

Coronary artery disease (CAD) is a serious condition that can lead to myocardial infarction (MI), limitations in patients' health status (symptoms, function and quality of life) and death. As a result of atherosclerosis, a narrowed coronary artery impedes optimal blood flow and decreases oxygen delivery to the cardiac muscle, making it difficult for the heart to function properly. When the heart muscle does not receive a sufficient supply of blood, this can result in myocardial ischemia known as angina pectoris or chest pain. This pain can, in turn, limit patients' ability to function optimally and often impairs their quality of life. Atherosclerotic plaque in the coronary tree can be so severe that it results in acute coronary syndrome, including ST-segment elevation myocardial infarction, non-ST segment elevation myocardial infarction, or unstable angina (UA) (American Heart Association [AHA], 2007).

The most common presentation of coronary artery disease is ACS, the consequence of significant coronary artery disease. The majority of ACS patients recover and resume a clinical course similar to that of patients with stable coronary disease at one to three months following the acute phase of ACS. Patients who have suffered an ACS usually require long-term medical therapy and secondary prevention for CAD (secondary prevention for CAD is synonymous to secondary prevention for ACS) at hospital discharge and during post-discharge care.

Acute coronary syndromes, including AMI, are the leading causes of hospitalization for veterans (Ravelo et al., 2003). These life-threatening cardiovascular disorders are a major cause of emergency medical care and hospitalization in the United States, as well as lost productivity of the American workforce. In 1997, there were over 5 million visits to U.S. emergency departments for the evaluation of chest pain and related symptoms (Krumholz et al., 1999). Although the exact incidence is difficult to ascertain, using first-listed and secondary hospital discharge data, there were 1,680,000 unique discharges for ACS in 2001 (Graves & Kozak, 1998). In 1996, the National Center for Health Statistics reported 1,433,000 hospitalizations for UA or non-ST segment elevation myocardial infarction (NSTEMI). According to the National Registry of Myocardial Infarction, an estimated 30% of ACS patients have had ST segment elevation myocardial infarction (STEMI) of which, 20% of men and 30% of women will die within one year after having an initial MI (AHA, 2002). The risk of further cardiac complications, including a subsequent heart attack, sudden death, angina pectoris, heart failure or stroke is substantial (Braunwald, 1996). Recent advances in the treatment of acute MI have led to declines in hospital mortality but despite this improvement, the risk of recurrent events and mortality remains substantial in the year after the index MI hospitalization (Gheorhiade et al., 1996; Babev et al., 2005; Masoudi et al., 2006)

2.2.1 Depressive Disorders in Cardiovascular Disease

In 2012, an estimated 16 million adults aged 18 or older had at least one major depressive episode in the past year. This represented 6.9 percent of all U.S. adults (Substance Abuse and Mental Health Services Administration [SAMHSA], 2013). Based on the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), major depressive disorder (MDD) is defined as a period of two weeks or longer during which a person has a depressed mood or a loss of interest or pleasure in daily activities. This mood must represent a change from the person's baseline mood; impaired social, occupational, educational functioning and the presence of 5 or more specific symptoms, including 1) depressed mood or irritable most of the day, nearly every day, as indicated by either subjective report; 2) decreased interest or pleasure in most activities; 3) significant change in weight (5%) or change in appetite; 4) insomnia or hypersomnia; 5) change in activity; 6) loss of energy or fatigue; 7) feelings of worthlessness or excessive or inappropriate guilt; 8) diminished ability to think or concentrate, or more indecisiveness; and 9) suicidality (American Psychiatric Association [APA], 2000).

Approximately 20% of patients with cardiovascular disease suffer from MDD (Thombs et al., 2006). In a systematic review of the literature, Elderon and Whooley (2013) sought to understand how depression triggers and/or worsens heart disease (Figure 3). The authors concluded that across many studies, several behavioral and biological mediators have been identified as influencing cardiovascular disease, including: low omega-3 fatty acid levels, toxicity from antidepressants, platelet activation and inflammatory processes, smoking, physical inactivity, poor diet, and medication non-adherence. However, despite the findings reported in their review of published studies, the authors acknowledge that the precise pathways and interactions that lead to heart disease remain largely undetermined. Choi, Kim, Marti, & Chen (2014) et al reported similar data from the National Health and Aging Trends Study (NHATS). Their study assessed cross-sectional associations and longitudinal relationships between depressive symptoms and cardiovascular disease among 5,414 patients on two waves of NHATS conducted in 2011 (Time 1) and 2012 (Time 2). At Time 1, patients were categorized as having CVD or CVD risk factors if they disclosed that they had ever been diagnosed with “a heart attack or myocardial infarction” or “any heart disease including angina or congestive heart failure” or a diagnosis hypertension, diabetes, or self-reported smoking. At Time 2, patients were asked about any new diagnoses since their last interview. Depressive symptoms and risk factors were assessed at Time 1 and Time 2. The study showed that depressive symptoms were higher among those with cardiovascular disease than those without CVD. Depressive symptoms at Time 1 had a strong impact on the risk of CVD at Time 2 with each point increase on depressive symptoms scores associated with a 1.21-fold increased odds of a new CVD diagnosis or episode.

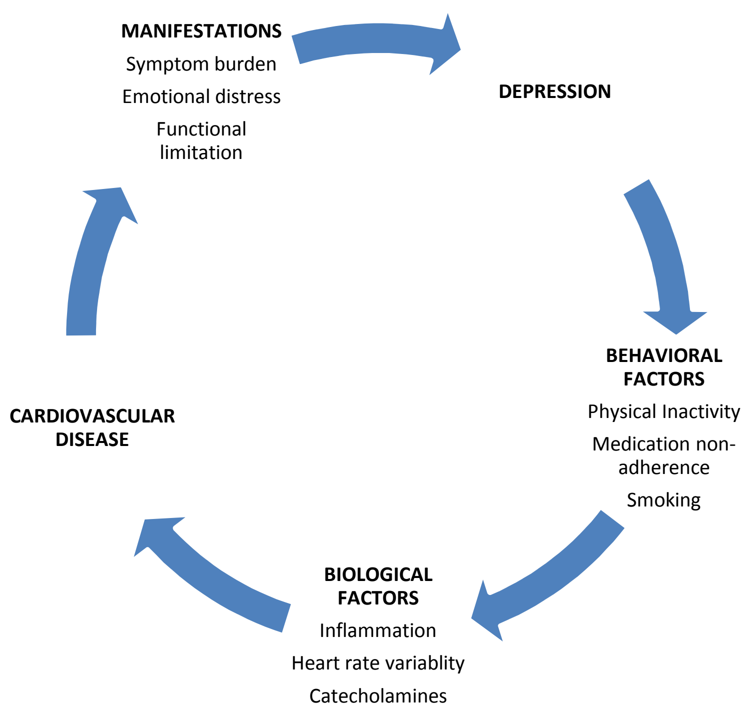


Figure 3. Relationship between depression and cardiovascular disorders (Elderon & Whooley, 2013)

Skala, Freedland and Carney (2005) reported that depressive disorders are more common in cardiac patients than they are in the general population with about half of patients who meet DSM-IV criteria for major depression following an AMI remain chronically depressed or relapse within 12 months. The authors point to evidence that suggests that as many as 30% of patients who were not depressed at the time of their AMI go on to develop minor or major depression within one year, with the majority of these cases developing during the first year. Approximately half of patients who have major depression at the time their CAD is diagnosed remain chronically depressed or relapse within one year, and 40% of those with minor depression at the time of diagnosis go on to develop major depression.

Identifying depressive symptoms in ACS patients is important because depression is known to predict outcomes for patients with ACS, including mortality, health services use and secondary prevention behaviors (Frasure-Smith, Lesperance, & Talajic, 1993; Lesperance, Frasure-Smith, Talajic, 2002; Ziegelstein et al., 2000). Patients with ACS who also have depression are at greater risk of further events than those without depression. Patients with depressive symptoms following an AMI are more likely to use cardiac and non-cardiac health care services following hospitalization and had a higher incidence of readmissions due to complications (Kurdyak, Gnam, Goering, Chong, & Alter, 2008; Lauzon et al., 2003; Parashar et al., 2006). In a prospective registry of AMI, Parashar (2006) measured depression during hospitalization and one month after discharge. Overall prevalence of moderate to severe depressive symptoms was 20% during hospitalization for MI, with 65% of patients with transient depression and 35% with persistent depression at one-month following discharge. Compared with non-depressed patients, patients with depression had worse outcomes including higher rates of re-hospitalization, mortality, more frequent angina, physical limitations and worse quality of life.

The Heart and Soul study, a prospective cohort study of psychosocial factors and cardiovascular outcomes in more than 1000 patients with stable CAD demonstrated that patients with baseline depressive symptoms had a 50% greater rate of subsequent cardiac events than patients without depressive symptoms (Whooley et al., 2008). The study found that several variables, including medication adherence, were potential mediators that intervene to explain the association between depressive symptoms and subsequent cardiovascular events.

Adverse cardiac outcomes have also been linked to behavioral factors, including poor adherence to prescribed medication regimens and cardiac rehabilitation and other lifestyle risk factors among patients with depression. The particular mechanism in which depression affects long-term prognosis is not completely understood, yet several studies have examined the relationship between depression and adherence to treatment recommendations. A meta-analysis of recent literature was conducted to examine the association between depression and medication adherence across a range of chronic diseases (Grenard et al., 2011). The primary outcome of interest across the 582 studies was medication adherence as defined by taking medication as prescribed by a health care provider. The studies covered a range of chronic diseases with the majority of studies on coronary heart disease, diabetes, hyperlipidemia and hypertension. The results of the meta-analysis showed a significant association between depression and poor medication adherence – the estimated odds of a depressed patients being non-adherent was 1.76

times that of the odds of a non-depressed patient. This corresponded to a risk-difference in non-adherence between depressed and non-depressed patients of 16%.

A separate study evaluating the association between depression and medication non-adherence found that after adjusting for potential confounders, depressed patients with stable CAD were more likely than those without to report not taking their medications as prescribed and deciding to skip their medications (Gehi, Hass, Pipkin, & Whooley, 2005). Patients with more severe depression had a 3-fold odds of being non-adherent and not taking medications as prescribed (OR, 3.1; 95% CI, 1.75-5.7; $p<.001$).

Ziegelstein (2000) interviewed patients three to five days following an AMI to assess symptoms and presence of depression. Patients' self-reported adherence to secondary prevention recommendations were also assessed four months following the hospitalization. The study showed that patients who were depressed during their hospitalization reported greater difficulty adhering to behavioral and lifestyle recommendations. Compared to non-depressed patients, patients with symptoms of mild to moderate depression or who had major depression and/or chronic depression during their hospitalization reported adhering less often to a low-fat diet, regular exercise, and stress reduction. Furthermore, patients with major depression and/or chronic depression also reported being less likely to take prescribed medications.

In a study of the relationship between depression and adherence to a prescribed cardiac medication in elderly patient with CAD, Carney et al. found that non-depressed patients adhered to their prescribed regimen on significantly more days than depressed patients (69% ± 27% versus 45% ± 31%, $p<.02$) (Carney, Freedland, Eisen, Rich, & Jaffe, 1995).

A meta-analysis of studies examining patients' treatment non-compliance with anxiety and depression found that depressed patients were three times as likely as non-depressed patients to be non-compliant (OR=3.03; 95% CI, 1.96-4.89) (DiMatteo, Lepper, Croghan, 2000). The authors hypothesized that depression impairs cognitive focus, energy and motivation which, in turn, may also affect a patient's willingness and ability to follow through with treatment recommendations and optimism that adherence to treatment is worthwhile. These findings are further supported in patients with other chronic illnesses. Ciechanowski, Katjon, & Russo (2000) explored the impact of depressive symptoms in primary care patients with diabetes on self-care, adherence to medication regimens, functioning and health care costs. Their study found that depressive symptom severity (low, medium, high) was significantly associated with worse adherence to a prescribed medication regimen with approximately twice as many interruptions in refills of oral hypoglycemic. Moreover, this finding was significantly associated with the degree of severity of depressive symptoms, with patients with high-severity having a significantly greater percentage of interruptions in their medication use than patients with low-severity. In a study of patients with diagnosed hypertension after controlling for potential confounding variables, Wang (2002) found that an increase in depression symptom severity was significantly associated with a lower odds of adherence with antihypertensive medications (OR=0.93, 95% CI, 0.87-0.99).

Depression has an important role in the course and outcome of common chronic diseases, such as asthma, arthritis, cardiovascular disease, cancer, diabetes, and obesity (Chapman, Perry, & Strine, 2014). Given the incidence of depression in ACS patients and their difficulty in adhering to secondary prevention recommendations, recognition of depression and depressive symptoms may be a factor that can be targeted to enhance patients' compliance with treatment regimens and ultimately improve their long-term prognosis.

2.3 Medication Adherence in Cardiovascular Disease

In 2003, the World Health Organization launched an initiative to improve global rates of adherence to medication therapies commonly used to treat chronic diseases and conditions (WHO, 2003). Through this initiative, WHO defined adherence as "*the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.*"

Studies have reported that an estimated 20% to 50% of patients with chronic diseases and conditions do not take medications as prescribed, with 20% to 30% of prescriptions never even filled (Kripalani, Yao, & Haynes, 2007; Peterson, Takiya, & Finley, 2003; Dunbar-Jacob & Mortimer-Stephens, 2001). Non-adherence to effective cardioprotective medications (β-blockers, statins, clopidogrel, and ACE-inhibitors/angiotensin II receptor blockers (ARBs) is a potentially modifiable risk factor that contributes to the persistently high risk of adverse outcomes following hospitalization for MI (Ho et al., 2006; Spertus et al., 2006; Jackevicious, Mamdani, & Tu, 2002). Prior studies have found that adherence to cardioprotective medications declines rapidly in the year following MI hospital discharge with approximately 60% of patients still taking statins routinely at 1-year (Maddox et al., 2007). Furthermore, approximately 20% of patients discontinue cardioprotective medications as early as 1 month following MI hospital discharge and these patients have significantly worse outcomes (Ho et al., 2006). Poor adherence to medications regimens accounts for substantial worsening of disease, death and increased health care costs in the United States (Osterberg & Blaschke, 2005). Of all medication-related hospital admissions in the United States, 33% to 69% are due to poor medication adherence at a cost of approximately $100 billion a year and as much as $290 billion per year in total avoidable medical spending (Mcdonnell & Jacobs, 2006; Senst et al., 2001; Osterberg & Blaschke, 2005).

Adherence-based savings in medical costs appear to be driven primarily by reductions in hospitalization rates at high levels of medication adherence. A review of 23 studies quantifying the cost consequences of noncompliance with medication for cardiovascular conditions showed that increased medication compliance/persistence leads to an increase in drug costs, but that the simultaneous increase in effectiveness of treatment and decrease of medical events offsets these higher drug costs resulting in an overall cost savings (Musbeck, Brixner, Benedict, Keskinaslan, & Khan, 2008). Sokol (2005) conducted a retrospective observational study to evaluate the impact of medication adherence on healthcare utilization and across diabetes, hypertension, hypercholesterolemia and congestive heart failure – among the major drivers of prescription drug expenditures. In their population-based study of over 137,000 patients, they found that high levels of medication adherence were associated with net savings in all-cause healthcare costs for diabetes, hypertension and hypercholesterolemia. Adherence-based savings in medical costs were primarily driven by reductions in hospitalization rates among patients with higher levels of adherence.

Patients treated for ACS require long-term secondary prevention therapies that are usually initiated during the initial hospitalization period and are frequently continued indefinitely as an outpatient. Studies suggest that medication adherence difficulties often begin at the time of hospital discharge and are common during the transition period that occurs from discharge to the outpatient setting (Makaryus & Friedman, 2005). As an example, one report shows that one in five post-AMI discharge prescriptions was left unfilled 120 days after discharge (Spertus et al., 2006). In another study assessing rates of medication discontinuation, 20% of patients discontinued use of cardioprotective medications (aspirin, ß-blockers, or statins) within 1 month after MI hospitalization (Ho et al., 2006). This study demonstrated that following AMI hospitalization, 1 in 8 patients discontinued aspirin, statin and β-blockers within 1 month of hospital discharge and this resulted in a 3-fold higher risk of mortality in the subsequent 11-months of follow up.

The Duke Databank for Cardiovascular Disease is a database of 31,750 patients who have undergone a cardiac procedure at Duke University Medical Center since 1969 and are still living with documented CAD during a follow-up survey period from 1995 to 2002. Since 1995, this survey has collected self-reported medication use by having patients list the medications they are currently taking. Newby (2006) examined the Duke Databank for Cardiovascular Disease and observed that, despite steady improvements in patient-reported use of evidence-based therapies, nearly 30% of patients were not consistently using aspirin and fewer than half reported consistent long-term use of *ß*-blockers, lipid-lowering therapy or combinations of these life-saving drugs. A separate study found that antiplatelet agents had the lowest fill rate among cardiovascular drugs, with only 44% of patients filling their prescriptions (Jackevicious, Li, & Tu, 2008).

Furthermore, a large cohort study of older patients found that 2-year statin adherence rates were approximately 40% for ACS patients, 36% for CAD and 25% for primary prevention. In a national VA cohort of ACS patients, Maddox (2007) demonstrated that only ~60% of patients discharged on statin therapy were still taking the medication at 1 year, a rate similar to that of non-VA populations. In the previously mentioned Heart and Soul Study, of the 1,015 participants with stable CAD, 8.2% reported non-adherence to their medications (Gehi, Ali, Na, & Whooley, 2007). After adjusting for baseline cardiovascular disease severity, depressive symptoms and other risk factors, self-reported non-adherence remained independently predictive of adverse cardiovascular events. Overall, 22.9% of non-adherent participants developed cardiac events compared with 13.7% of adherent patients (p = .03).

As can be expected from the reports discussed above, patient non-adherence to medications is a significant and major risk factor for adverse outcomes. In a meta-analysis of 21 observational studies across a variety of treatment groups, Simpson (2006) demonstrated a consistent association between adherence and positive health outcomes, including decreased mortality. Non-adherence to cardioprotective medications is prevalent among outpatients with CAD and is associated with a broad range of adverse outcomes, including all-cause and cardiovascular mortality, cardiovascular hospitalizations and revascularization procedures (Ho et al., 2008). Among patients with chronic CAD, non-adherence to cardioprotective medications had a prevalence of ~21-29%, depending on the medication. Non-adherent patients had a 10-40% relative increase risk of cardiovascular hospitalizations and a 50-80% relative increase risk of mortality. In addition, poor medication adherence has been associated with more physician visits, hospital admissions and longer hospital stays, in addition to the lost productivity associated with missed days of work. Among MI patients treated with a drug-eluting stent (DES) treated enrolled in the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) study, nearly 14% of them stopped thienopyridine therapy within 30 days and consequently had significantly higher rates of cardiac hospitalizations and were more likely die within the next 11 months (Spertus et al., 2006). The rate of cardiovascular re-hospitalization between 30 days and 1 year also tended to be greater in those who discontinued therapy. Among patients who discontinued therapy within 30 days, the rate of re-hospitalization for a cardiac condition was 23% compared to 14% among patients who continued therapy at 30 days.

A population-based study of post-AMI patients sought to identify factors of and outcomes associated with non-adherence to discharge prescriptions (Jackevicious, Li, & Tu, 2008). This study found that primary non-adherence was associated with an increased risk of death 1 year after AMI and patients who did not fill their discharge medications within 120 days after AMI had an 80% increased odds of death and those who filled only some of their medications had a 44% increased odds of death.

Decreased medical events and reduced costs can only be expected if patients achieve optimal treatment benefits from adhering to appropriately prescribed medication therapy (Wei et al., 2002). For instance, optimal medication use is a strong and independent predictor of lower 1-year mortality among patients admitted for ACS (Yan et al., 2007). Choudhry et al. (2014) compared patients randomized to full prescription coverage versus usual coverage groups to quantify the relationship between medication adherence and post-MI event-free survival. The study demonstrated that adherence to cardioprotective medications was associated with better outcomes – patients in the full prescription coverage group were significantly less likely to be readmitted for a major vascular event or coronary revascularization.

2.3.1 Causes of Medication Non-Adherence

The nature and determinants of non-adherence are complex and not well understood. The World Health Organization (2003) has categorized potential reasons for medication non-adherence into 5 broad categories including: 1) patient-related factors; 2) health system/health care team factors; 3) disease/condition-related factors, 4) therapy-related factors; and 5) socioeconomic-related factors.

Patient factors that may contribute to poor adherence include advanced age, cognitive impairment, depression, attitudes and perceived benefits of medications, availability of social support and complexity of medication regimens (Simpson, 2006; Robertson & Keller, 1992).

The health care system also creates barriers to medication adherence through limiting access to care, high-priced drugs and copayments (Osterberg & Blaschke, 2005). Doshi, Zhu, Lee, Kimmel, & Volpp (2009) conducted a quasi-experimental study to examine the impact of copayment increases on lipid-lowering medication adherence among veterans. Using the proportion of days covered and a continuous gap measures as the outcomes of interest, the study found that after an increase in co-payments, the percent of patients who were adherent declined most significantly among patients who were required to pay co-payments for all prescription drugs (-19.2%) followed by patients subject to some co-payments (-19.3%) relative to patients exempt from any co-pays (-11.9%). Similarly, the incidence of a continuous gap among both groups with all or some co-payment increased at twice the rate of the co-pay exempt group. Choudry et al. (2008) performed a cost-effectiveness analysis that assessed the incremental value of providing post-MI Medicare beneficiaries with full prescription drug coverage compared to current levels of drug coverage over their lifetime. The model in the study predicted that beneficiaries who received full prescription drug coverage would live an average of 8.56 quality-adjusted life-years and incur $111,600 in disease-related costs compared to patients with usual drug coverage that would live 8.21 quality-adjusted life-years and incur $114,000 in cardiovascular disease-related costs. The cost savings that were calculated were attributed to reductions in non-drug expenditures and cumulative cost-savings and improvements in survival occurred within the first year following the cardiac event. In a separate study, Choudry, Avorn, Antman, Schneeweiss, & Shrank (2007) developed a model to estimate the changes in event rates and healthcare spending if combination pharmacotherapy was provided with no out-of-pocket expenses to MI patients with some prescription drug coverage. Using less conservative cost inputs, the study estimated that providing patients with full prescription drug coverage would result in an increase in adherence from 50% to 76% and that for every 100 patients, there would be 1.1 fewer deaths, 13.1 fewer non-fatal MIs, 1.2 fewer nonfatal strokes, and 6.6 fewer readmissions for congestive heart failure. When applying more conservative cost inputs, the study found an increase in adherence from 50% to 63% and result in 0.4 fewer deaths, 5.7 fewer non-fatal MIs 0.5 fewer nonfatal strokes and 1.8 fewer readmissions for congestive heart failure for every 100 patients.

Therapy-related factors such as the complexity of prescribed medication regimens also hampers adherence to medications (Ingersoll & Cohen, 2008). Chapman et al. (2005) examined the patterns and predictors of concomitant adherence among 8,000 adults who had concomitant antihypertensive and lipid-lowering treatment. Adherence was measured using pharmacy refill data in 3-month intervals and was defined as having 80% of days covered during each interval. The study found that adherence rates dropped from 44.7%, 35.9%, and 35.8% at each 3-month interval and patients who took fewer other medications were more likely to be adherent compared to patients taking six or more medications. Similarly, Eisen, Miller, Woodward, Spitznagel, & Przybeck (1990) sought to determine the relationship between prescribed daily dose frequency and patient medication compliance among 105 hypertensive patients. Patient's adherence to antihypertensive medications was monitored by special pill containers that electronically recorded the date and time the patient removed medication from the container. Compared to patients with once-daily dosing, patients who took their medication three times per day had poorer adherence (83.6% versus 59%, respectively).

Associations have also been found between socioeconomic status, demographic-related factors and medication non-adherence. Jackevicious (2008) conducted a population-based cohort study to characterize the factors associated with primary non-adherence following AMI. Primary non-adherence was divided into 3 categories: patients who filled all, some or none of their prescribed medications within 120 days post-hospital discharge. Among the patients in the study cohort, lower income status was one of the most significant factors associated with filling all compared to none of the prescribed medications.

In a similar study, Marcum et al. (2013) studied the prevalence and correlates of self-reported medication non-adherence among older adults with chronic cardiovascular conditions. Self-reported medication non-adherence outcomes were assessed using a cost-related non-adherence scale and the validated Morisky Medication Adherence Scale (MMAS). Among the 6 factors that were examined, only black race was found to be significantly associated with non-adherence based on the MMAS. After controlling for various demographic, health status and access to care factors, black participants were between 85% to 114% more likely to report medication non-adherence than white participants.

2.3.2 Measures of Adherence

To date, medication adherence behavior can be divided into two main components: adherence and persistence (Figure 4) (Ho, Bryson, & Rumsfeld, 2009; Cramer et al., 2008). Medication *adherence* refers to the extent to which a patient conforms to provider recommendations regarding timing, dosage and frequency of medication taking. Medication *persistence* refers to the act of conforming to a recommendation of continuing treatment for the prescribed length of time. Persistence, which is based on the patient's length of therapy, informs whether a patient's length of therapy meets or exceeds a certain threshold (Fairman & Motheral, 2000). Individuals who are classified as persistent with medication therapy refill their medications frequently and regularly (Sikka, Xia, & Aubert, 2005). Persistence analyses must always include a "permissible gap" defined as a pre-specified limit of the number of days allowed between refills.

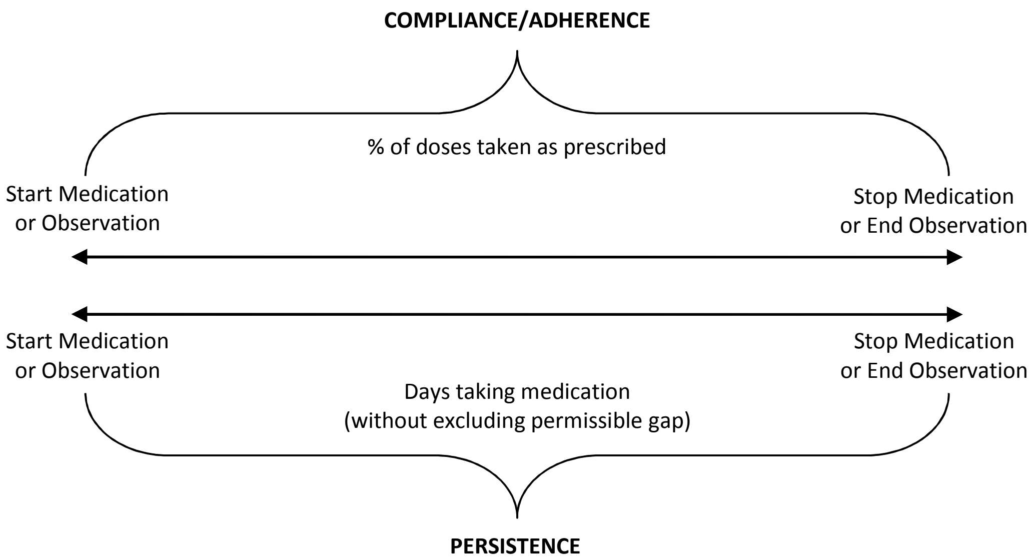


Figure 4. Definitions of compliance (adherence) and persistence (Cramer et al., 2008).

There are a variety of methods, both direct and indirect, for measuring medication adherence (Table 2). *Direct methods* include measurement of levels of medicine, metabolites or biological markers in a patient's blood or directly observed therapy. These direct methods pose limitations which make them unreliable, expensive and impractical for routine use. *Indirect methods* include patient self-report, questionnaires, rates of prescription refills, electronic medication monitors, and pill counts. However, patient bias, recall and manipulation are limiting factors for the reliability of these measures. Pill counts tally the number of pills that a patient has not consumed by the time of their next scheduled appointment. Adherence is calculated by subtracting the number of remaining pills from the number prescribed pills within the time period since the medication was dispensed (Farmer, 1999). While easy to perform, pill counts do not accurately capture the exact timing of medication taking, and data can be easily manipulated by patients. Pill counts rely on knowing the exact dates of refills and patients must bring in all of the medication they have not consumed. Some patients may deliberately not return medications to mask their non-adherence. Furthermore, pill counts do not provide information regarding the patient's pattern of adherence. The use of specific methods to measure adherence ultimately depends on the clinical situation and availability of data.

Table 2: Methods of Measuring Adherence (Osterberg & Blaschke, 2005)

Test	Advantages	Disadvantages
Direct methods		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them; impractical for routine use
Measurement of the level of medicine or metabolite in blood	Objective	Variations in metabolism and "white coat adherence" can give a false impression of adherence; expensive
Measurement of the biologic marker in blood	Objective; in clinical trials, can also be used to measure placebo	Requires expensive quantitative assays and collection of bodily fluids
Indirect methods		
Patient questionnaires, patient self-reports	Simple; inexpensive; the most useful method in the clinical setting	Susceptible to error with increases in time between visits; results are easily distorted by the patient
Pill counts	Objective, quantifiable, and easy to perform	Data easily altered by the patient (e.g. pill dumping)
Rates of prescription refills	Objective; easy to obtain data	A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system
Assessment of the patient's clinical response	Simple; generally easy to perform	Factors other than medication adherence can affect clinical response
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of taking medication	Expensive; requires return visits and downloading data from medication vials
Measurement of physiologic markers (e.g. heart rate in patients taking beta-blockers)	Often easy to perform	Marker may be absent for other reasons (e.g. increased metabolism, poor absorption, lack of response)
Patient diaries	Help to correct for poor recall	Easily altered by the patient
When the patient is a child, questionnaire for caregiver or teacher	Simple; objective	Susceptible to distortion

Electronic pharmacy data can serve as a proxy measure of patients' adherence behavior. Pharmacy claims databases include patient-level prescription information that is systematically collected and stored in a centralized location and is often used in closed health care systems that include integrated pharmacy services. However, the use of pharmacy prescription refill data necessitates that patients obtain their medications within a closed pharmacy system. The act of obtaining refills and the frequency with which the refills are acquired reflect different aspects of adherence behavior, and adherence based on pharmacy refill data have been correlated with a broad range of patient outcomes including higher all-cause mortality (Ho et al., 2008). The most common pharmacy-based measures are the medication possession ratio (MPR) and proportion of days covered (PDC), both of which are defined by the number of doses dispensed in relation to a dispensing period. The main distinction between these two measures is the maximum number of days covered. The maximum proportion of days covered is 1.0, which indicates full adherence, whereas the medication possession ratio accounts for oversupplies and can have a value >1.0. The medication possession ratio and proportion of days covered measures correlate well with the quantity of doses taken but not the timing of the doses, and the assessment of adherence using these measures is more difficult to ascertain when the length of follow-up varies among patients (Choo et al., 1999).

In general, for measures relying on pharmacy refill data, patients with medications available 80% of the time have generally been categorized as adherent (Ho, Bryson, & Rumsfeld, 2009). This cut-off has been adopted in the majority of medication adherence studies and has been associated with patient outcomes. The appropriate cut-off point for different measures of medication adherence will ultimately depend on the specific medication, its formulation and the specific disease condition.

2.3.3 Strategies for Improving Adherence

To date, interventions to improve medication adherence have produced mixed results across various chronic diseases. In general, single-strategy interventions have been less successful than multi-modal interventions because the reasons for non-adherence are multi-factorial (Kripalani, Yao, & Haynes, 2007; Petrilla, Benner, Battleman, Tierce, & Hazard, 2005; McDonald, Garg, & Haynes, 2002; Schroeder, Fahey, & Ebrahim, 2004). In contrast to uni-modal interventions that focus on a single intervention strategy, multi-modal interventions combine multiple interventions to produce a desired outcome above and beyond what could be achieved through a solitary intervention.

In a systematic review of 33 randomized controlled trials, McDonald, Garg, & Haynes (2002) examined several interventions aimed at improving patients' adherence to prescribed medication regimens. A total of 39 different interventions including single intervention strategies and combination strategies were examined, including patient education; enhanced communication and counseling; facilitating the convenience of care; improving patient activation; special pill packaging; and reinforcement and rewards for improved adherence and treatment response. Approximately half (49%) of the studies that were reviewed demonstrated a statistically significant increase in adherence although even the most effective interventions did not result in large improvements in adherence and only showed modest improvements in treatment outcomes.

Peterson et al conducted a meta-analysis of randomized controlled studies of interventions targeted at patients and caregivers to improve medication adherence (Peterson, Takiya, & Finley, 2003). Interventions were categorized as either behavioral (tools or actions that would change a patient's skill level or routine) or educational (strategies that taught the patients about their medication or disease). The findings revealed an increase in adherence of 4-11%, however the study suggested that because of the many varying factors that impact patients' adherence, no one approach emerged as the most effective. In a similar study, Roter et al. (1998) conducted a separate meta-analysis to evaluate the effectiveness of interventions to improve patient compliance. Interventions were classified into 3 categories based on their underlying theoretical focus (educational, behavioral, and affective). Measures of adherence were calculated by health outcomes, direct methods, and indirect methods, self-report and health care utilization. Across the 153 studies that were included in the meta-analysis, no single strategy or programmatic focus showed any clear advantage over another strategy, however interventions that included a combined theoretical approach were shown to be more effective than single-focus interventions. Ho et al. (2014) conducted a randomized control trial to assess the effect of a multi-faceted intervention designed to improve adherence to cardioprotective medications versus usual care following hospitalization for ACS. The intervention included 4 main components: 1) pharmacist-lead medication reconciliation and tailoring; 2) patient education; 3) collaborative care; and 4) medication reminder and medication refill calls through an automated voice messaging system. Compared to patients in the usual care group, patients receiving the intervention had higher medication adherence (73.9% versus 89.3%, $p = .003$). The effect of the intervention, which adapted components of components of other successful adherence interventions, supports the use of a multifaceted patient-centered approach in improving adherence.

The results from these studies provide further evidence to support that the most effective interventions for medication adherence include multi-faceted, patient-centered strategies that are aimed at minimizing the assorted challenges that patients face with adhering to their prescribed medication regimens.

2.3.4 Psychosocial and Behavioral Factors and Medication Adherence

Patients with chronic health problems, particularly older populations with multiple diseases, frequently require numerous and complicated medication regimens. Therefore, good cognitive skills are required for proper medication management for these chronic comorbid conditions. Estimates of medication adherence in older adults without cognitive impairment have been previously reported in the range of 26% to 84%, compared to 42% to 97% among adults with cognitive impairments (Cooper, Love, & Raffoul, 1982; Poon, Lal, Ford, & Braun, 2009).

An evidence-based systematic review of 597 studies identified a number of barriers to medication adherence among the cognitively impaired. These barriers included poor memory, lack of medication knowledge, deficient health literacy, concern for adverse effects and cost (Campbell et al., 2012). Furthermore, this study found that short or inadequate interactions between patients and their healthcare providers contribute not only to poor patient-provider relationships but creates a fundamental barrier to medication adherence. Patients with cognitive impairments lack the ability required for self-care management activities and the poor communication with the health care provider becomes an important limitation for patients to retain information about new medications or change in existing medications. In a separate study, Hawkins et al. (2012) examined cognitive impairment in a population of outpatient veterans with heart failure. Unrecognized cognitive impairment was found in over half of patients. The results of regression analyses revealed a statistically significant association between increasingly severe cognitive impairment and poorer medication adherence. Subjects with no cognitive impairment had an adherence rate of 78%, those with mild cognitive impairment had adherence of 70% and those with severe cognitive impairment had adherence of 73%. Compared to no cognitive impairment, medication adherence worsened by 8 percentage points (78% to 70%, $p = .017$) for patients with mild cognitive impairment but did not continue to worsen for patients with dementia.

Among other factors, self-efficacy has gained increasingly strong recognition as a predictor of medication adherence. Cameron et al. (2010b) developed an assessment tool to evaluate patients' understanding of how medication is to be taken – specifically, patients' self-efficacy related to concepts of both understanding and using prescription medications. This tool sought to better understand the gap between a provider's provision of information to a patient and the patient's ultimate adherence or lack thereof. The previously defined MUSE scale addresses patients' learning about their medications and adherence to prescribed medication regimens (Cameron et al., 2010a).

Patients with symptoms of depression are more likely to have poor adherence to prescribed medication regimens than those without depressive symptoms. In a study of heart failure patients, Wu, Lennie, Dekker, Biddle & Moser (2013) examined the combination of depressive symptoms and medication adherence as a predictor of cardiac event-free survival. Consistent with other findings, heart failure patients who were adherent to prescribed medications had a lower risk of cardiac events than those who were non-adherent. Similarly, patients with depressive symptoms were at higher risk for emergency department visits, hospitalizations or death than those without depression. The risk of experiencing a cardiac event was 5 times greater for patients with depressive symptoms and medication non-adherence, after adjusting for covariates. For patients with only one risk factor, the risk of experiencing a cardiac event was only 1.3 times greater than patients with neither medication non-adherence nor depressive symptoms.

2.4 Health Literacy

In 2003, the National Assessment of Adult Literacy (NAAL) surveyed over 19,000 adults age 16 or older to directly measure health literacy (White & Dillow, 2005). Nearly 40% of the general population scored in the "basic" or "below basic" categories. While low health literacy is frequent within the general population, certain groups of individuals have an even higher prevalence of the problem, including the elderly, minorities, individuals with lower educational attainment, those with English as a second language, and people living in poverty (Berkman et al., 2011). The association between these socio-demographic factors and health literacy has consistently shown that non-white minorities, educational attainment and quality, and being elderly are related to declining levels of health literacy.

Health literacy encompasses specific skills related to an individual's ability to adequately function in the healthcare environment. Lack of knowledge or the inability to comprehend the range of health literacy actions that individuals are likely to face in their daily lives, ranging from determining the correct dosage of over-the-counter medicine to understanding health insurance forms, limits one's ability to take good care of their own health. Adherence to prescription drugs, compliance with medical treatment, self-management of disease, and communication with health care professionals are among fundamental health activities that are compromised in individuals with limited health literacy skills.

More than 90 million adult Americans currently lack the ability to understand the basic health information needed to effectively function in the health care system (Kutner, Greenberg, Jin, & Paulsen, 2006; Carmona, 2006). The financial cost related to the sum of these aspects of limited health literacy was estimated at $69 billion in 1996 (Institute of Medicine [IOM], 2004). Additional health care expenditure related to poor literacy is due to the increased health care services utilization among individuals with limited health literacy.

In addition to issues related to simple lack of comprehension, limited health literacy impacts an individual's health care experience in multiple other ways. In particular, limited health literacy often goes undetected in part because individuals feel ashamed and do not admit reading difficulties or vocabulary limitations. A study assessed patients' disclosure of reading difficulty, coping mechanisms and feelings of shame (Parikh, Parker, Nurss, Baker, & Williams, 1996). When asked about the potential association of shame and low literacy, more than half of all patients with low literacy stated feeling so ashamed they would not talk to anyone about their difficulty reading. Over two-thirds of these patients had never told their spouses and more than half had never told their children, relatives or friends of their reading problems. These important results call attention to the strong impact of non-cognitive aspects of limited literacy on the effectiveness of health care.

In recent years an increasing number of studies have examined the association between health literacy and health outcomes, but relatively few have explored potential mediators of this association. A systematic review of interventions designed to improve health outcomes revealed that most interventions have been implemented to improve health knowledge and comprehension by people with low literature skills (pignone, DeWalt, Sheridan, Berkman, & Lohr, 2005). Efforts to improve health outcomes by increasing health knowledge or teaching health behaviors are fundamental, yet an understanding of the intricacies of doctor-patient relationship including communication and the role of shared decision-making specific to individuals with limited health literacy skills is not well established.

Studies have examined the relationship between health literacy and multiple indicators of health status, health outcomes, health services utilization and medical self-management. These studies draw attention to the profound implications that limited health literacy skills has for the health care system and, importantly, for the overall health, longevity and quality of life of the individual. Surprisingly, the relationship and determinants of health literacy and medication adherence among patients with chronic diseases has only recently received some attention. A study examining the factors associated with this relationship suggested that low health literacy was a predictor for poor refill adherence, with 40% of patients having low medication refill adherence (Gazmararian et al., 2006). Marvanova et al. (2011) examined the association of health literacy, cognitive function, number of pre-admission medications and other factors on patients' understanding of their pre-hospitalization medication regimen. This cross-sectional assessment using baseline data from the Pharmacist Intervention for Low Literacy in Cardiovascular Disease (PILL-CVD) Study, demonstrated that inadequate or marginal health literacy and cognitive impairment were associated with low medication understanding. Kaphingst, Goodman, MacMillan, Carpentar, & Griffey, 2014) also examined the role of cognitive dysfunction in the relationship between age and health literacy. In their study of among adult patients, they hypothesized that age would be inversely related to health literacy and that this association would be reduced by excluding older adults with cognitive impairments. Scores of all assessments of health literacy and numeracy differed significantly across patient subgroups defined by age and cognitive impairment. Older adults with cognitive impairments had significantly lower scores on all health literacy assessments compared to older patients with no cognitive dysfunction or younger patients.

Nguyen et al. (2013) examined the relation of cognitive function to health literacy in older adults with diabetes. Diabetes management necessitates a number of complex skills which rely heavily on printed and verbal instructions that require a high degree of health literacy skills. After adjusting for education and other confounders, this study found a clear relationship between cognitive function and health literacy. Across the three measures of cognitive function that were used in this study, the findings showed that higher cognitive functioning was significantly associated with an increased odds of having adequate health literacy. These findings suggested that patients with poor medication understanding measured by health literacy necessitate intensive counseling about safe and effective medication use.

Paasche-Orlow & Wolf's (2007) conceptual model explains the causal pathways linking health literacy to health outcomes. Based on an evidence-based analysis of health literacy, the authors described the systematic, interactional and self-care mechanisms that explain the association between limited health literacy and health outcomes. This model underscores the importance of a contextual appreciation of health literacy and recognizes that the causal mechanisms of the health literacy-health outcomes relationship are due to both patient factors and health care system factors. At different points along the continuum of care, limited health literacy is shown to influence access and utilization of health care, intrinsic and extrinsic patient factors, and patient-provider interactions. Osborn, Paasche-Orlow, Bailey, & Wolf (2011) sought to validate one-third of the Paasche-Orlow and Wolf model and focused on the patient self-care pathway in patients with hypertension. Taking into account patients' demographics, health literacy, disease-specific knowledge, self-efficacy and health status, their model demonstrated the association between health literacy and self-reported health via a sequence of intervening variables. The results of the path analytic models revealed significant associations were found with different relationships, such as health literacy and disease-specific knowledge ($r = 0.22$, $p < .001$); knowledge and self-efficacy ($r = 0.13$, $p < .001$); self-efficacy and physical activity ($r = 0.17$, $p < .01$); and physical activity and health status ($r = 0.17$, $p < .01$).

2.4.1 Health Literacy, Health Status and Health Outcomes

Health literacy, health status and health outcomes vary considerably depending on multiple variables, a particularly important one being age. The issue of health literacy among the elderly is compounded by issues related deteriorating health. Sudore et al. (2006) prospectively studied an elderly cohort of participants in the Health, Aging and Body Composition (Health ABC) study from 1999 to 2004. All participants were well-functioning at baseline and literacy was assessed in year three of this prospective study. Nearly 25% of the study participants had limited literacy and this group accounted for a higher percentage of deaths and all-cause mortality compared to those with adequate literacy. The study also found that elderly persons with limited literacy had a 9% increase in risk of death over five years.

2.4.2 Assessing Health Literacy in Clinical Settings

A doctor-patient relationship is usually a complex one due to multiple variables on both sides of the relationship. From the patient’s side, the recognition of his or her literacy skills is often overlooked, but it is nonetheless critically important and must be assessed. Considering the aforementioned issues related to the reluctance of individuals with limited health literacy to reveal or admit reading difficulties to close family members or friends, these individuals are likely to use a number of strategies to hide their limited literacy skills from their health care providers.

Most health professionals are unaware that low literacy is common and may assume that patients do not understand medical information because of a lack of capacity to learn (Rogers, Wallace, & Weiss, 2006). In a study of family medicine resident physicians' ability to accurately identify patients with a limited understanding of medical information, the authors found that residents correctly identified less than half of patients with inadequate or marginal literacy as individuals who might have below average ability to understand medical information. Additionally, inadequate functional health literacy may also pose a barrier to assessing medication adherence since these patients are more likely to have difficulties in accurately reporting what medications they are taking Youmans & Schillinger, 2003). These misconceptions can lead to poor knowledge transfer between physician and patient, resulting in noncompliance with medication, increased health care services utilization and worse health outcomes.

Several tools have been developed to assess functional health literacy in the clinical setting. The most widely used measures are the Rapid Estimate of Adult Literacy in Medicine (REALM) and the Test of Functional Health Literacy in Adults (TOFHLA). These tests measure selected domains that are thought to be markers for an individual's reading capacity (Baker, 2006). The REALM is a 66-item word recognition and pronunciation test that measures the extent of the patient's vocabulary (Davis et al., 1993). The TOFHLA consists of a 50-item reading comprehension and 17-item numerical ability test to assess individuals' capacity to read and understand actual hospital documents and labeled prescription bottles (Parker, Baker, Williams, & Nurss, 1995). A shortened version, S-TOFHLA includes 4 numeracy items and 2 prose passages. The maximum time for administration was reduced from 22 minutes

(TOFHLA) to 12 minutes (S-TOFHLA) (Baker, Williams, Parker, & Gazmararian, 1999). The S-TOFHLA has demonstrated good internal consistency, reliability, and validity as a practical measure of health literacy.

Both tests are easily administered and have been shown to predict knowledge, behaviors and outcomes.

2.4.3 Health Care Utilization and Health Literacy

The risk of hospitalization among individuals with inadequate literacy was examined in 3,260 Medicare managed care enrollees (Baker et al., 2002). Individuals with inadequate and marginal functional health literacy were more likely to be hospitalized than were those with adequate health literacy and were also more likely to be hospitalized two or more times. These results underscore the value of health literacy and how lack of it results in higher health care costs due to increased use of health care services. In a similar study, Baker investigated the association between patient literacy and hospitalization (Baker, Parker, Williams, & Clark, 1998). Despite dissimilarities in the study populations, the study suggested that patients' reading ability was independently associated with their risk of hospitalization. Patients with inadequate literacy had more than twice the risk of being hospitalized and were more likely to have been hospitalized two or more times.

Baker found that self-reported health was strongly related to literacy in a sample of English- and Spanish-speaking patients in Los Angeles and patients in Atlanta (Baker, Parker, Williams, Clark, & Nurss, 1997). Overall, patients with inadequate or marginal health literacy were more likely to report their health as poor and were more likely to have been hospitalized in the previous year.

2.4.4 Mechanisms Linking Psychosocial and Behavioral Factors with Health Literacy

One possible explanation for increased health service utilization among patients with limited health literacy may be attributed to the self-management skills – or lack thereof - in this population. As stated above, health literacy encompasses cognitive skills needed to access information and understand and process information in ways that help to maintain health. An individual with limited literacy will find challenging to manage a health condition that requires detailed knowledge and skills. In fact, individuals with low health literacy are less knowledgeable about diseases and less capable of properly caring for themselves (Wolf, David, Tilson, Bass, & Parker, 2006). For example, the failure to pay attention to warnings or special instructions on medicine bottles has been shown to negatively impact the safe administration of medication and consequently results in patients receiving little or no benefit from their medication or becoming ill. In their study of misunderstanding of prescription warning labels (PWLs) among patients with low literacy, Wolf et al. found that the rate of PWL comprehension ranged widely from 0% to78% (Wolf et al., 2007). Among the common causes of misunderstanding were single-step versus multi-step instructions, reading difficulty of text, use of icons and use of colors. In a separate study of literacy and HIV medication adherence, Wolf et al. (2007) reported that patients with low literacy had the highest rate of non-adherence and were more likely to possess poorer knowledge of their HIV treatment. The predictors of the ability to correctly identify medications and describe how they should be taken, collectively referred to as medication management capacity, were evaluated looking for an association with literacy, cognitive function, regimen complexity and socio-demographic characteristics (Kripalani et al, 2006). The study found that 38% of patients were unable to identify all of their medications, despite being able to look at the bottle, label, or pills. Furthermore, over half of the patients with inadequate literacy skills were unable to identify all of their medications compared with 25% of those with marginal literacy and 7% of those with adequate literacy skills.

In addition to adequate cognitive skills required for proper adherence to medication, in some cases, patients' knowledge of chronic disease management also requires comprehension of medical advice and patient education and skills of how to use medical devices (Barrett & Puryear, 2006). Williams, Baker, Parker & Nurss (1998) examined the relationship between functional health literacy level and knowledge of disease and treatment among patients with hypertension and diabetes. The diseases examined in this study required patients to understand how to properly take multiple medicines, make lifestyle modifications and, in the case of diabetes, an understanding of the diabetic diet, insulin injection and home glucose monitoring. The study found that almost half of the patients had insufficient functional health literacy and these patients had significantly less knowledge of their disease, of the importance of lifestyle modifications and of essential self-management skills. In a separate study, Williams, Baker, Honig, Lee, & Nowlan (1998) investigated the relationship of patients' literacy skills with asthma knowledge and metered-dose inhaler (MDI) techniques. Proficiency in MDI skills was measured by asking patients to demonstrate their usual MDI technique against a six-step scale that assessed the patients' ability to correctly use their inhaler. Poor MDI skills were found in 89% of patients with low literacy compared to only 48% of patients with adequate literacy. Levinthal, Morrow, Tu, Wu, & Murray (2008) examined the role of cognitive and sensory abilities as mediators of age and education in determining health literacy among patients with hypertension. After controlling for cognitive and sensory variables, the relationship between years of education and health literacy scores health literacy scores had only a marginally significant association with age. Cognitive and sensory variables accounted for a large part of the variance in health literacy scores compared to age. These findings suggested that cognitive function was more strongly associated than education for explaining any age-related differences in health literacy.

Overall, these studies support the conclusion that individuals with limited health literacy are not always able to fully comprehend medical advice and develop the self-management skills needed to control and prevent adverse health outcomes.

2.5 Conceptual Framework

The World Health Organization has categorized potential reasons for medication non-adherence into five broad categories including: health system, type of disease condition, patient, therapy, and socioeconomic-related factors (Figure 5) (WHO, 2003). The multiplicity of these factors implies that, to be successful, interventions designed to improve medication adherence must address all the multiple components related to the various different reasons underlying non-adherence.

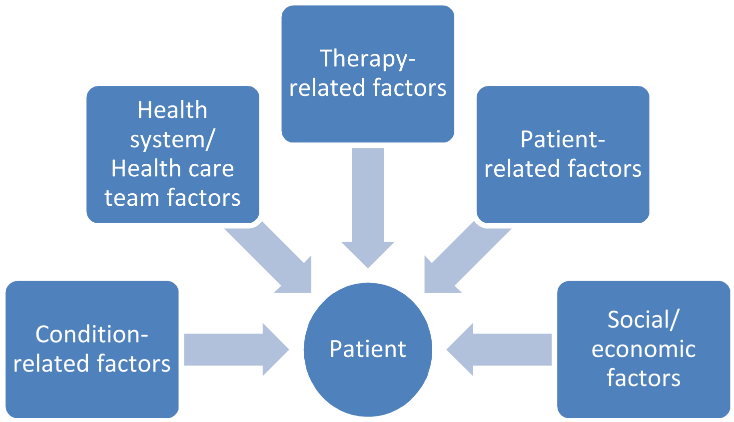


Figure 5. The Five Dimensions of Adherence (WHO, 2003)

Each of these factors contribute to fundamental constructs found across models of health behavior which must be understood within the context of the individual patient and the desirable behavior in order to induce a positive change.

Central to the current study is the role of specific patient-related factors (e.g. self-efficacy, health literacy, depression and cognitive functioning) that impact medication adherence. Understanding the interaction between underlying patient- and condition-related factors that interfere with medication adherence is vital to developing strategies that address these factors and for improving deficits in health literacy, self-efficacy and treating depression and mitigating the impact on patients' adherence behaviors. Based on the evidence presented above, this study examines a hypothesized predictive model and mediation model of medication adherence. Figure 6 presents the conceptual framework for this study which presents the pathways between patient- and condition-related factors including health literacy, self-efficacy, cognitive functioning, depression and medication adherence. In brief, three separate but interrelated and reciprocally influencing variables, e.g., cognitive function, health literacy and depression, result in variable degrees of self-efficacy which, in turn, becomes the basic determinant of medication adherence and, eventually, influences the degree of success of the prescribed medication regimen.

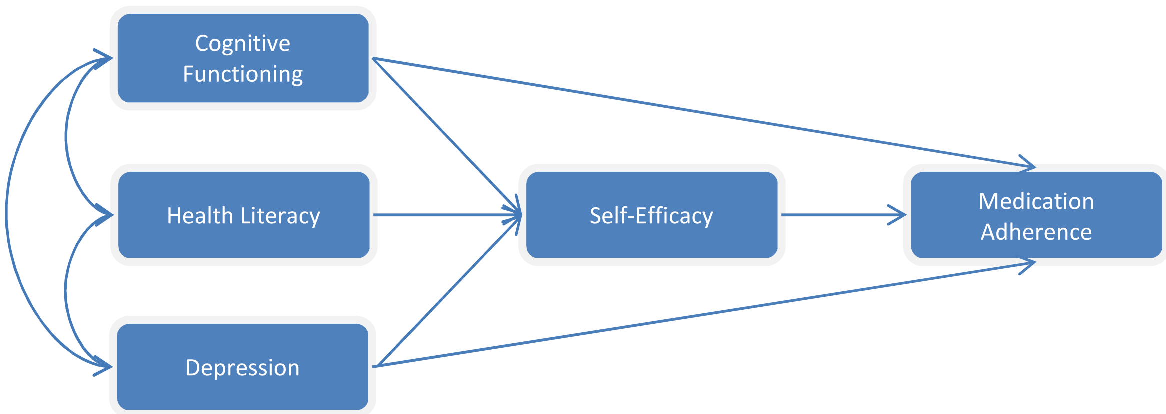


Figure 6. Conceptual Framework

In addition, this study offers a model that suggests that the effects of the predictor variables - health literacy, depression and cognitive functioning - on medication adherence may be partially mediated through self-efficacy. This model hypothesizes that when self-efficacy has been controlled for, any previous relationship between each of the predictor variables will significantly decrease in size or will no longer be significant indicating evidence of mediation (Baron & Kenney, 1986).

CHAPTER 3: DESIGN AND METHODS

3.1 Research Design

This study is a cross-sectional, secondary analysis of data from the MEDICATION study (**M**ulti-Facet**ED I**ntervention to Improve **C**ardiac Medication **A**dherence and Secondary Preven**TION** Measures). The MEDICATION study was a three-year multi-site patient-level prospective randomized controlled trial to evaluate usual care compared to a multi-faceted patient-centered intervention aimed at improving adherence to cardioprotective medication among veterans following an ACS hospital discharge.

The multi-faceted patient-centered intervention adapted elements of prior successful adherence interventions and included the following core components: collaborative care (between pharmacists, primary care providers, and cardiologists), patient education (tailored to patient needs and provided on a regular ongoing basis), tailoring of medication regimens (i.e., simplification of dosing, use of pill boxes, synchronization of refill dates), and tele-monitoring via interactive voice response (IVR) technology as well as patient-specific aides based on identified needs.

This dissertation study will examine the role of health literacy, self-efficacy, depression and cognitive functioning as potential predictors of adherence to cardioprotective medications in veterans who have been hospitalized for an ACS event. In keeping with the underlying theoretical framework for this study – the Social Cognitive Theory - the primary variable of interest is self-efficacy. This study will explore reported levels of this variable among veterans and its impact on health literacy, cognitive function and depression and overall medication adherence.

3.2 Study Setting

The Veterans Administration (VA) was established in 1930 when Congress authorized the President to "consolidate and coordinate Government activities affecting war veterans." The three component agencies - the Veterans Bureau, the Bureau of Pensions of the Interior Department, and the National Home for Disabled Volunteer Soldiers - became bureaus within the VA. The Veterans Health Administration (VHA) is home to the United States' largest integrated health care system consisting of 150 medical centers, nearly 1,400 community-based outpatient clinics, community living centers, Vet Centers and Domiciliaries. The VA health care system has grown to include 152 hospitals; 800 community based outpatient clinics; 126 nursing home care units; and 35 domiciliaries. Together, these health care facilities and the more than 53,000 independent licensed health care practitioners who work within them provide comprehensive care to more than 8.7 million veterans each year (National Center for Veterans Analysis and Statistics, 2014). VA health care facilities provide a broad spectrum of medical, surgical, and rehabilitative care.

The VA has a large and relatively controlled managed care system with data collected on all patients through a very well-established electronic medical record system. Veterans have access to care and receive medications from the VA formulary at low co-pays or no cost at all. The primary study was conducted at 4 Veterans Integrated Service Networks located in Colorado, Washington, North Carolina and Arkansas. These Medical

Centers are all tertiary referral hospitals within their respective VISN and provide a full spectrum of cardiac care services.

3.3 Study Population

This study cohort included veterans who used one of the 4 VISNs mentioned above for routine medical care defined as having ≥1 primary care visit within the 12 months prior to hospital admission. All patients who were admitted with ACS as the primary reason for hospital admission were screened for eligibility to participate. ACS was defined as acute myocardial infarction (both ST-elevation MI and non-ST elevation MI) or unstable angina. The presence of acute myocardial infarction was verified using standard definitions from an international consensus statement (Thygesen et al. 2012), based on the following: a rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit and at least one of the following: 1) symptoms of ischemia; 2) ECG change indicative of new ischemia (new ST-T changes or new left bundle branch block); 3) development of pathological Q waves in the ECG; or 4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality (Thygesen et al., 2007). Unstable angina was defined by the presence of ischemic symptoms and ECG changes indicative of new ischemia but without biomarker evidence of myonecrosis (i.e., biomarker ST segment elevation) and no evidence of new pathological Q waves, loss of viable myocardium or regional wall motion abnormality.

Exclusion criteria included: 1) patient admitted for primary non-cardiac diagnosis and develop ACS as a secondary condition (e.g. perioperative MI); 2) planned discharge to nursing home or skilled nursing facility; 3) irreversible, non-cardiac medical condition (e.g. metastatic cancer) likely to affect 6-month survival or ability to execute study protocol; 4) lack of telephone/ cell phone; 5) VA is not primary source of care; 6) regularly fill medications at non-VA pharmacy.

The primary study was powered to detect an anticipated ≥ 15% improvement in the proportion of adherent patients (Table 3). The estimated number of AMI patients (n=369) was expected to under-estimate of the potential pool of eligible ACS patients because patients with unstable angina were not included. Therefore, given conservative estimates that unstable angina patients would increase the potential ACS population by another 20% (n=74), the study anticipated that there would be ~440 patients annually and ~660 patients over 18 months during the recruitment period. It was expected that ~80% would meet eligibility criteria (n=528). Of these eligible patients, it was estimated that ~80% would agree to participate resulting in a potential study population of 422 patients which exceeds the enrollment target of 280 patients.

Table 3: Primary study sample size estimates based on proportions at one year

Adherence in the Usual Care arm	Increased proportion adherent in intervention that would be detectable (80% power; α=0.05)	
	N=100 each group	N=125 each group
50%	70% (+20)	68% (+18)
60%	77% (+17)	76% (+16)
70%	87% (+17)	85% (+15)

A large number of lost-to-follow was not anticipated since patients typically do not leave the VA system or relinquish the VA pharmacy benefits given the cost of cardiovascular medications in other healthcare settings. However, adherence could still be assessed even for those patients who do not return for subsequent study visits since adherence can be measured using VA pharmacy refill data.

3.4 Data Collection Procedures

Recruitment for this study occurred at the time the patient is ready to be discharged from the hospital. Staff from the medicine and/or cardiology service notified the research team of patients being discharged after ACS admission to ensure that all potentially eligible patients were identified and screened. On a daily basis, a study research assistant at each site also actively monitored for potentially eligible patients. Once a patient was identified, the patient's medical record was reviewed to assess the patient for eligibility. If the patient met all of the study inclusion criteria, they were approached at the bedside regarding the study. An informed consent form was reviewed with the patient and for those who are unable to read, the consent form was read to them. If the patient agreed to participate, they were randomized to the intervention or usual care group at that time. Figure 7 depicts the timeline and patient flow for the primary study.

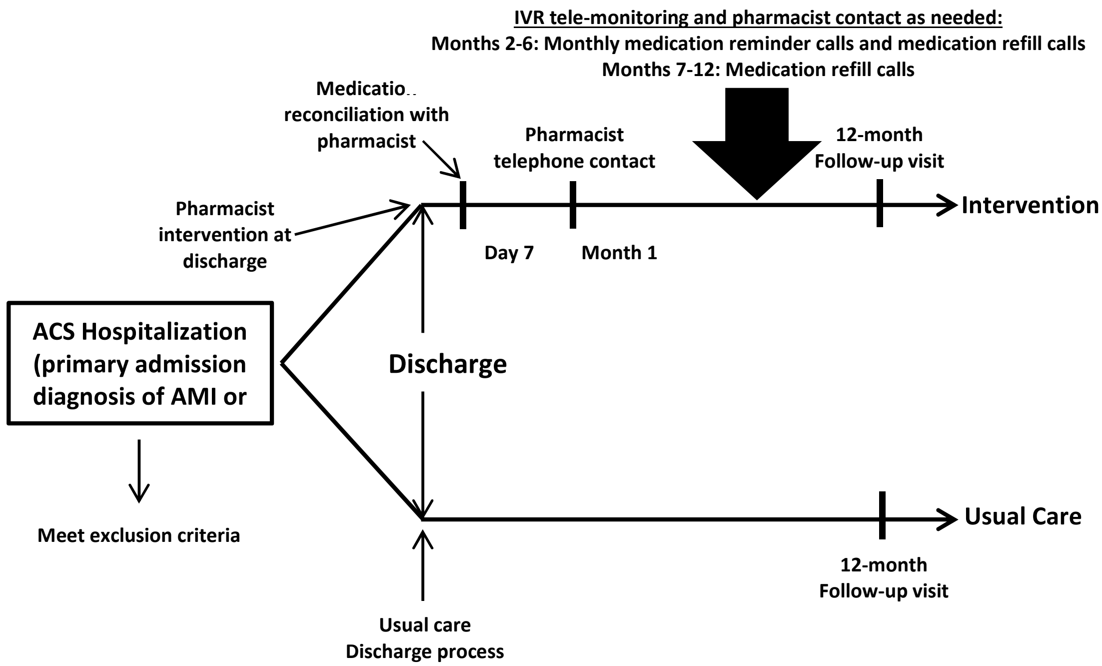


Figure 7. Protocol for patients randomized to intervention versus usual care

At the baseline visit, all patients received standard ACS discharge instructions (e.g. numbers to call, follow-up appointments, diet and exercise advice), a discharge medication list and educational information about cardiac medications consistent with usual care discharge processes at each of the three sites. The educational materials were adapted from current AHA/ACC materials. Emphasis was placed on the importance of continuing to take cardioprotective medications as prescribed and any questions were answered regarding the patient's prescribed medication regimen. Patients were also notified of their 12-month clinic visit. Both usual care and intervention patients were scheduled for a follow-up 12-month clinic visit. At this visit, 3 blood pressure measurements were taken by an individual blinded to patients' study group assignment.

Patients were referred for a laboratory blood draw to assess LDL-cholesterol levels. If a patient had a value checked within the prior month and the dosing of anti-lipemic medication(s) has not changed, this value was used as the end of study LDL-cholesterol for outcomes assessment for the primary study. In addition, all patients were asked about interim procedures and/or hospitalizations outside of the VA and if an interim event had occurred, permission was requested to obtain the patient's records for review.

For patients randomized to usual care, following standard discharge instructions, patients were reminded to pick up their medications from the pharmacy and to contact their primary care provider about further medication-related questions after hospital discharge. This care is consistent with usual care practices at the 4 VA medical center sites.

For patients randomized to intervention, following usual discharge instructions, the pharmacist implemented the following interventions prior to hospital discharge and/or during the course of the 12-month intervention period:

1. *Tailoring of medication regimen and medication reconciliation*: The pharmacist obtained the patients' medications, provided them with a pill box, and instructed them on how to fill their pill boxes on a weekly basis. In addition, the pharmacist contacted the patient by phone within 7 days of hospital discharge to address any medication problems or side effects, and also to reconcile any differences in medications between the pre-hospital and the post-hospital regimens. In-person clinic visits occurred at the request of the patient or at the pharmacists' discretion. The pharmacist also reviewed the medication regimen and provided suggestions for simplifying dosing where possible to once daily dosing medications or

combination pills. These recommendations were placed in a Computerized Patient Record System (CPRS) note and orders were entered for the primary care provider to co-sign the note and sign off on the medication changes if they were in agreement.

2. *Patient education*: Patients received education about medications at the point of hospital discharge but also continued to receive education following hospital discharge to ensure retention of the information. This occurred at one week and one month following discharge during the pharmacist telephone calls with the patients. Thereafter, educational messages were provided through the interactive voice response (IVR) tele-monitoring system and pharmacist telephone calls when requested by the patient. As part of the telephone calls, the pharmacist followed a script that addressed any new medication(s) since last contact, patient's knowledge regarding new medication(s), and any new or recurrent problems/side effects with the medications. Based on any identified knowledge gaps, the pharmacist provided education addressing these gaps. Educational content focused on the perceived need, effectiveness, and safety of each prescribed cardioprotective medication.
3. *Collaborative care*: The pharmacist notified the patient's primary care provider (PCP) and cardiologist that the patient was enrolled in the primary study by having them co-sign the pharmacist's initial enrollment CPRS note. This enrollment note included the pharmacists' contact information so that the PCP and/or cardiologist could reach the pharmacist via telephone and/or email depending on their preference. Furthermore, clinicians could contact the

pharmacist to notify them of newly prescribed medications or changes to dosing of current medications so that medication refill reminder calls could be set up. Through these collaborative interactions, medication non-adherence became a point of continuing dialogue between care providers and patients and thus ensuring that problems with medication non-adherence are prospectively addressed and resolved.

4. *Tele-monitoring using* Interactive voice recognition (*IVR*) *technology*: IVR technology is a computer-based telephone system that initiates and receives calls, delivers health education and can be used to remind patients about upcoming appointments and refill prescriptions (Oake, Jennings, van Walraven, & Forster, 2009). The IVR system contacted patients at regularly scheduled intervals. There were two types of IVR calls – medication reminder and medication refill calls. The medication reminder calls occurred monthly. During these calls, patients received reminder messages about the importance of taking medications as prescribed and had the opportunity to request a call from the pharmacist if needed to address problems/questions related to their medication regimen. The medication refill calls were synchronized to when a medication refill was due. The calls occurred seven days prior to the refill due date, on the due date and seven days after the due date. Prior to each medication refill call, the tele-monitoring system assessed whether the medication had been refilled and, if it was, the patient did not receive the refill call. If the patient still had not refilled their medication at day 14 after the refill due date, the pharmacist reviewed the medical record to make sure that the medication has not been discontinued by a

clinician and called the patient to determine if they had run out their medications and address any medication problems. As part of these medication refill calls, the patient had the option to be connected directly to the pharmacy refill line. The patient was also provided with the opportunity to listen to adherence messages as well as request a call from the pharmacist. During months 2 through 6 of the intervention, patients received both medication reminders (monthly) and medication refill calls (timed to refill dates). During months 7 through 12 of the intervention, patients only received medication refill calls.

3.5 Protection of Human Subjects

Data for this study were completely de-identified and assigned a unique study ID prior to making it available for analysis. The study coordinating center at the VA Eastern Colorado Health Care System created a study-specific analytic file which was only accessible through a Virtual Private Network (VPN). All analyses were conducted on the VA's servers, which could only be accessed via VPN by authorized users.

The primary MEDICATION study was a randomized trial and the study team monitored patients closely to detect any problems posed by the intervention, and all standards of IRB and privacy (HIPAA) review and monitoring were in effect (including full IRB review for the 4 sites, use of approved consents, reporting of serious adverse events, etc.). The study posed minimal safety risks to patients. No experimental devices or drugs will be used, and there have been no reported adverse events with the use of tele-monitoring or adherence interventions in general (rather, the increased surveillance may be a patient-safety measure).

All recruitment and enrollment procedures were designed and conducted according to IRB and HIPAA regulations. To protect confidentiality, all study records referred to patients only by an assigned unique study number. The only exception was in the randomization and tracking forms which included the patient's name, SSN, and the names of contacts. The randomization form served as the cross-reference master, linking the patient's name to his/her randomization number. Both the randomization and tracking forms were kept separate from other research material. Access to the records was limited to research staff. All paper records were maintained in locked file cabinets within locked offices. Electronic data files were encrypted/password-protected in computers maintained in a secure environment per VA security regulations.

Authority for monitoring data and safety resided with the VA-mandated central Data and Safety Monitoring Board (DSMB) for multi-site interventional health services studies/randomized trials (VA Health Service Research and Development, 2005). Reporting to the DSMB followed established VA regulations.

The current study was reviewed and received a approved by The George Washington University Institutional Review Board. The IRB determined that this study did not meet the definition of human subjects research and, as a result, did not require further IRB oversight.

3.6 Measures

3.6.1 Demographic and Clinical

The data to be analyzed in this study were collected from the MEDICATION study. The Self-Efficacy for Appropriate Medication Use Scale (SEAMS) was added to the primary study prior to the data collection process solely for the purpose of the current analysis. Patient surveys were administered during the patient interview at the time of hospital discharge to identify patients' specific needs and barriers to adherence. Age, gender, race and ethnicity, and clinical variables were determined at the enrollment visit from medical records and patient self-report. Medical history variables were collected including ischemic heart disease (prior MI, prior PCI, prior CABG), hyperlipidemia, hypertension, diabetes, and other major co-morbidities. In addition, vital signs (weight and height for BMI calculation), smoking status, and current medications were obtained. Select laboratory test results that were assessed during the hospitalization were also obtained from the CPRS. For patients undergoing coronary angiography, the findings of the angiogram as well as any intervention performed were collected through the CART-CL database which is the VA's national cardiac catheterization database.

3.6.2 Medication Adherence

The Pharmacy Quality Alliance (PQA) has developed and tested several measures of medication adherence. The PQA has endorsed the proportion of days covered (PDC) as a standard method for calculating medication adherence utilizing prescription refill data. The PDC calculation is based on fill dates and days supply for each fill of a prescription. In contrast to the aforementioned medication possession ratio (MPR), the PDC does not simply sum the days supplied. The patient's measurement period is defined as the index prescription date to the end of the calendar year, disenrollment or death. The denominator for PDC is the number of days between the first fill of the medication during the defined measurement period and the end of the measurement period. The numerator is the number of days covered by the prescription fill based on prescription fill date and days supplied during the measurement period. The number of days covered in the numerator is divided by the number of days in the measurement period. The result is multiplied by 100 to obtain the PDC as a percentage. Patients with a PDC rate of at least 80% are considered adherent. Rasmussen, Chong, & Alter (2007) proposed an alternate definition of adherence using the PDC which further classifies levels of adherence – a PDC less than or equal to 80% is considered adherent; 40%-79% is considered partially adherent and less than 40% is considered non-adherent. PDC scores were further analyzed and based on the distribution of scores in the sample, a new cutoff of 90% was used to classify patients as highly adherent.

In this study, adherence to cardioprotective medications including ß-blockers, statins, ACE-inhibitors and clopidogrel was based on the PDC calculation via pharmacy refill data. These medications are all class I recommended medications for patients at ACS discharge. ß-blockers, statins and ACE-inhibitors are generally recommended indefinitely following ACS hospital discharge, while clopidogrel is generally recommended for 12 months, regardless of whether patients receive or do not receive PCI. Adherence to aspirin was not assessed since a majority of veterans obtain it over the counter making it unfeasible to assess using pharmacy refill data.

As long as patients remained within the VA healthcare system and used the VA pharmacy, their adherence to cardioprotective medications could be assessed via the VA's electronic health record, Computerized Patient Record System. Pharmacy refill data is part of the CPRS and clinicians can easily determine when a patient refills a medication and whether there are gaps between refills at the point of care. In the case of patients who fill their medications at non-VA pharmacies, the study obtained pharmacy refill records from the patient.

3.6.3 Health Literacy

The Rapid Estimate of Adult Literacy in Medicine, Revised (REALM-R) is a validated (correlation coefficients ≥0.88 against 3 standardized reading tests) and reliable (test-retest reliability was 0.99) tool that assesses a patients' literacy, or ability to read and pronounce common medical terminology and lay terms for body parts and illnesses (Davis et al., 1993). The REALM-R was designed to be a shortened version of the 66-item REALM. It consists of 11 items and patients with a score of 6 or less are at risk for poor health literacy. The REALM-R was designed as a rapid word-recognition test to assess how well patients read words that they commonly experience and are expected to understand in the course of interacting with their physician (Bass, Wilson & Griffith, 2003). Its predecessor, the REALM, is a well-validated instrument but the time required to administer the 66-item word recognition test is impractical in a busy medical setting. Bass et al. (2003) sought to revise the REALM to shortened literacy screening instrument. The REALM-R was administered to 157 patients and found to be correlated with another commonly used word recognition test, the Wide Range Achievement Test-Revised (WRAT-R) (.64). The REALM-R identified 26 of 30 persons scoring more than 1 standard deviation below the mean on the WRAT-R, corresponding to a sixth grade reading level and also identified a substantial number of people who scored poorly on the WRAT-R. They further examined two item characteristics from the full scale REALM - items with an item-whole correlation of greater than 0.40, and then selected those that maximized discrimination by being as close as possible to a 50/50 correct/incorrect split. The shortened REALM-R demonstrated a Cronbach's α of 0.91. The part-whole correlation between the REALM-R and the REALM was 0.72. The words ultimately chosen for the REALM-R included osteoporosis, allergic, jaundice, anemia, fatigue, directed, colitis, and constipation. The words fat, flu and pill are also included but not scored and are positioned at the beginning of the REALM-R to decrease test anxiety and enhance confidence. Patients are given the list of REALM-R words and asked to read the 11 words out loud. Any word that is not attempted or mispronounced by the patient is counted as incorrect. A score of six words or less is considered to be at risk for poor health literacy.

This study examined patients' functional health literacy based on their numeric REALM-R scores. Individuals' numeric scores were used to identify their level of functional health literacy. Individuals with a score of 6 or less were considered to have low health literacy. Individuals with a score greater than 6 were considered to have a functional level of health literacy. The scores were also analyzed as a continuous variable in order to allow for greater discernment of functional health literacy status. While a score of 6 or less is typically considered to indicate low functional health literacy, based on the distribution of scores in the sample, a score of 7 or above was applied to indicate high functional health literacy.

3.6.4 Medication Self-Efficacy

The theoretical basis for this study is derived from the self-efficacy construct in the social cognitive theory. A vast amount of research has established the effect of self-efficacy on health behaviors. The belief an individual has in his or her own ability to produce desired changes by their own actions is the pathway through which psychosocial influences affect health functioning (Bandura, 2004). Self-efficacy, in particular medication self-efficacy, is an important construct in relation to health literacy and medication adherence. As it relates to the study's proposed measurement models, the construct of self-efficacy is hypothesized to be a factor in a poorer adherence behavior. Since an individual's self-efficacy beliefs determine how they view obstacles and impediments, they must believe that they have the power to exercise control of actions related to their own health. In this study, the expected action was the individuals' ability to adhere to their prescribed medication regimens. The relationship in the proposed model presumed that individuals with limited health literacy would have lower self-efficacy and, as a result, would have less belief in their ability to perform the actions related to medication adherence.

The Self-Efficacy for Appropriate Medication Use Scale (SEAMS) (Appendix A) is a reliable and validated instrument designed to provide healthcare providers with a tool to help understand and assess medication self-efficacy in chronic disease management in patients with low literacy skills (Risser, Jacobson, & Kripalani, 2007). SEAMS was originally developed as a 21-item scale that was later reduced to 13 items. Each item is assessed using a three-point Likert-type scale (1 = not confident; 2 = somewhat confident; 3 = very confident). The scale was validated in patients with chronic diseases including coronary heart disease, hypertension, hypercholesterolemia, and diabetes. The 13-item SEAMS was found to have a high internal consistency and reliability in both low-and high-literacy patients ($\alpha = 0.89$ and 0.88, respectively). Psychometric analysis by patients' literacy level also revealed good internal consistency in literacy subgroups, indicating that the scale was reliable even among patients with low literacy skills. Sensitivity and specificity of SEAMS has not been reported. Factor analysis of the SEAMS revealed 2 dimensions of medication self-efficacy. The *first* dimension, taking medications under difficult circumstances, relates to scenarios such as when a patient is busy or has multiple medications to take. The *second* dimension relates to taking medications under uncertain or changing circumstances, such as when a patient is unsure about how to take medications or when changes occur in their medication regimen.

While the SEAMS tool is a validated measure of self-efficacy, there is no established scoring criteria. As a result, the distribution of baseline scores across the sample was examined to determine the appropriate cut-off for low versus high self-efficacy.

3.6.5 Cognitive Functioning

The Saint Louis University Mental Status Examination (SLUMS) is a screening tool used to detect mild cognitive impairment. The SLUMS consists of 11 items, and measures specific aspects of cognition. 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 registrations (2-part math story problem); semantic fluency (naming as many animals as possible within 1 minute); working memory (reciting numbers backwards); visual spatial function (recognizing geometric figures); and contextual verbal memory (listening to a short story and answering 4 questions about the story's content) . Scores range from

0 to 30, with scores of 27-30 considered normal in a person with a high school education. Scores between 21 and 26 suggest Mild Neurocognitive Disorder, and scores between 0 and 20 indicate dementia. In contrast to the widely-used Mini-Mental State Examination (MMSE), the SLUMS was developed to address the limitations of the MMSE by including enhanced tasks corresponding to attention, numeric calculation, immediate and delayed recall, animal naming, digit span, clock drawing, figure recognition/size differentiation, and immediate recall of facts from a paragraph. To determine validity and reliability of the SLUMS, Tariq et al recruited 702 patients who were clinically classified as having normal cognitive functioning, mild neurocognitive disorder or dementia based on Diagnostic and Statistical Manual Fourth Edition (DSM-IV) criteria. Researchers found that both tools reliably detected dementia, suggesting that both SLUMS and MMSE have comparable sensitivities and specificities, but only the SLUMS recognized a subset of patients with mild cognitive problems.

3.6.6 Depression

The Patient Health Questionnaire (PHQ-9) is a validated and reliable short version of the PHQ (Kroenke, Spitzer & Williams, 2001). The PHQ-9 is based directly on the diagnostic criteria for major depressive disorder in the DSM-IV. There are two components of the PHQ-9: 1) assessing symptoms and functional impairment to make a tentative depression diagnosis, and 2) deriving a severity score to help select and monitor treatment.

Kroenke et al. (2001) examined the PHQ-9 as a reliable and valid measure of depression severity among 6,000 patients in primary care and obstetrics and gynecology clinics. Construct validity was assessed using the 20-item Short-Form General Health Survey, self-reported sick days and clinic visits, and symptom-related difficulty. Criterion validity was assessed against an independent structured mental health professional interview among a sample of 580 patients. Using the mental health professional structured psychiatric interview as a criterion standard, a PHQ score ≥10 had a sensitivity of 88% and specificity of 88% for major depression. The internal reliability of the PHQ-9 was high in both patient samples ($\alpha = 0.89$ in the Primary Care Study and $\alpha = 0.86$ in the PHQ Ob-GYN Study).

The PHQ provides a continuous measure of depressive symptoms (9 items; administration time <3 minutes), allowing for identification of mild, moderate, moderately severe, and severe depressive symptoms (Table 4). Major depression is diagnosed if 5 or more of the 9 depressive symptom criteria have been present at least "more than half the days" in the past 2 weeks, and 1 of the symptoms is depressed mood or anhedonia (i.e. the inability to experience pleasure from activities usually found enjoyable). Other depression is diagnosed if 2, 3, or 4 depressive symptoms have been present at least "more than half the days" in the past 2 weeks, and 1 of the symptoms is depressed mood or anhedonia. One of the 9 symptom criteria ("thoughts that you would be better off dead or of hurting yourself in some way") counts if present at all, regardless of duration. As a severity measure, the PHQ-9 score can range from 0 to 27, since each of the 9 items can be scored from 0 (not at all) to 3 (nearly every day). Before making a final diagnosis, clinicians are expected to rule out any physical causes of depression, normal bereavement, and history of a manic episode. Patients who score ≥ 10 are considered to have clinically significant depressive symptoms (positive for mild to severe depression).

Table 4: PHQ-9 Scoring (Kroenke et al., 2001)

PHQ-9 Score	Depression Severity
0-4	None-minimal
5-9	Mild
10-14	Moderate
15-19	Moderately Severe
20-27	Severe

|3.7 Statistical Analysis Plan

3.7.1 Sample Selection

Prior to data analysis, the dataset was examined for data accuracy, outliers and missing data. Specific selection criteria were applied to the primary study cohort to identify patients for the current study sample. The primary focus of this study included 4 psychosocial variables as predictors of patients' medication adherence behavior. As such, the current study sample was limited to those patients who had completed both assessments for the key variables of self-efficacy and the primary outcome of interest, medication adherence. Patients with a baseline assessment of self-efficacy as measured by the Self-Efficacy for Appropriate Medication Use Scale and patients with a documented adherence rate calculated by the proportion of days covered method were included in the final study sample. The sample was further examined for any missing data in the remaining psychosocial variables of depression, cognitive functioning and health literacy. The dataset was examined to determine if data were missing at random which would suggest there was no pattern related to missing data. Given the small sample size, the option for dealing with missing data in this sample was to analyze the available data and ignore missing values.

Since the sample in this study was derived from the primary study cohort, the next step in the analysis was to test for differences between the two groups. Group 1 was designated as the sample for the current study and Group 2 included patients from the primary study who did not meet the inclusion and exclusion criteria of having a baseline self-efficacy score and calculated adherence rate.

3.7.2 Patient Characteristics

Baseline patient characteristics were analyzed and presented as frequencies and measures of central tendency (mean, median or mode), standard deviations, and ranges, as appropriate. Chi-square test was conducted for categorical variables and t-tests for continuous variables. Categorical variables were summarized as numbers and proportions and distributions as means and standard deviations for all continuous variables. Race and age were the two available demographic variables from the primary study that were analyzed for the current study sample. The following comorbidities were included in the assessment of patients' medical history: hypertension, hyperlipidemia, history of CAD, diabetes, chronic kidney disease, chronic lung disease, peripheral arterial disease, prior heart failure and cerebrovascular disease. Patients' body mass index (BMI) was calculated based on standard weight status categories associated with BMI ranges.

ACC/AHA clinical practice guidelines recommend that at the time of hospital discharge for an ACS event, patients are prescribed a variety of medications, including β-blockers, statins, clopidogrel, ACE-inhibitors, and/or aspirin. Previous studies have confirmed the relationship between the complexity of patients' medication regimens and poor adherence. As such, the study examined the distribution of the total number of guideline-recommended cardioprotective medications that were prescribed per patient. A new categorical variable (Total CV Meds) was created to assess concomitant medications. This new variable sub-divided the number of medications into 3 groups: 1-2 medications; 3 medication; 4 medications.

An independent samples *t*-test for continuous variables and chi-square test for categorical variables were conducted to detect and differences in demographic, psychosocial and medical history characteristics between groups.

3.7.3 Identification of Covariates

A bivariate analysis was conducted to detect relationships between variables that were believed to be associated with one another based on published literature and which held a theoretical basis. Chi-square test was used to evaluate the association between each of the psychosocial factors (health literacy, self-efficacy, cognitive functioning, depression) and medication adherence to cardioprotective medications. The chi-square test compared the observed frequencies of cases that occurred within each of the groups. The objective of this analysis was to evaluate the manner in which the variables interact with each other and further explore any statistically significant associations and identify the key variables that would be included in the subsequent regression models.

Additional tests of association were conducted to examine for statistically significant associations between the selected patient characteristic variables and health literacy and self-efficacy. The health literacy measure was dichotomized into two groups to make the distinction between patients with high versus low health literacy. Chi-square test was conducted to explore the relationship between the psychosocial variables, concomitant medication use and race by functional health literacy levels. The self-efficacy measure was dichotomized into two groups to make the distinction between patients with high versus low self-efficacy. A chi-square test was conducted to explore the relationship between concomitant medication use, cognitive function and depression by level of self-efficacy.

Based on the results of the covariate testing, an independent samples t-test was conducted to compare the mean self-efficacy scores for each of the 13 items in the SEAMS between patients with high versus low adherence. A comparison of the mean total SEAMS scores between groups was also analyzed for a statistically significant difference in scores.

3.7.4 Logistic Regression Analyses

A logistic regression model was developed to determine the impact of multiple independent variables for predicting medication adherence. The result of this analysis was also used to reveal the specific relationships and strength of each of the independent variables as a predictor of medication adherence. For the cognitive functioning variable, normal cognitive function was set as the referent group in the model. Based on the regression analysis, each variable was examined to determine which of the independent variables were associated with medication adherence while controlling for the relationship among potential confounding variables. The baseline model was created to examine the independent relationship between health literacy, depression, cognitive functioning and self-efficacy and medication adherence. Once the model was fit and the relationship between the independent variables and dependent variables was quantified, additional variables were considered to be included in subsequent versions of the model. A secondary model was tested that included two variables for concomitant medications and race. For both models, each was examined to measure the independent contribution of the independent variables in medication adherence and quantify the strength of the variables as predictors of medication adherence. The goodness of fit test was evaluated in both models for an overall indication of how well each of the models performed. The Cox & Snell R square Nagelkerke R square were assessed to determine the amount of variation in medication adherence that was explained by each of the models. The Wald test was used to understand the contribution of each of the predictor variables in each model. Variables with a statistically significant value were determined to be strong predictors in the model. Finally, the odds ratio for each of the variables was examined to estimate the change in odds for adherence for each unit increase in the predictor variables.

3.7.5 Mediation Analysis

This study proposed further exploring the effect of self-efficacy as possible mediator where the presence of self-efficacy changes the nature of the relationships between the remaining predictor variables and medication adherence. Specifically, self-efficacy was to be analyzed as a possible mediator that operated between the relationship among each of the independent predictor variables (health literacy, depression, cognitive functioning) and medication adherence. The mediation analyses would only be carried out if there was an independent and statistically significant relationship between the key predictor variables and medication adherence.

Although a path analysis was initially considered as part of the analysis plan for this study, the reciprocal causality among the variables could not justify that all of the arrows in the path diagram would point in one direction. As a result, the path analysis was dropped from the study.

3.7.6 Hypothesis Testing

3.7.6.1 Hypothesis 1

Hypothesis 1: Among veterans hospitalized for an ACS event, rates of functional health literacy levels will approximate rates of health literacy within the general U.S. population.

The test for hypothesis 1 employed a simple univariate analysis to determine the proportion of patients in the study sample that had low versus high health literacy. The rate of functional health literacy was compared to the most recently reported national rates of health literacy in the U.S. population.

3.7.6.2 Hypothesis 2

Hypothesis 2: Among veterans, there will be a positive association between functional health literacy and self-efficacy.

The testing for hypothesis 2 employed a chi-square test to explore the relationship between the self-efficacy variables stratified by functional health literacy levels.

3.7.6.3 Hypothesis 3

Hypothesis 3: The effects of health literacy, depression and cognitive functioning on medication adherence will be partially mediated through self-efficacy.

For hypothesis 3, before any mediation testing took place, the analysis determined whether each of the independent variables was associated with the dependent variable, medication adherence. The first step employed a chi-square test to identify statistically significant covariates among the predictor variables and medication adherence. The next step included a logistic regression analysis to further examine if the independent variables were significant and strong predictor of medication adherence. Only variables with a statistically significant relationship would be included in mediation models. If the results of the analyses showed no statistically significant relationship with medication adherence, the mediation model would be abandoned in this study.

3.7.6.4 Hypothesis 4

Hypothesis 4: Among veterans hospitalized for an ACS event, individuals with low self-efficacy will have worse medication adherence compared to veterans with high levels of self-efficacy.

The testing for hypothesis 4 used a chi-square test for independence to identify statistically significant relationship between self-efficacy and medication adherence. Next, a logistic regression analysis was used to determine if self-efficacy was a significant and strong predictor of medication adherence in the model. An independent samples t-test was conducted to compare mean total self-efficacy scores between patients with low versus high medication adherence.

3.7.7 Sub-Analyses

As a secondary analysis, this study was interested in further examining the differences between patients in the current study sample based on their assignment to the usual care group versus the intervention group. Chi-square test for independence was conducted to explore differences between treatment groups and the primary patient demographic, psychosocial and medical history factors that were of primary interest in the current study. Next, an independent t-test was conducted to compare the mean scores on each of the psychosocial measures between the usual care group and intervention group.

The primary study included data on 12-month clinical endpoints for patients. As the underlying theoretical basis for this study, self-efficacy was further analyzed to identify whether there were any differences in outcomes between patients with high self-efficacy versus patients with low self-efficacy. A chi-square test was used to detect statistically significant differences among clinical endpoints including MI, revascularization, all-cause hospitalization and mortality.

For the final analysis, the self-efficacy measure was the only assessment that was conducted at baseline and at the 1-year follow up visit. The final sub-analysis examined differences between treatment groups on self-efficacy scores that were measured at baseline assessment and at the 12-month follow-up visit. A one-way between-groups analysis of covariance was conducted to evaluate the impact of the multifaceted intervention on the follow-up self-efficacy scores while controlling for patients' baseline self-efficacy scores. The independent variable was defined as follow-up SEAMS scores that were assessed post-intervention. Patients' scores on the pre-intervention administration of SEAMS were used as the covariate in this analysis.

The results of the analyses will be presented in Chapter 4. All analyses will be performed using SPSS for Windows version 21.0 (SPSS, Inc., Chicago, IL).

CHAPTER 4: RESULTS

Chapter 4 presents the results obtained using the methods described in Chapter 3. It begins with a description of the data collected for this study, followed by a brief description of the study sample selection criteria. Demographic and psychosocial characteristics of the study participants will be described. The overview includes a discussion of recoding that was performed on selected variables to prepare them for statistical analysis. This chapter then describes the steps taken to build the statistical models and presents the results from the statistical analyses used to analyze the study hypotheses.

4.1 Selection Criteria

The target population included patients who were enrolled in a multi-site, patient-level prospective randomized clinical trial testing the effect of a multifaceted patient-centered intervention to improve adherence to cardioprotective medication regimens versus usual care for veterans following hospitalization for ACS. A total of 789 patients were screened for the primary study, resulting in 361 potentially eligible patients. Of those, 253 patients were randomized – 129 to the intervention and 124 to usual care. For this study, the sample was further selected by including patients for whom a baseline level of medication-taking self-efficacy was obtained through the Self-Efficacy for Appropriate Medication Use Scale (SEAMS). Of the 245 patients in the primary study sample, 152 patients were eliminated because they did not complete the baseline SEAMS assessment. This subset of 97 patients was further selected by eliminating patients who were missing pharmacy refill data needed to assess medication adherence. One patient was found to be missing assessments for the remaining psychosocial variables of depression, cognitive functioning and health literacy and was eliminated from the analysis. A total of 92 patients remained in the final sample for analysis in this study.

4.2 Patient Demographics and Medical History

Table 5 presents the demographic characteristics of the study sample overall. Patients were predominantly male (96.7%) and white (73.9%) versus non-white (26.1%). The median age was 63.2 years and the mean was 64.8 years (SD = 9.2).

The majority of the patients in the sample reported a number of comorbidities, including hypertension (92.4%), hyperlipidemia (77.2%) and history of CAD (59.8%) and diabetes (35.9%). Over half of the patients in the sample had a prior PCI (51.1%) and 13% of patients had a documented prior CABG. The median BMI was 30 and the mean was 30.5 (SD = 7.1). Based on BMI, more than half of patients were obese (51.1%) followed by overweight (33.7%) and normal (15.2%). Patients were also more likely to be smokers (75.0%) versus non-smokers (25.0%).

Participants had high use of concomitant medications; 12.0% were prescribed 0 to 2 cardiovascular medications, 28.3% were prescribed 3 cardiovascular medications and the larger proportion of patients was prescribed 4 cardiovascular medications (59.8%).

Table 5: Participant Characteristics ($N = 92$)

	Mean (%)
Male, gender	89 (96.7%)
Age (years), mean ± SD	64.8 ± 9.2
Race	
White	68 (73.9%)
Non-white	24 (26.1%)
Overall adherence (PDC>0.90)	63 (68.5%)
Medication self-efficacy (SEAMS)	
Lower self-efficacy (SEAMS < 31)	36 (39.1%)
High self-efficacy (SEAMS ≥ 31)	56 (60.9%)
Health Literacy	
Lower functional health literacy	20 (21.7%)
High functional health literacy	72 (78.3%)
Cognitive Functioning	
Dementia	19 (20.7%)
MNCD	46 (50.0%)
Normal	27 (29.3%)
Depression	28 (30.1%)
Not depressed	64 (69.6%)
Depressed	27 (29.3%)
Medical History	
Hypertension	85 (92.4%)
Hyperlipidemia	71 (77.2%)
Diabetes	33 (35.9%)
History of coronary artery disease	55 (59.8%)
Prior PCI	47 (51.1%)
Prior CABG	12 (13.0%)
BMI, mean ± SD	30.5 ± 7.1
Normal	14 (15.2%)
Overweight	31 (33.7%)
Obese	47 (51.1%)
Smoker	69 (75.0%)
Total CV Meds	
0-2	11 (12.0%)
3	26 (28.3%)
4	55 (59.8%)

Values are presented as *N* (%) unless otherwise noted.

4.3 Psychosocial Characteristics

Table 6 shows each of the measures applied in this study to assess psychosocial variables of interest and the corresponding range of scores, overall mean scores within the sample and interpretation of scores.

Table 6: Self-efficacy, health literacy, depression and cognitive functioning and medication adherence scores (*N* = 92)

Measures	Possible range	Mean ± SD	Interpretation of scores
Self-efficacy[1]	13-39	31.65±6.67	Adequate self-efficacy
Health literacy[2]	0-11	6.85±2.12	Adequate functional health literacy
Cognitive functioning[3]	0-30	23.93±4.25	Mild neurocognitive functioning
Depression[4]	0-27	7.30±6.09	Not depressed
Medication adherence[5]	0-100	90.08±15.56	High medication adherence

[1]As measured by the Self-Efficacy for Appropriate Medication Use Scale (SEAMS)
[2]As measured by the Rapid Estimate of Adult Literacy in Medicine, Revised (REALM-R)
[3]As measured by the Saint Louis University Mental Status Examination (*SLUMS*)
[4]As measured by the Patient Health Questionnaire (PHQ-9)
[5]As measured by the Proportion of Days Covered (PDC)

4.3.1 Self-Efficacy

All patients completed the Self-Efficacy for Appropriate Medication Use Scale at baseline to assess levels of medication-taking self-efficacy. For each individual item, the possible range of responses was 1 to 3 (with 1 = not confident; 2 = somewhat confident; 3

= very confident). The range of total SEAMS scores was 13 to 39, with a median SEAMS score of 34.00 and a mean score of 31.65 (SD=6.67). The scores were divided into equal groups according to the distribution of patients' total SEAMS score. A cut-off score of 31 was used to classify patients as having high self-efficacy (SEAMS ≥ 31) or low self-efficacy (SEAMS < 31). Approximately 39% of patients had low medication taking self-efficacy compared to nearly 61% of patients that reported high levels of self-efficacy.

4.3.2 Health Literacy

Functional health literacy was assessed for the vast majority of the enrolled patients (98.9%) using the Rapid Estimate of Adult Literacy in Medicine, Revised (REALM-R). Possible REALM-R scores range from 0 to 11 but in this sample, scores ranged from 0 to 8. The median score was 8 and the mean REALM-R score was 6.85 (SD = 2.12). A score of 6 or less is typically considered to be at risk for poor health literacy. REALM-R scores were analyzed as a continuous variable in order to allow for greater discernment of functional health literacy status. Based on the distribution of REALM-R scores in this sample, health literacy was recoded into a categorical variable using a cutoff of 7 to indicate whether patients had functional levels of health literacy. In this sample, the majority of patients (78.3%) had functional health literacy while 21.7% of patients had limited literacy.

4.3.3 Cognitive Function

Cognitive impairment was assessed using the Saint Louis University Mental Status Examination (SLUMS). SLUMS scores range from 0 to 30 - scores from 0 to 20 are an indication of dementia; 21 to 26 suggests mild neurocognitive disorder (MNCD); and scores from 27 to 30 are considered normal in an individual with a high school education. The median SLUMS score in this sample was 25.0 and mean score was 23.93 (SD = 4.25). Cognitive impairment was found in the majority of patients (70.7%), with 20.7% of patients classified as having dementia and 50.0% with MNCD; 29.3% of patients were classified as having normal cognitive function.

4.3.4 Depression

The Patient Health Questionnaire (PHQ-9) was used to identify mild, moderate, moderately severe, and severe depressive symptoms. As a severity measure, the PHQ-9 score ranges from 0 to 27. In this sample, the range of scores was 0 to 26. The median PHQ-9 score was 6.00 and the mean score was 7.30 (SD = 6.09). Nearly one-third of patients were clinically depressed as measured by the PHQ-9 (Kroenke et al., 2001).

4.3.5 Medication Adherence

As the primary outcome of this study, medication adherence was calculated based on the 4 classes of medications (β-blockers, statins, clopidogrel, ACEI/ARB. Medication adherence was determined by calculating the proportion of days covered (PDC) for each patient. PDC scores range from 0 to 100% - PDC rates of at least 80% are considered adherent. PDC scores for patients in this sample ranged from 20.3% to 100%. The median PDC score was 96.5 and the mean score 90.1 (SD = 15.56). Based on the distribution of PDC scores, medication adherence was recoded into a categorical variable using a cutoff of 90% to indicate high medication adherence. The majority of patients in this sub-study were classified as highly adherent (68.5%) compared to 31.5% of patients who had a PDC score below 90%.

Table 7 illustrates the results of the comparisons of demographic, medical history and psychosocial characteristics between the current sub-study sample and the remaining patients in the primary study cohort who were excluded from the current analyses. Overall, the 92 patients in this analysis did not differ significantly different when compared to the 152 patients in the primary study.

Table 7: Demographic Characteristics, by Group

	Group 1 (n=92)		Group 2 (n=152)		Analysis	
	N	%	N	%	χ^2 (df)	p
Age (years), mean ± SD	64.8±9.2		63.4±8.8			.232
Gender, Male	89	96.7%	149	98.0%	.396 (1)	.529
Race						
White	68	73.9%	124	81.6%	2.01 (1)	.156
Non-white	24	26.1%	28	18.4%		
Medication adherence						
PDC<0.90	29	31.5%	50	33.8%	.131 (1)	.717
PDC≥0.90	63	68.5%	98	66.2%		
Medication self-efficacy						
SEAMS < 31	36	38.7%	2	50.0%	.189 (1)	.663
SEAMS ≥ 31	56	60.9%	2	50.0%		
Health Literacy						
REALM-R < 7	20	21.7%	64	42.4%	10.77(1)	*.001*
REALM-R ≥ 7	72	78.3%	87	57.6%		
Cognitive Functioning						
Dementia	19	20.7%	18	11.8%	3.86 (2)	.167
MNCD	46	49.5%	81	53.3%		
Normal	27	29.0%	53	34.9%		
Depression						
PHQ < 9	64	70.3%	93	61.2%	2.08 (1)	.149
PHQ ≥ 9	27	29.7%	59	38.8%		
Medical History						
Hypertension	85	92.4%	137	90.1%	.357 (1)	.550
Hyperlipidemia	71	77.2%	138	90.8%	8.65 (1)	*.003*
Diabetes	33	35.9%	78	51.3%	5.51 (1)	*.019*
History of CAD	55	59.8%	104	68.4%	1.89 (1)	.170
Smoker	69	75.0%	97	63.8%	3.67 (2)	.160
Total CV Meds						
0-2	11	12.0%	26	17.1%	6.14 (2)	*.046*
3	26	28.3%	60	39.5%		
4	55	59.8%	66	43.4%		

4.4 Identification of Covariates

This study examined covariates to confirm associations between variables, describe the relationship between covariates and the dependent variable, and attempt to evaluate the way in which covariates interact with each other in regression models (Table 8). Bivariate analysis was used to identify important covariates as determined by independent variables that were associated with medication adherence.

The analysis revealed a significant relationship between medication adherence and self-efficacy, χ^2 (1, $N = 92$) = 12.38, ($p<.0005$). The results showed a non-significant relationship between medication adherence and health literacy, χ^2 (1, $N = 92$) = 0.96, ($p=.356$); depression χ^2 (1, $N = 92$) = 0.38, ($p=.846$); and mental status χ^2 (2, $N = 92$) = 1.64, ($p=.356$). Patients with high self-efficacy had an 86% chance of being adherent compared to patients with low self-efficacy who only had a 47% chance of being adherent.

Table 8: Patient Psychosocial Characteristics, by Medication Adherence

	Adherent (n=64)		Non-Adherent (n=29)		Analysis	
	N	%	N	%	χ^2 (df)	p
Self-efficacy						
High self-efficacy	46	73.0%	10	34.5%	12.38 (1)	*<.0005*
Low self-efficacy	17	27.0%	19	65.5%		
Health Literacy						
Low health literacy	12	19.0%	8	27.6%	0.96 (1)	.356
Functional health literacy	51	81.0%	21	72.4%		
Cognitive Function						
Dementia	15	23.8%	4	13.8%	1.64 (2)	.441
MNCD	29	46.0%	17	58.6%		
Normal	19	30.2%	8	27.6%		
Depression						
Not depressed	44	71.0%	20	69.0%	0.38 (1)	.846
Depressed	18	29.0%	9	31.0%		

Additional tests of association were conducted to identify relationships between selected patient characteristics and two of the primary variables of interest in this study. The findings showed a non-significant relationship between health literacy and the majority of the patient characteristics (Table 9). However, mental status approached a statistically significant association with health literacy, χ^2 $(2, N = 92) = 5.94$, ($p<.051$).

Table 9: Patient Characteristics, by Functional Health Literacy Levels

	Low Health Literacy (n=20)		High Health Literacy (n=72)		Analysis	
	N	%	N	%	χ^2 (df)	p
Race						
White	12	60.0%	56	77.8%	2.57 (1)	.109
Non-white	8	40.0%	16	22.2%		
Total CV Medications						
0 to 2 medications	4	20.0%	7	9.7%	4.84 (2)	.089
3 medications	2	10.0%	24	33.3%		
4 medications	14	70.0%	41	56.9%		
Self-Efficacy						
Low self-efficacy	6	30.0%	30	41.7%	0.89 (1)	.344
High self-efficacy	14	70.0%	42	58.3%		
Cognitive Function						
Dementia	7	35.0%	12	16.7%	5.94 (2)	*.051*
MNCD	11	55.0%	35	48.6%		
Normal	2	10.0%	25	34.7%		
Depression						
Not depressed	14	70.0%	50	70.4%	0.00 (1)	.971
Depressed	6	30.0%	21	29.6%		

Similar non-significant associations were observed between levels self-efficacy and all of the independent variables (Table 10).

Table 10: Patient Characteristics, by Level of Self-efficacy

	Low Self-efficacy (n=36)		High Self-efficacy (n=57)		Analysis	
	N	%	N	%	χ^2 (df)	p
Total CV Medications						
0 to 2 medications	3	8.3%	8	14.3%	.777 (2)	.678
3 medications	11	30.6%	15	26.8%		
4 medications	22	61.1%	33	58.9%		
Cognitive Function						
Dementia	9	25.0%	10	17.9%	.936 (2)	.626
MNCD	16	44.4%	30	53.6%		
Normal	11	30.6%	16	28.6%		
Depression						
Not depressed	23	63.9%	41	74.5%	1.18 (1)	.277
Depressed	13	36.1%	14	25.5%		

The covariate testing revealed a highly significant relationship between medication adherence and self-efficacy and, as a result, an independent-samples t-test was conducted to compare the self-efficacy scores among adherent and not-adherent patients (Table 11). Patients with high overall adherence rates had higher self-efficacy compared to patients with lower adherence that had lower self-efficacy. The findings revealed a statistically significant difference in total SEAMS scores between adherent patients (M = 33.16, SD = 5.60) versus non-adherent patients (M = 28.38, SD = 7.61); t (42.72) = -3.02, p = .004. Across all 13 items in the *Self-efficacy* for Appropriate Medication Use scale, patients with high adherence rates (PDC ≥ 90) had statistically significant higher mean scores on the vast majority of items when compared to patients with lower adherence. Only two items did not differ significantly between adherent and non-adherent patients. For the item *"How confident are you that you can take your medicines correctly when you take medicines more than once a day?"* the difference in mean scores between adherent patients (M = 2.73, SD = .48) and non-adherent patients (M = 2.52, SD = .69) was not statistically significant; t (-1.51) = 41.15, p = .140. Similarly, for the item *"How confident are you that you can take your medicines correctly when you are not sure how to take the medicine?"* the difference in mean scores between adherent patients (M = 2.37, SD = .75) and non-adherent patients (M = 2.10, SD = .77) did not differ significantly; t (-1.54) = 90, p = .126.

Table 11: Mean scores for Self-efficacy for Appropriate Medication Use by Medication Adherence

	Medication Adherence						95% CI for Mean Difference			
	Non-Adherent (PDC < 9)			Adherent (PDC ≥ 9)						
	M	SD	n	M	SD	n		t	df	Sig
Q1. When you take several different medicines each day	2.55	.69	29	2.86	.35	63	-.58,-.03	-2.26	40.00	*.030*
Q2. When you take medicines more than once a day	2.52	.69	29	2.73	.48	63	-.50,.07	-1.51	41.15	.140
Q3. When you are away from home	2.21	.77	29	2.60	.58	63	-.72,-.07	-2.46	43.22	*.018*
Q4. When you have a busy day planned	2.07	.80	29	2.63	.55	63	-.90,-.24	-3.46	40.58	*.001*
Q5. When they cause some side effects	2.00	.85	29	2.42	.69	62	-.75,-.09	-2.51	89.00	*.014*
Q6. When no one reminds you to take the medicine	2.24	.69	29	2.70	.56	63	-.73,-.19	-3.39	90.00	*.001*
Q7. When the schedule to take the medicine is not convenient	2.10	.82	29	2.45	.67	63	-.67,-.03	-2.15	89	*.034*
Q8. When your normal routine gets messed up	1.97	.73	29	2.33	.72	63	-.69,-.05	-2.27	90	*.026*

Q9. When you are not sure how to take the medicine	2.10	.77	29	2.37	.75	63	-.60,.075	-1.54	90	.126
Q10. When you are not sure what time of day to take your medicine	2.14	.83	29	2.51	.64	63	-.69,-.05	-2.33	90	*.022*
Q11. When you are feeling sick (you know, like having a cold or the flu)	2.14	.79	29	2.57	.62	63	-.73,-.13	-2.87	90	*.005*
Q12. When you get a refill of your old medicines and some of the pills look different than usual	2.07	.75	29	2.44	.69	63	-.69,-.06	-2.36	90	*.021*
Q13. When a doctor changes your medicines	2.28	.80	29	2.62	.55	63	-.07,-.01	-2.10	40.80	*.042*
Total SEAMS Score	28.38	7.61	29	33.16	5.60	63	-7.80,-1.59	-3.02	42.72	*.004*

* $p < .05$.

4.5 Factors Associated with Medication Adherence

A logistic regression model was developed to examine if selected psychosocial factors explain the difference in adherence rates among patients hospitalized for an ACS event. Self-efficacy was the only variable identified as a covariate through the univariate analyses and for that reason, it was included in the model. Patient characteristics including gender, age and medical history variables were not included in this model. While the other psychosocial variables were not found to be statistically significant, the model did include functional health literacy, depression and cognitive functioning as theoretically important variables that have been shown in other studies to be associated with medication adherence. In this model, mild neurocognitive disorder and dementia were used as indicators of cognitive functioning.

The first model included self-efficacy, which was shown to be significantly associated with medication adherence through the bivariate analysis and independent samples t-test. The other main predicator variables (functional health literacy, depression, cognitive functioning and medication adherence) were expected to explain medication adherence and were also included in the model. The goodness of fit test revealed that full model containing all predictors was statistically significant, $\chi 2$ (5, N = 92) = 18.04, p = .003, indicating that the model was able to distinguish between patients with high rates of medication adherence versus those with low rates of adherence (Table 12).

The Cox & Snell R Square and Nagelkerke R Square were used to indicate the amount of variation in medication adherence that was explained by the model. The model as a whole explained between 18.0% (Cox & Snell R square) and 25.2%

(Nagelkerke R square) of the variance in adherence and correctly classified 74.7% of cases. The Wald test was used to assess the significance of prediction of each predictor variable. The Wald statistic identified self-efficacy as contributing significantly to the predictive ability of the model 13.24 ($p < .0005$). Self-efficacy was the strongest predictor of adherence with an odds ratio of 7.11 (95% CI = 2.47,20.47) indicating that patients with higher self-efficacy have 7 times the odds of being adherent than those with lower self-efficacy, controlling for the other factors in the model. The 3 other predictors of medication adherence in this model, health literacy, cognitive function and depression, were not statistically significant. However, while the odds ratio for functional health literacy (OR = 2.61) was not statistically significant it is in the direction that would suggest that patients with higher health literacy are more likely to be adherent. The confidence interval (95% CI = .77,8.83) is wide enough to infer that health literacy has an influence on medication adherence. While the CI is consistent with the possibility that health literacy is an important predictor, it was not confirmed due to the p-value (p=.124).

Table 12: Model 1: Summary of Logistic Regressions for Factors Predicting Medication Adherence

							95% CI for OR	
	B	S.E.	Wald	df	*p*	OR	Lower	Upper
Self-efficacy	1.96	.54	13.24	1	<*.0005*	7.11	2.47	20.47
Functional health literacy	.96	.62	2.37	1	.124	2.61	.77	8.83
Depression	.38	.58	.437	1	.509	1.46	.47	4.51
MNCD	.95	.80	1.42	1	.234	2.58	.54	12.25

Dementia	-.46	.60	.59	1	.441	.63	.19	2.04

A second model was developed to include other independent variables known to be associated with medication adherence. The first model was directly connected to the conceptual framework and included variables that were of primary interest in this study. In contrast, the second model included additional variables that were not the primary focus of this study but have been supported in the literature as being factors in non-adherence. Concomitant medications and race have been identified in other studies as predictors of medication adherence. The second model was fit with these additional variables to control for potential confounding of these variables and assess if the new model was significantly different from the first model (Table 13). The goodness of fit test revealed that this model was statistically significant, $\chi 2$ (8, N = 92) = 24.80, p = .002. The Cox & Snell R Square and Nagelkerke R Square were used to indicate the amount of variation in medication adherence that was explained by the model. The model as a whole explained between 23.9% (Cox & Snell R square) and 33.4% (Nagelkerke R square) of the variance in adherence and correctly classified 75.8% of cases. The Wald statistic identified self-efficacy as contributing significantly to the predictive ability of the model 13.66 ($p < .0005$). Similar to the first model, self-efficacy was the strongest predictor of adherence, (OR = 9.30, 95% CI = 2.85,30.37), indicating that patients with higher self-efficacy were over 9 times more likely to be adherent than those with lower self-efficacy when controlling for other factors in the model. The results also revealed that race had a statistically significant contribution in the model; Wald test statistic of

4.31 with 1 degree of freedom and an associated *p*-value of .038. In this model, race was a moderately strong predictor of adherence (OR = 3.80, 95% CI = 1.08, 13.41). White patients were nearly 4 times as likely to be adherent compared to non-white patients in this study. The predictor variable for total cardiovascular medications was not found to be a predictor of adherence in this model; however the trend suggests a positive association between a higher number of prescribed medications and greater adherence. Patients prescribed 3 or more medications were 2.46 as likely to be adherent compared to patients prescribed only 1-2 medications.

Table 13: Model 2: Summary of Logistic Regressions for Factors Predicting Medication Adherence

							95% CI for OR	
	B	S.E.	Wald	df	*p*	OR	Lower	Upper
3 medications	.90	.92	.96	1	.327	2.46	.41	14.89
4 medications	1.22	.85	2.09	1	.148	3.40	.65	17.80
Depression	.48	.62	.62	1	.43	1.62	.49	5.43
MNCD	1.51	.92	2.70	1	.101	4.52	.75	27.37
Dementia	-.45	.62	.53	1	.467	.64	.19	2.15
Race, White	1.34	.643	4.31	1	*.038*	3.80	1.08	13.41
Self-efficacy	2.23	.60	13.66	1	*<.0005*	9.30	2.85	30.37
Functional health literacy	.93	.68	1.87	1	.171	2.54	.67	9.64

4.6 Hypothesis Testing

Hypothesis 1: Among veterans hospitalized for an ACS event, rates of functional health literacy levels will approximate rates of health literacy within the general U.S. population.

Among veterans who have been hospitalized for an ACS event, the rate of functional health literacy was not found to be similar to the rate of health literacy within the general population. The 2003 National Assessment of Adult Literacy (NAAL), the first large-scale national assessment to include a component designed specifically to measure health literacy, reported that approximately 40% of the U.S. population scored in the "basic" or "below basic" categories of health literacy. As reported in the NAAL, while low health literacy is significant within the general population, certain groups of individuals have an even higher prevalence of the problem, including the elderly, minorities, individuals with lower educational attainment, those with English as a second language and people living in poverty. The frequency distributions of patient characteristics revealed that the patients in the current study sample were elderly with a mean age of 64.8 (SD ± 9.2) and the overall sample was predominantly white (73.9%). Educational level, household income and primary language spoken were not collected in the primary study and thus, not available for analysis in this sample. The mean functional health literacy score in this sample was 6.85 (SD ± 2.12), indicating a high level of health literacy among patients. Overall, this sample had a high rate of functional health literacy (78.3%). When compared to results reported from the 2003 NAAL, there were higher levels of health literacy among this sample of veterans when compared to the reported national rates. Therefore, the <u>results of the analysis did not support hypothesis 1 in this study.</u>

Hypothesis 2: Veterans with low functional health literacy will have similarly low levels of self-efficacy.

This study hypothesized that patients with low functional health literacy would tend to be more easily discouraged and less likely to succeed with performing self-management behaviors, such as adhering to prescribed medication regimens. As a result, these patients would have correspondingly lower levels of self-efficacy. Table 9 illustrates the findings from the covariate analysis that examined key patient characteristics by functional health literacy levels. The results of this analysis did not support hypothesis 2 for patients with limited health literacy – the association between health literacy and self-efficacy was not statistically significant, χ^2 (1, N = 92) = 0.89, (p = .344). Race, total number of CV medication, cognitive function and depression were also examined as possible predictors of health literacy. No other variable was found to have a statistically significant relationship with health literacy; however, the relationship between cognitive functioning and health literacy approached statistical significance χ^2 (2, N = 92) = 5.94, (p = .051).

Hypothesis 3: The effects of health literacy, depression and cognitive functioning on medication adherence will be partially mediated through self-efficacy.

The conceptual framework for this study predicted that health literacy, depression and cognitive functioning had a direct pathway to medication adherence. Hypothesis 3 suggests that each of the predictor variables may not directly affect medication adherence, but rather each factor has a direct influence on self-efficacy, which in turn, affects medication adherence. The findings from the covariate analysis (Table 8) did not find a significant relationship between health literacy, depression or cognitive functioning and medication adherence. However, self-efficacy was shown to be a highly significant predictor of medication adherence, with an odds ratio of 7.11 (95% CI = 2.47,20.47), (p<.0005).

The logistic regression model further examined whether these key variables explained the difference in adherence rates in this sample (Table 12). While the full model was statistically significant, $\chi 2$ (5, N = 93) = 18.04, p = .003, only self-efficacy was confirmed as a strong predictor of adherence. The model did not support a relationship between health literacy, depression and medication adherence.

The lack of a statistically significant relationship between health literacy, depression or cognitive functioning and medication adherence, did not support further testing of self-efficacy as a possible mediator of the relationship between these variables and adherence.

Hypothesis 4: Among veterans hospitalized for an ACS event, individuals with low self-efficacy will have worse medication adherence.

The results supported hypothesis 4 that individuals with low self-efficacy have poorer medication adherence. Self-efficacy was shown to be a highly significant predictor of medication adherence, χ^2 (1, N = 92) = 12.38, (p<.0005) (Table 8) and this relationship was further supported by the logistic regression model (Table 12) which revealed that patients with higher self-efficacy were over 7 times as likely to be adherent compared to patients with lower levels of self-efficacy. In addition, the results of the independent-samples t-test comparing self-efficacy scores between adherent and not-adherent patients revealed a statistically significant difference in total SEAMS scores for adherent (M = 33.16, SD = 5.60) versus non-adherent patients (M = 28.38, SD = 7.61); t

(42.72) = -3.02, p = .004. The association between self-efficacy and medication adherence was consistent between the 2 groups. High adherence was associated with higher levels of self-efficacy and lower adherence was associated with lower levels of self-efficacy (Table 11).

4.7 Sub-Analyses

As previously reported, the MEDICATION Study randomized patients to the multifaceted intervention group or usual care group prior to hospital discharge. While not an aim of this study, additional analyses were conducted to explore relationships between groups and observe frequencies or proportion of cases that occur in each of the treatment groups. Of the 92 patients in the current sample, 47 patients were assigned to the intervention group and 45 were assigned to usual care.

Chi-square test for independence was conducted to explore the association between treatment groups and the primary patient psychosocial and medical factors that were of primary interest in the current study (Table 14). Overall, the data did not indicate significant associations between study arm and the majority of variables. However, the analysis showed a significant association between the treatment groups and medication adherence, χ^2 (1, n = 92) = 12.31, $p<.0005$. In addition, the analysis also showed that the total number of CV medications was also significantly different between the intervention and usual care groups, χ^2 (2, n = 92) = 6.89, p=.032.

Table 14: Patient Characteristics, by Treatment Group

	Intervention Group 1 (n=47)		Usual Care Group (n=45)		Analysis	
	N	%	N	%	χ^2 (df)	*p*
Age (years), mean ± SD	64.3±9.68		65.3±8.8 4			.628
Gender, Male	46	97.9%	43	95.6%	0.39 (1)	.532
Race						
White	36	76.6%	32	71.7%	0.36 (1)	.549
Non-white	11	23.4%	13	28.9%		
Medication adherence						
PDC<0.90	7	14.9%	22	48.9%	12.31 (1)	*<.0005*
PDC≥0.90	40	85.1%	23	51.1%		
Medication self-efficacy						
SEAMS < 31	17	36.2%	19	42.2%	0.35 (1)	.552
SEAMS ≥ 31	30	63.8%	26	57.8%		
Health Literacy						
REALM-R < 7	9	19.1%	11	24.4%	0.38(1)	.538
REALM-R ≥ 7	38	80.9%	34	75.6%		
Cognitive Functioning						
Dementia	13	27.7%	6	13.3%	3.69 (2)	.158
MNCD	24	51.1%	22	48.9%		
Normal	10	21.3%	17	37.8%		
Depression						
PHQ < 9	35	76.1%	29	64.4%	1.48 (1)	.224
PHQ ≥ 9	11	23.9%	16	35.6%		
Medical History						
Hypertension	43	91.5%	42	93.3%	0.11 (1)	.739
Hyperlipidemia	35	77.8%	36	78.3%	0.18 (1)	.893
Diabetes	20	42.6%	13	28.9%	1.87 (1)	.172
History of CAD	29	61.7%	26	57.8%	0.15 (1)	.701
Smoker	37	78.7%	32	71.1%	0.71 (1)	.399
Total CV Meds						
0-2	2	4.3%	9	20.0%	6.89 (2)	*.032*
3	17	36.2%	9	20.0%		
4	28	59.6%	27	60.0%		

An independent t-test was conducted to compare the mean scores on each of the psychosocial measures for both treatment groups (Table 15). There was no significant difference in self-efficacy, depression, health literacy and cognitive functioning scores for patients in the different treatment groups. However, overall medication adherence scores were significantly different for patients in the treatment group (M = 0.96, SD = 0.09) compared to patients in the usual care group (M = 0.84, SD = 0.19); t (63.6) = -3.66, p <*.0005* (two –tailed). The magnitude of differences in the means (mean difference = -0.11, 95% CI: -0.17 to -0.5) was large (eta squared = 0.124) which indicated that 12% of the variance in medication adherence was explained by treatment group.

Table 15: Mean scores for Psychosocial Measures by Treatment Group

	Treatment Group						95% CI for Mean Difference	t	df	Sig
	Intervention			Usual Care						
	M	SD	n	M	SD	n				
Self-efficacy	32.66	5.95	47	30.60	7.26	45	-4.80, .68	-1.49	90	.140
Health literacy	6.81	2.18	47	6.89	2.07	45	-.80, .96	.18	90	.857
Cognitive functioning	23.38	4.48	47	24.52	3.95	44	-.62, 2.90	1.28	89	.203
Depression	6.59	5.80	46	8.02	6.35	45	-1.10, 3.97	1.13	89	.263
Medication adherence	.96	.09	47	.84	.19	45	-.17, -.05	-3.66	63.6	<*.0005*

The following clinical endpoints were included in the primary study: MI, revascularization, all-cause hospitalization and death. Using the primary variable of interest in the current study, self-efficacy, a second chi-square test for independence was conducted to examine differences in outcomes between patients with high self-efficacy versus those with low self-efficacy. Across all clinical endpoints, there were no statistically significant differences between patients with high self-efficacy compared to patients with low self-efficacy (Table 16).

Table 16: Clinical Endpoints, by Self-efficacy

	Low Self-Efficacy (n=36)		High Self-Efficacy (n=56)		Analysis	
	N	%	N	%	χ^2 (df)	p
MI						
Yes	4	11.1%	6	10.7%	.004 (1)	.952
No	32	88.9%	50	89.3%		
Revascularization						
Yes	8	22.2%	7	12.5%	1.52 (1)	.218
No	28	77.8%	49	87.5%		
All-cause hospitalization						
Yes	24	66.7%	38	67.9%	.014 (1)	.905
No	12	33.3%	18	32.1%		
Mortality						
Yes	2	5.6%	5	8.9%	.355(1)	.551
No	34	94.4%	51	91.1%		

The final sub-analysis examined differences between treatment groups on self-efficacy scores that were measured at baseline and at the 12-month clinic visit. A total of 53 patients completed a baseline SEAMS assessment and follow-up SEAMS assessment. Within this sub-group of patients with pre- and post-self-efficacy scores, 28 patients were in the usual care group and 25 patients were in the intervention group. A one-way between-groups analysis of covariance was conducted to evaluate the impact of the multifaceted intervention on SEAMS scores while controlling for patients' baseline self-efficacy scores (Table 17). The independent variable consisted of self-efficacy scores on the SEAMS administered after the intervention was completed. Patients' scores on the pre-intervention administration of SEAMS were used as the covariate in this analysis. After adjusting for pre-intervention scores, there was no statistically significant difference between the treatment groups on post-intervention self-efficacy scores, $F(1,50) = .58$, $p = .45$, partial eta squared = .01. There was a strong relationship between the pre-intervention and post-intervention self-efficacy scores, as indicated by a partial eta squared value of .26.

Table 17: ANCOVA Summary Table
Dependent Variable: SEAMS (post-intervention)

Source	Sum of Squares	df	Mean Square	F	*p*	Partial Eta Squared
SEAMS (baseline)	269.40	1	269.40	17.91	<.0005	.264
Treatment Group	8.68	1	8.68	.58	.451	.011
Error	752.31	50	15.05			

CHAPTER 5: DISCUSSION

5.1 Summary

The primary aims of this study were to examine how various psychosocial factors impact medication adherence behaviors. Specifically, this study sought to closely explore levels of functional health literacy, self-efficacy, depression and cognitive functioning among a subset of veterans who had been hospitalized for an ACS event. These variables were examined to determine if they were independent predictors of medication adherence as well as if they were associated with one another in a meaningful way. This study was also interested in understanding whether the population of veterans in this study differed from the general U.S. population in either the prevalence of these factors or degree to which these characteristics were evident.

This study tested the hypothesis that specific risk factors commonly shared among veterans with cardiovascular disease impact patients' adherence to cardioprotective medications following hospitalization for acute coronary syndrome events. Self-efficacy, health literacy, depression and cognitive functioning were independently examined to understand their impact on overall adherence. In addition, the role of self-efficacy was carefully examined as a potential mediator of medication adherence.

The overall medication adherence rates in the study sample were unexpectedly higher than expected rates of adherence among patients hospitalized for ACS. Based on the widely-used proportion of days covered (PDC) calculation, the majority of patients in this study were classified as highly adherent (68.5%). Because of the distribution of PDC scores in this population, this study used a modified PDC cutoff score of 90% compared to the standard 80% cutoff. The results from this study differ from findings from previous studies. Other studies have reported lower adherence rates in the range of 20% - 40% across cardiovascular medications (Spertus et al., 2006; Ho et al., 2008). While the sample in this study had a higher overall rate of adherence compared to previously published studies, there still remain approximately 30% of patients in this study who were not considered adherent.

Within this population of veterans, medication-taking self-efficacy scores as measured by the Self-Efficacy for Appropriate Medication Use Scale indicated that 39% of patients had low self-efficacy. No other known studies have specifically examined medication-taking self-efficacy in the veteran population. The theoretical foundation of this study is centered on the Social Cognitive Theory, which emphasizes the construct of self-efficacy as a determinant of individual behavior (Bandura, 1977a). The results of this study uphold the Social Cognitive Theory's belief that individuals who perceive themselves as having a strong sense of self-efficacy are more persistent, motivated and more likely to attempt specific behaviors required to achieve specific goals. According to the Social Cognitive Theory, the concept of reciprocal determinism emphasizes the interplay between personal factors, environmental factors and behavior. Individuals have a role in influencing their environment and producing conditions that affect their behavior. Furthermore, individuals' personal factors, such as self-efficacy, and their behaviors can also act as determinants of each other. In this study, an individual's medication-taking self-efficacy was hypothesized to influence their medication adherence behaviors. It was expected that in the subgroup of veterans who perceived themselves as having high levels of medication-taking self-efficacy would have higher rates of medication adherence compared to veterans who perceived themselves as having lower levels of self-efficacy related to medication-taking behaviors. This study sought to investigate the independent relationship between self-efficacy and medication adherence alone as well as the relationship between self-efficacy, health literacy, cognitive functioning, depression, and medication adherence. The most notable finding in this study was the significant relationship between self-efficacy and overall medication adherence. Patients with higher rates of medication adherence also reported higher levels of self-efficacy. Highly adherent patients reported higher mean SEAMS scores compared to non-adherent patients (33.16 ± 5.60, 28.38 ± 7.61, respectively). This finding supports the hypothesis that individuals with low self-efficacy have poorer medication adherence and is consistent with this study's underlying basis in the Social Cognitive Theory. Despite the lack of published studies specifically examining the role of self-efficacy and medication adherence among veterans with ACS, this study's findings are consistent with other studies that have examined self-efficacy as a determinant of medication adherence among subjects with other chronic illnesses such as HIV, diabetes and more broadly defined coronary disease (Unni & Farris, 2011; Sarkar et al., 2007; Aljasem et al., 2001). These studies have also demonstrated that higher self-efficacy is predictive of higher rates of medication adherence.

While self-efficacy alone was predictive of medication adherence, the role of self-efficacy as a mediator was not supported in this study. In contrast, Cha et al. (2008) and Wolf et al. (2007) both examined the role of self-efficacy as a mediating factor between health literacy, depression, treatment knowledge and medication adherence. In both studies, self-efficacy was a significant mediating factor that independently predicted medication adherence. In this study, we expected to find that health literacy, cognitive function and depression would be associated with self-efficacy and that self-efficacy would be associated with medication adherence. In order to test for partial mediation, we would have been expected these variables to be associated with adherence. However, the present study examined the key factors of health literacy, depression, and cognitive functioning in the context of medication adherence yet found no significant relationship between each of these predictor variables and medication adherence. The regression model (Table 12) supported that self-efficacy had an independent association with adherence yet it did not support the direct impact of the other variables on medication adherence and did not address the association between self-efficacy and the other predictor variables.

Both self-efficacy and health literacy play a significant role in influencing medication adherence behavior. Prior studies have independently confirmed the association between self-efficacy and self-management behaviors, such as medication adherence, for chronic health disorders (Chen et al., 2014). In keeping with the Social Cognitive Theory, individuals with a high self-efficacy, who perceive themselves as having the capability to carry out specific behaviors (e.g. obtaining, processing and understanding basic health information needed to make appropriate health decisions) will be more likely to succeed with self-management activities than individuals who do not believe themselves capable of performing these actions. Similarly, the present study did not have information about whether patients participated in cardiac rehabilitation. Cardiac rehabilitation is indicated as a class I indication for secondary prevention of MI and other cardiovascular conditions and participation in cardiac rehabilitation has been strongly associated with adherence to cardioprotective medications (Shah et al., 2009). Identifying whether patients participated in cardiac rehabilitation may explain whether the high adherence rate in this study was attributable to tailored risk factor modification, counseling, and education that patients receive through cardiac rehabilitation.

Similarly, health literacy encompasses specific skills needed to access, understand and process information in ways useful to maintaining health; however individuals with limited health literacy will be challenged to properly care for themselves. When compared to results from the 2003 NAAL, there were higher levels of health literacy among this sample of veterans when compared to the reported national rates. It is worth noting that the methods for assessing literacy in the NAAL are not analogous to the REALM-R used in this study. However, different methods of assessing health literacy can still shed light on the overall health literacy skills of a target population. In this study, the REALM-R was used as a proxy indicator to represent the concept of health literacy despite the absence of the same measurement method used in the NAAL.

Individuals with low health literacy often go undetected because they feel ashamed (Parikh et al., 1996). This study hypothesized that patients with low functional health literacy would also have lower self-efficacy and, as a result, tend to be more easily discouraged and less likely to succeed with performing actions necessary to be considered adherent to their prescribed medications. The absence of a significant relationship between individuals with poor self-efficacy and low health literacy was unexpected. This could be explained by the finding that, in the specific veteran population utilized in this study, the majority of patients in this sample had high functional health literacy. Alternatively, it is possible that medication instructions provided by the VA at the time of hospital discharge were properly implemented and therefore effective enough to explain the lack of the expected association.

Observed rates of functional health literacy showed that over 75% of this study population had adequate functional health literacy, which was significantly higher than expected. This finding was not compatible with the hypothesis that health literacy levels in this sample of veterans would be similar to the general population. The most recent national assessment of adult literacy that measured health literacy showed that approximately 60% of the general population had adequate functional health literacy (White & Dillow, 2005). Because the overall rates of health literacy were high in the present study, this may contribute to the lack of significant association between health literacy and the other psychosocial characteristics which have previously been supported in other studies. These findings highlight a number of questions that should be investigated to better understand factors specific to the veteran population that may enhance self-care behaviors. For example, does being in the military, expose individuals to extra education and training that are not exclusively related to battle performance, but also apply to general behavior, medical care, and survival skills? Furthermore, does this exposure enhance individual responsibility which then has a positive effect on self-care behaviors related to medication adherence?

Worth noting, the findings from the covariate analysis revealed a relationship between health literacy and mental status that approached statistical significance. Prior research has shown that older adults with cognitive impairments have lower scores on health literacy assessments compared to older patients with no cognitive dysfunction or younger patients (Kaphingst et al., 2014). This observation is further supported by studies that have demonstrated a relationship between deterioration of cognitive functioning among older adults that affect cognitive abilities that are associated with health literacy and self-care activities (Marvanova et al., 2011; Levinthal et al., 2008; Benson & Forman, 2002). These findings are relevant and important to the population of older Veterans targeted in this study. The median age of Veterans in this cohort was 64.8 years which is consistent with the median age of the male Veteran population in the U.S. of 64 years. Given the current and projected growth of the older segment of the veteran population (Department of Veterans Affairs Office of Policy and Planning, 2011), the implications of the impact of age-related deterioration of cognitive function are likely to be reflected through worsening of health literacy skills which may exacerbate issues of medication non-adherence.

In this cohort of patients, cognitive impairment was reported in the majority of patients with over 70% of patients classified as having some degree of impaired cognitive functioning. Mild cognitive functioning has been associated with memory problems, attention deficits and problem solving, all of which hinder an individual's ability to comply with prescribed medication regimens (Sauvé, Lewis, Blankenbiller, Rickabaugh, & Pressler, 2009). Prior assessments to diagnose cognitive impairment in the veteran population have estimated the prevalence of dementia at 7.3% among veterans 65 years and older (Phelan, Borson, Grothaus, Balch, & Larson, 2012). It is not known why the prevalence of dementia was substantially greater in this study population compared to general estimates in the veteran population.

Surprisingly, the present study found no association between cognitive impairment and medication adherence. In contrast, Hawkins et al. (2012) examined cognitive impairment in a similar population of outpatient veterans and found a significant association between increasing severity of cognitive impairment and medication non-adherence. Moreover, when mental status was included as a predictor in our logistic regression models, there was an inverse relationship between cognitive functioning and medication adherence. It seems counterintuitive that individuals with impaired cognitive functioning would result in patients being adherent to medication regimens considering that published studies have demonstrated that cognitive impairment negatively impacts a patient's ability to take their medications correctly. Because the overall rates of medication adherence were high, this may contribute to the lack of the expected association between cognitive dysfunction and medication adherence. Another possible explanation for the unexpectedly high rate of medication adherence is that patients with recognized cognitive impairment may take full advantage of caregivers or other support systems within the Veteran Administration system and consequently patients' adherence to prescribed medications is substantially enhanced. Prior qualitative studies have shown that the role of a caregiver or spouse has a positive impact on increased medication adherence through the practical support provided by their caregivers (such as sorting multiple and sometimes complicated medications and providing direct supervision of medication administration). Wu et al. (2013) found that higher perceived social support predicted better medication adherence, and consequently event-free survival in patients with heart failure.

Routine screening for dementia has important implications for interventions and strategies that can be implemented to improve care and reduce health care utilization and associated costs among older patients with dementia. McCarten et al. (2012) screened over 8,000 veterans with no prior diagnosis of cognitive impairment to assess the effect of a comprehensive evaluation on diagnosing cognitive impairment. Routine screenings combined with further evaluation with a healthcare professional trained in dementia care resulted in a two- to threefold increase in diagnoses of cognitive impairments. While the current study's findings did not support the relationship between impaired cognitive function and medication non-adherence, the high rate of cognitive impairment in this sample suggests that these veterans are likely to have multiple comorbidities and increased utilization of healthcare. Prior studies have found that veterans with newly-diagnosed dementia had significantly greater levels of medical comorbidities, higher numbers of hospitalizations, longer average length of stays and increased usage of outpatient services (Wray, Wade, Beehler, Hershey, & Vair, 2013).

As measured by the PHQ-9, the present study's results revealed that 29.3% of the patients in this study were clinically depressed. According to the VA's National Registry for Depression, 11% of veterans aged 65 and older have major depression and among younger veterans (age 21 to 39), 9.3% have experienced at least one major depressive episode (U.S. Department of Veterans Affairs, 2011; SAMHSA, 2008). While the prevalence of depression in the veteran population is already elevated compared to rates in the general U.S. population (3-7%), a much higher percentage of patients in the current study were clinically depressed. Among the veteran population, depression is commonly associated with posttraumatic stress disorder (PTSD), traumatic brain injury (TBI) and cognitive dysfunction (Byers & Yaffe, 2014; Whooley, 2014). Data on the VA population have already demonstrated a strong relationship between cardiovascular risk factors and cognitive impairment. As it relates to cardiovascular disease, Skala, et al. (2005) and Choi et al. (2014) found that depressive symptoms and depressive disorders and are more common in cardiac patients than in the general population. The considerably higher rate of depression in this sample may be explained by the fact that these patients had a number of predisposing factors that made them more susceptible to depressive disorders and symptoms. Considering that veterans have an already elevated rate of depression which places them at increased risk for poor cognitive functioning combined with their recently experienced cardiac event, the likelihood that these patients experience higher than expected rates of depression becomes very plausible.

Poor medication adherence is one of the most common explanations linking depression and worse outcomes (Wu et al., 2013). However, in the current study, depression was not found to be a predictor of adherence. Based on the link between depression and feelings of hopelessness, social isolation, and lack of social support networks, this study expected that individuals with depression would be more likely to have lower self-efficacy. Despite the fact that high self-efficacy was predictive of better adherence, it is possible that the unexpectedly high rates of adherence and depression in this population may alter the expected relationship between adherence and psychosocial variables.

In the absence of systematic screening for depression, less than half of the patients with depression will be identified and, of those, only a proportion will be adequately treated even though treatment rates are generally higher within the VA health care system (burnett-Zeigler, Kivin, & Ilgen, 2012; U.S. Department of Veterans Affairs, 2009). The prevalence of depression in the current study was higher than the general population which suggests that veterans may have received adequate screening and diagnosis.

Overall, the present study confirmed the expectation that high self-efficacy would be associated with greater medication adherence and, as a result, adds to the growing body of literature that examines the role of psychosocial factors, such as perceived self-efficacy as a predictor of behavior.

5.2 Limitations

Various limitations of this study should be considered. The primary study cohort was powered to detect an improvement of 15% or greater in the proportion of adherent patients. However, in this study, the sample was further reduced to include only those patients who had completed the SEAMS. Out of the 253 patients in the original cohort, only 93 patients completed the SEAMS which further limited the population for this study. The small sample size resulted in a lack of statistical power to detect significant differences. Future analyses with adequate sample sizes would enable additional research to be undertaken that allows for further stratifications by patient sub-groups. The current analysis did not distinguish between patients with unstable angina, STEMI or NSTEMI because each of these subgroups would have been exceedingly small in size. Lastly, the sample size also dictated that the cut-points for various measures (adherence, health literacy and self-efficacy) be adjusted based on the distribution of scores for this population. For the dichotomous measures, these somewhat subjective cut-points based on the sample size may have influenced the comparison of results between groups.

The primary study was selectively conducted at 4 VA medical centers, and included a predominantly older, male population and may not be generalizable to other patient populations such as younger, female veterans and patients receiving care outside of the VA. The VA is the nation's largest integrated health care system and veterans who receive care through the VA health care system have access to medical services and medications via prescription medication coverage. The integrated inpatient and outpatient pharmacy at VA medical centers may make it easier for patients to obtain their medications compared to patients who receive medical care in an open health care system.

Cost is a frequently cited reason for medication non-adherence (Osterberg & Blaschke, 2005). Prescription drug coverage is a benefit provided by VA Pharmacy Service and is available to all veterans who are eligible for and enrolled in and receiving health care from the VA health care system. Because of the comprehensive health benefits that veterans receive through the VA, cost-related issues that are often cited as reasons for poor adherence were not considered in this study. Veterans' prescription drug coverage charges no premiums and has relatively limited copayments for prescriptions. It is not known whether the lack of a financial barrier buffers these patients from cost-related medication non-adherence.

In addition, the patients enrolled in the primary study volunteered to participate and, as a result, this may reflect a bias whereby these patients may be inherently different from other patient populations both within the VA health care system and the general population. One explanation may be that by virtue of the informed consent process, the patients that self-selected to volunteer in this study may have included patients who were already inclined to be more adherent. Therefore, it is possible that certain characteristics among this sample of patients differ from non-volunteers and may result in observed associations that are systematically different.

The measure of adherence used in this study relied on pharmacy refill data from the VA's closed pharmacy system to estimate patients' adherence. While this type of administrative data is broadly accepted as a valid method for measuring adherence, it does not allow investigators to assess whether patients actually consumed their prescribed medications. However pharmacy refill data and, specifically, the proportion of days covered (PDC) calculation that was used in this study has been widely validated as a measure of adherence in other studies. However, a number of different methods can be used to measure medication use behavior. Medication persistency is another method that is commonly used when evaluating medication use. Medication persistency attempts to capture the amount of time a patient remains on chronic drug therapy. Individuals who are persistent with therapy are considered to be continuous with their medication-taking behavior during a specified length of time. Persistency is measured as a function of medication possession at a fixed point in time. This approach measures patients' possession of medication on a fixed date after the initial prescription. The focus of this study was specifically on adherence which examined the degree to which patients adhered to their prescribed medications following hospital discharge. An evaluation of persistency would allow for greater understanding of the overall duration of time represented by the interval between when a patient started their medication through discontinuation of the medication. Future studies may benefit from examining the influence of both adherence and persistence in an effort to understand the short- and long-term implications of different types of medication-taking behaviors.

The overall rate of adherence in this study was significantly higher than nationally reported rates of medication adherence. As a result, the findings related to adherence may not generalize to other patient populations. The high rate of adherence in this study does not account for patients' previous adherence behavior. Assessing a patient's prior adherence may have implications on his or her medication-taking self-efficacy, and as a result, may affect current estimates of adherence. Future studies could enhance the understanding of the role of self-efficacy on medication adherence by examining changes in pre and post-intervention assessments of self-efficacy. The current study obtained a limited number of baseline and follow-up SEAMS scores. In addition, the lack of a baseline measure of adherence limits the ability to observe the relationship between baseline medication adherence and self-efficacy and a 12-month assessment of these same measures. However, an extension of the current study that is sufficiently powered to detect a difference in change scores following a multi-faceted intervention which includes baseline and follow-up assessments of self-efficacy and adherence would provide useful insight into whether interventions positively impact patients' self-efficacy and adherence behaviors.

The growing interest in the determinants of medication adherence presents an opportunity to conduct future research to elucidate whether the occurrence of other medical events and adherence to guideline-recommended secondary prevention measures impact adherence behavior. Additional studies are needed to better understand whether exposure to other medical events alter patients' future self-efficacy and perceived benefits related to adhering to treatment regimens and avoiding future medical events.

The high number of patients in this study with diagnosed depression suggests that these patients may have been previously treated with antidepressant pharmacotherapy. Prior medication adherence was not assessed among the patients who consented participate in the MEDICATION study. Over 85% of patients in this study were prescribed 3 or more cardioprotective medications following their ACS event and higher numbers of prescriptions have been shown to be associated with lower medication adherence (Marvanova et al., 2011).

Because this study was a secondary analysis, there are limitations with respect to the tools that were selected for assessing key patient characteristics and methods used for data collection. The primary intervention study did not include assessments of patients' education, income, and primary language spoken at home. The highest grade level completed, poverty and English as a second language have all been shown to be associated with lower levels of functional health literacy (White & Dillow, 2005). Due to the lack of access to data on education, income and primary language, these variables were not included as potential covariates in this analysis. Additional information on patients' socio-demographic characteristics could offer additional insight into other factors that may influence depression, cognitive functioning and self-efficacy.

In addition, the timing of the patient surveys may have magnified the rate of depression in this sample. Patient surveys, including the PHQ-9, were administered at the baseline visit which occurred prior to hospital discharge. Depression is common among patients hospitalized for an MI. In-hospital studies have reported that the prevalence of major depression among MI patients ranges between 15% to 27% (Bush et al, 2005; Thombs, Bass, & Ford, 2006).

While the findings of this study may not uniformly apply to patients in non-VA health care settings, they still may be helpful when evaluating non-veteran patients who are older and have co-existing psychosocial issues.

5.3 Conclusions

Considering the prevalence of depression, and cognitive impairment resulting from PTSD and TBI in the veteran population, proper screening and management of these patients may be effective in not only treating diagnosed psychiatric conditions, but may result in a secondary benefit of modifying other factors such as self-efficacy and medication adherence. Current evidence suggests that treatment of depression in elderly patients improves improved memory and cognitive ability. Impaired cognitive functioning negatively impacts the ability to understand and carry out self-care activities related to chronic conditions. Given the high percentage of patients receiving care within the VA health care system, health care providers should verify patients' understanding of information related to prescribed medication regimens and incorporate strategies during these clinical encounters to ensure patients' comprehension of their treatment plan that can help promote adherence. Furthermore, if patients with cognitive dysfunction are shown to have improved medication adherence as a result of existing social support systems, then future research should examine specific components of these social networks that can be incorporated into practical interventions to improve medication adherence and patient outcomes among patients with diagnosed cognitive impairment.

Depression is a common factor among elderly populations who also bear the burden of chronic diseases and multiple co-morbid conditions. The U.S. Census Bureau estimates that in 2012, adults aged 65 and older made up 13.7% of the American population and is expected to grow to 20% of the population by 2030 (Ortman,Velkoff, & Hogan, 2014). Thus, the older adult population is at greater risk for developing chronic diseases (e.g. cardiovascular disease) and depression. The association between depression, cardiovascular disease and medication adherence has important implications for clinical practice. Individuals with high levels of depressive symptoms are at increased risk of MI and those individuals are also less likely to adhere to recommended lifestyle and behavioral changes following an MI (Chapman et al., 2014; Lesperance et al., 2000). These patients are frequently at high risk for medication non-adherence. Similar to the earlier suggestion of routinely screening individuals for cognitive impairment, accurately diagnosing depression among patients should become a standard of care in general and specifically among patients with cardiovascular disease.

Varying levels of cognitive impairment, depression and health literacy underscore the importance of implementing measures to identify and correct it. For example, studies have shown that cognitive dysfunction impacts the accurate assessment of the different domains of health literacy across different health literacy screening instruments (Wolf et al., 2012). The higher than average rates of cognitive impairment and depression in this study population supports the need for validated screening instruments that are appropriate for use among patients with competing psychosocial issues.

The findings from this study have a number of potential research and policy implications. Given the burden of cardiovascular disease on health care utilization and costs to the U.S. health care delivery system, improving medication adherence among the millions of patients with cardiovascular disease has the potential to improve patient outcomes and minimize unnecessary utilization of health care services and reduce costs.

Medication non-adherence is not a one-dimensional issue. Valid assessments are needed to identify the array of factors that patients contend with in their personal lives that become contributing factors to their adherence behaviors. Screening tools that are pragmatic, uncomplicated and easily administered in routine health care settings will facilitate the practice of identifying the factors that are pertinent for an individual patient. This type of patient-centered approach will enable health care providers to individualize a patient's plan of care that lead to improved adherence to recommended treatments.

Routine screenings represent an initial step in a broader strategy to improve medication adherence. However, interventions to improve health-related behaviors are not consistently grounded in health behavior theories or models. Prevailing theories and models, such as the Social Cognitive Theory, can help inform the development of interventions by providing the basis for explaining the underlying forces that impact behavior and determining the best approach for promoting changes in behavior. Future research that explores how best to integrate health behavior theory into interventions aimed at resolving the complex and multi-layered issue of medication non-adherence is warranted.

While research can help inform the strategies for improving medication adherence at the patient-level, consideration should be given to broader policy decisions that can have more far-reaching impact on resolving the challenge of poor medication adherence. The health care system can go beyond increasing awareness of the pervasiveness of medication non-adherence. The health care system can urge providers to take notice of their patients' medication-taking patterns and the determinants of their behavior, but should also consider incentivizing them to take action through pay for performance programs that links physicians' reporting on performance measures and quality metrics to payment incentives (or penalties).

While this study did not specifically explore the role of out-of-pocket expenses as a factor in patients' adherence, it is known that veterans have prescription drug coverage that grants them minimal to no out-of-pocket expenses for their prescribed medications. As a plausible contributing factor to the overall high rate of adherence in this study's sample, this idea warrants additional research and possible policy changes. While not a minor type of reform, additional consideration should be given to how insurance benefits for prescription drug coverage are structured. Minimizing co-payments may yield improved adherence rates that result in overall cost-savings through reductions in avoidable hospitalizations.

The factors examined in this study represent a number of crucial issues that patients are commonly faced with. Awareness of patients' limitations provides an opportunity for healthcare providers to intervene and address the specific needs of patients and take into consideration the complexity of their individual treatment regimens. By incorporating principles of health behavior theories, future interventions can build off of established models that provide a framework for identifying key stimuli of behavior change. The results of this study demonstrated a significant association between low self-efficacy and poorer medication adherence. In keeping with the Social Cognitive Theory, future medication adherence interventions that center around the four triggers (performance accomplishments, vicarious experiences, verbal persuasion and emotional arousal) that most influence an individual's expectation of their own self-efficacy holds great potential to drive and cultivate positive behavior change. As such, the lessons learned from this study suggest that interventions to improve medication adherence should be tailored to the needs of each patient, the specifics of each health condition and the qualification of their caregivers.

REFERENCES

Aljasem LI, Peyrot M, Wissow L, Rubin RR. (2001). The impact of barriers and self-efficacy on self-care behaviors in type 2 diabetes. *The Diabetes Educator, 27,* 393-404.

Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, … Society for Academic Emergency Medicine. (2007). ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *JACC, 50*(7), e1-e157.

Antman EM,. Antman, Hand M, Armstrong PW, Bates ER, Green LA, ... Yancy CW. (2008). 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration With the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, Writing on Behalf of the 2004 Writing Committee. *J Am Coll Cardiol*, *51*, 210-247.

American Heart Association. Acute Coronary Syndrome. Retrieved from: http://www.americanheart.org/presenter.jhtml?identifier=3010002. Accessed January 10, 2007.

American Heart Association. (2002) Heart Disease and Stroke Statistics - 2003 update. Dallas, TX: American Heart Association.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). doi:10.1176/appi.books.9780890423349

Babev A, Frederick PD, Pasta DJ, Every N, Sichrovsky T, Hochman JS, & NRMI Investigators. (2005). Trends in the management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA*, *294*, 448-454.

Baker DW. (2006). The meaning and the measure of health literacy. *J Gen Int Med*, *21*, 878-883.

Baker DW, Gazmararian JA, Williams MV, Scott T, Parker RM, Green D, … Peel J. (2002). Functional health literacy and the risk of hospital admission among Medicare managed care enrollees. *Am J Public Health, 92*(8), 1278-1283.

Baker DW, Parker RM, Williams MV, & Clark WS. (1998). Health literacy and the risk of hospital admission. *J Gen Intern Med, 13*, 791-798.

Baker DW, Parker RM, Williams MV, Clark WS, & Nurss J. (1997). The relationship of patient reading ability to self-reported health and use of health services. *Am J Public Health, 87,*1027-1030.

Baker DW, Williams MV, Parker RM, Gazmararian JA, & Nurss J. (1999). Development of a brief test to measure functional health literacy. *Patient Educ Couns, 38*(1), 33-42.

Bandura A. Social Learning Theory. (1977a). Englewood Cliffs, NJ: Prentice-Hall, Inc.

Bandura A. (1977b). Self-efficacy: toward a unifying theory of behavioral change. *Psychological Review, 84*(2), 191-215.

Bandura A. (1978). The self system in reciprocal determinism. *Am Psychologist*, *33*, 344–358.

Bandura A. (1986). The Social Foundations of Thought and Action: A Social Cognitive Theory. Englewood Cliffs, NJ: Prentice-Hall, Inc.

Bandura A. (1989). Human Agency in Social Cognitive Theory. *American Psychologist*; *44*, 1175–1184.

Bandura A. (2004). Health promotion by social cognitive means. *Health Education and Behvior, 31*, 143-164.

Bandura A, & Cervone D. (1983). Self-evaluative and self-efficacy mechanisms governing the motivational effects of goal systems. *Journal of Applied and Social Psychology, 45*, 1017-1028.

Barrett SE, & Puryear JS. (2006). Health literacy: Improving quality of care in primary care settings. *Journal of Health Care for the Poor and Underserved, 17*, 690-697.

Baron RM, & Kenney DA. (1986). The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J of Personality and Social Psychology*, *51,* 1173-1182.

Bass PF, Wilson JF, & Griffith CH. (2003). A shortened instrument for literacy screening. *J Gen Intern Med*, *18*, 1036-1038.

Benson JG, & Forman WB. (2002). Comprehension of written health care information in an affluent geriatric retirement community: use of the Test of Functional Health Literacy. *Gerontology, 48*, 93-97.

Berkman ND, Sheridan SL, Donahue KE, Halpern DJ, Viera A, Crotty K, … Viswanathan M. (2011). Health Literacy Interventions and Outcomes: An

Updated Systematic Review. Evidence Report/Technology Assesment No. 199. (Prepared by RTI International–University of North Carolina Evidence-based Practice Center under contract No. 290-2007-10056-I. AHRQ Publication Number 11-E006. Rockville, MD. Agency for Healthcare Research and Quality.

Braunwald E. (1996). Acute myocardial infarction - the value of being prepared. *N Engl J Med*, *334*, 51-52.

Bush DE, Ziegelstein RC, Patel UV, Thombs BD, Ford DE, Fauerbach JA, …Bass EB. (2005). Post-Myocardial Infarction Depression. Evidence Report/Technology Assessment No. 123. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-02-0018.) AHRQ Publication No. 05-E018-2. Rockville, MD: Agency for Healthcare Research and Quality.

Burnett-Zeigler I, Kivin K, & Ilgen M. (2012). Depression treatment in older adult veterans. *Am J Geriatr Psychiatry*, *20,* 228-238.

Byers AL, & Yaffe K. (2014). Depression and dementias among military veterans. *Alzheimer's & Dementia*, *10*, S166-S173.

Cameron KA, Ross EL, Clayman ML, Bergeron AR, Federman AD, Bailey SC, … Wolf MS. (2010). Measuring patients'self-efficacy in understanding and using prescription medication. *Patient Educ Couns, 80*(3), 372-376.

Campbell NL, Boustani MA, Skopelja WN, Gao S, Unverzagt FW, & Murray MD. (2012). Medication adherence in older adults with cognitive impairment: a systematic evidence-based review. *Am J Geriatr Pharmacother*, *10*(3), 165-77.

Carmona RH. (2006). Health literacy: A national priority. *Journal of General Internal Medicine, 21*, 803.

Carney RM, Freedland RM, Eisen SA, Rich MW, & Jaffe AS. (1995). Major depression and medication adherence in elderly patients with coronary artery disease. *Health Psychol, 14*(1), 88-90.

Cha E, Erlen JA, Kim KH, Sereika SM, & Caruthers D. (2008). Mediating roles of medication-taking self-efficacy and depressive symptoms on self-reported medication adherence in persons with HIV: A questionnaire survey. *Int J Nurs Stud, 45*, 1175-1184.

Chapman DP, Perry GS, & Strine TW. (2005). The vital link between chronic diseases and depressive disorders. *Prev Chronic Dis*. [online serial] 2005 Jan [September 13, 2014]. Available from: http://cdc.gov.pcd/issues/2005/jan/04_00666.htm

Chapman RH, Brenner JS, Petrilla AA, Tierce JC, Collins SR, Battleman DS, & Schwartz JS. (2005). Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med, 165*(10), 1147-1152.

Chen AMH, Yehle KS, Albert NM, Ferraro KF, Mason HL, Murawski MM, & Plake KS. (2014). Relationships between health literacy and heart failure knowledge, self-efficacy, and self-care adherence. *Res Social Adm Pharm*, *10*(2), 378-386.

Choi NH, Kim J, Marti CG, & Chen GJ. (2014) Late-life depression and cardiovascular disease burden: examination of reciprocal relationship. *Am J Geriatr Psychiatry,* doi: 10.1016/j.jagp.2014.04.004. [Epub ahead of print]

Choo PW, Rand CS, Inui TS, Lee ML, Cain E, Cordeiro-Breault M, Canning C, & Platt R. (1999). Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Med Care, 37*, 846–857.

Choudhry NK, Avorn J, Antman EM, Schneeweiss S, & Shrank WH. (2007). Should patients receive secondary prevention medications for free after a myocardial infarction? An economic analysis. *Health Affairs, 26*(1), 186-194.

Choudhry NK, Glynn RJ, Avorn J, Lee JL, Brennan TA, Reisman L, … Shrank WH. (2014). Untangling the relationship between medication adherence and post-myocardial infarction outcomes: medication adherence and clinical outcomes. *Am Heart J*, *167*, 51-58.

Choudhry NK, Patrick AR, Antman EM, Avorn J, & Shrank WH. (2008). Cost-effectiveness of providing full drug coverage to increase medication adherence to post-myocardial infarction Medicare beneficiaries. *Circulation, 117,* 1261-1268.

Ciechanowski PS, Katon WJ, & Russo JE. (2000). Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Arch Intern Med, 160*, 3278-3285.

Cooper JK, Love DW, & Raffoul PR. (1982). Intentional prescription nonadherence (noncompliance) by the elderly. *J Am Geriatr Soc, 30*, 329–333.

Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, & Wong PK. (2008). Medication compliance and persistence: Terminology and definitions. *Value in Health*, *11*, 44-47.

Davis TC, Long SW, Jackson RH, Mayeaux EJ, George RB, Murphy PW, & Crouch MA. (1993). Rapid estimate of adult literacy in medicine: a shortened screening instrument. *Fam Med, 25*, 391-395.

Department of Veterans Affairs Office of Policy and Planning, National Center for Veterans Analysis and Statistics [VetPop2011]. Available at: http://www.va.gov/vetdata/veteran_population.asp.

DiMatteo MR, Lepper HS, & Croghan TW. (2000). Depression is a risk factor for noncompliance with medical treatment: Meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med*, *160*, 2101-2107.

Doshi JA, Zhu J, Lee BY, Kimmel SE, & Volpp KG. (2009). Impact of a prescription copayment increase on lipid-lowering medication adherence in veterans. *Circulation, 119*, 390-397.

Dunbar-Jacob J, & Mortimer-Stephens MK. (2001). Treatment adherence in chronic disease. *J Clin Epidemiol, 54*, S57-S60.

Eisen SA, Miller DK, Woodward RS, Spitznagel E, & Przybeck TR. (1990). The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med, 150*(9), 1881-1884.

Elderon L, & Whooley MA. (2013). Depression and Cardiovascular Disease. *Prog Cardiovasc Dis,* 55(6), 511-523.

Fairman K, & Motheral B. (2000). Evaluating medication adherence: which measure is right for your program? *J Managed Care Pharm, 6,* 499-504.

Farmer KC. (1999). Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther, 21*(6), 1074-1090.

Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke DR, … Capewell S. (2007). Explaining the decrease in U.S. deaths from coronary disease, 1998-2000. *N Engl J Med*, *356*, 2388-2398.

Frasure-Smith N, Lesperance F, & Talajic M. (1993). Depression following myocardial infarction: Impact on 6-month survival. *JAMA, 270,* 1819-1825.

Gazmararian JA, Kripalani S, Miller MJ, Echt KV, Ren J, & Rask K. (2006). Factors associated with medication refill adherence in cardiovascular-related diseases. *J Gen Intern Med*, *21*, 1215-1221.

Gehi AK, Ali S, Na B, & Whooley MA. (2007). Self-reported medication adherence and cardiovascular events in patients with stable coronary heart disease. *Arch Intern Med*, *167*, 1798-1803.

Gehi AK, Haas D, Pipkin S, & Whooley MA. (2005). Depression and medication adherence in outpatients with coronary heart disease. *Arch Intern Med, 165*, 2508-2513.

Gheorhiade M, Ruzumna P, Borzak S, Havstad S, Ali A, & Goldstein S. (1996). Decline in the rate of hospital mortality from acute myocardial infarction: Impact of changing management strategies. *Am Heart J*, *131*, 250-256.

Glanz, K, Rimer, BK and Lewis, FM (eds). (2002) *Health Behavior and Health Education: Theory, Research and Practice*, 3rd edition. Jossey-Bass, San Francisco, CA.

Graves EJ, & Kozak LJ. (1998). Detailed diagnoses and procedures. National Hospital Discharge Survey, 1996. National Center for Health Statistics. *Vital Health Stat, 13, 138*, 1-151.

Grenard JL, Munjas BA, Adams JL, Suttorp M, Maglione M, McGlynn EA, & Gellad WF. (2011). Depression and medication adherence in the treatment of chronic diseases in the United States: A meta-analysis. *J Gen Intern Med*, *26*(10), 1175-1182.

Hawkins LA, Kilian S, Firek A, Kashner TM, Firek CJ, & Silvet H. (2012). Cognitive impairment and medication adherence in outpatients with heart failure. *Heart & Lung, 41*(6), 572-582.

Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, … Interdisciplinary Council on Quality of Care and Outcomes Research. (2011). Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*, *123*(8), 933.944.

Ho MP, Magid DJ, Shetterly SM, Olson KL, Maddow TM, Peterson PN, … Rumsfeld JS. (2008). Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. *Am Heart J, 155*, 772-779.

Ho MP, Spertus JA, Masoudi FA, Reid KJ, Peterson ED, Magid DJ, ... Rumsfeld JS. (2006). Impact of medication therapy discontinuation on mortality after ,myocardial infarction. *Arch Intern Med, 166*, 1842-1847.

Ho PM, Bryson CL, & Rumsfeld JS. (2009). Medication adherence: Its importance in cardiovascular outcomes. *Circulation, 119*, 3028-3035.

Ho PM, Lambert-Kerzner A, Carey E, Fahdi IE, Bryson CL, Melnyk SD, … Del Giacco EJ. (2014). Multifaceted intervention to improve medication adherence and secondary prevention measures after acute coronary syndrome hospital discharge: a randomized clinical trial. *JAMA Intern Med, 174*(2), 186-193.

Ingersoll KS, & Cohen J. (2008). The impact of medication regimen factors on adherence to chronic treatment: a review of literature. *J Behav Med*, *31*(3), 213–224

Institute of Medicine. (2004). Health Literacy: A Prescription to End Confusion. Washington, DC: The National Academies Press.

Jackevicious CA, Li P, & Tu JV. (2008). Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. *Circulation*, *117*, 1028-1036.

Jackevicious CA, Mamdani M, & Tu JV. (2002). Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA*, *288*, 462-467.

Kaphingst KA, Goodman MS, MacMillan WD, Carpentar CR, & Griffey RT. (2014). Effect of cognitive dysfunction on the relationship between age and health literacy. *Patient Education and Counseling,* 95, 218-225.

Kripalani S, Henderson LE, Chiu EY, Robertson R, Kolm P. & Jacobson TA. (2006). Predictors of medication self-management skill in a low-literacy population. *J Gen Intern Med, 21*(8), 852-856.

Kripalani S, Yao X, & Haynes RB. (2007). Interventions to enhance medication adherence in chronic medical conditions: a systematic review. *Arch Intern Med*, *167*, 540-550.

Kroenke K, Spitzer RL, & Williams JB. (2001). The PHQ-9: validity of a brief depression severity measure. *JGIM*, *16,* 606-613.

Kronish IM, Rieckmann N, Halm EA, Shimbo D, Vorchheimer D, Haas DC, Davidson KW. (2006). Persistent depression affects adherence to secondary prevention behaviors after acute coronary syndromes. *J Gen Intern Med, 21*, 1178-1183.

Krumholz HM, Chen J, Wang Y, Radfor MJ, Chen YT, & Marciniak TA. (1999). Comparing AMI mortality among hospitals in patients 65 years of age and older: evaluating methods of risk adjustment. *Circulation, 99*, 2986–2992.

Kurdyak PA, Gnam WH, Goering P, Chong A, & Alter DA. (2008). The relationship between depressive symptoms, health service consumption, and prognosis after acute myocardial infarction; a prospective cohort study. *BMC Health Services Research*, *8,* doi:10.1186/1472-6963-8-200.

Kutner M, Greenberg E, Jin Y, & Paulsen C. (2006). The Health Literacy of America's Adults: Results from the 2003 National Assessment of Adult Literacy (NCES 2006-483). U.S. Department of Education. Washington, DC: National Center for Education Statistics.

Lauzon C, Beck CA, Huynh T, Dion D, Racine N, Carignan S, … Pilote L. (2003). Depression and prognosis following hospital admission because of acute myocardial infarction. *CMAJ, 168*, 547-552.

Lee JK, Grace KA, & Taylor AJ. (2006). Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol. *JAMA, 296*, 2563-2571.

Lesperance F, Frasure-Smith N, Talajic M, & Bourassa MG. (2002). Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation, 105*, 1049-1053.

Levinthal BR, Morrow DG, Tu W, Wu J, & Murray MD. (2008). Cognition and health literacy in patients with hypertension. *J Gen Intern Med*, *23*(8), 1172-1176.

Maddox TM, Plomondon ME, Ho PM, Fihn SJ, Bryson CL, Spertus JA, & Rumsfeld JS. (2007). Factors associated with statin adherence after acute coronary syndrome. Abstract – 8th Scientific Forum on Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke.

Makaryus AN, & Friedman EA. (2005). Patients' understanding of their treatment plans and diagnosis at discharge. *Mayo Clinic Proc, 80*(8), 991-994.

Marcum ZA, Zheng Y, Perera S, Strotmeyer E, Newman AB, Simonsick EM, … Health ABC Study. (2013). Prevalence and correlates of self-reported medication non-adherence among older adults with coronary heart disease, diabetes mellitus, and/or hypertension. *Res Social Adm Pharm, 9*(6), 817-827.

Marvanova M, Roumie CL, Eden SK, Cawthon C, Schnipper JL, & Kripalani S. (2011). Health literacy and medication understanding among hospitalized adults. *J Hosp Med*, *6*(9), 488-493.

Masoudi FA, Foody JM, Havranek EP, Wang Y, Radford MJ, Allman RM, … Krumholz HM. (2006). Trends in acute myocardial infarction in 4 U.S. states between 1992 and 2001: Clinical characteristics, quality of care, and outcomes. *Circulation, 114*, 2806-2814.

McCarten JR, Anderson P, Kuskowski MA, McPherson SE, Borson S, & Dysken. (2012). Finding dementia in primary care: the results of a clinical demonstration project. *J Am Geriatr Soc, 60*(2), 210-217.

McDonald HP, Garg AX, & Haynes RB. (2002). Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA, 288*, 2868-2879.

McDonnell PJ, & Jacobs MR. (2006). Hospital admissions resulting from preventable adverse drug reactions. *Ann Pharamcother, 36*, 1331-1336.

McGee HM, Doyle F, Conroy RM, La Harpe D, & Shelley E. (2006). Impact of briefly-assessed depression on secondary prevention outcomes after acute coronary syndrome: a one-year longitudinal survey. *BMC Health Services Research*, *6,* doi:10.1186/1472-6963-6-9.

Miller NH, Hill M, Kottke T, Ockene IS, For the Expert Panel on Compliance. (1997). The Multilevel Compliance Challenge: Recommendations for a Call to Action: A Statement for Healthcare Professionals. *Circulation, 95*, 1085-1090.

Munger MA, Van Tassell BW, & LaFleur J. (2007). Medication nonadherence: An unrecognized cardiovascular risk factor. *Med Gen Med, 9*, 58-69.

Musbeck N, Brixner D, Benedict A, Keskinaslan A, & Khan ZM. (2008). The economic consequences of noncompliance in cardiovascular disease and related conditions: a literature review. *International Journal of Clinical Practice*, *62*, 338-351.

National Center for Veterans Analysis and Statistics. (2012). *VA Benefits and Health Care Utilization*. U.S. Department of Veterans Affairs. Washington, DC.

National Center for Veterans Analysis and Statistics. (2014). Available from http://www.va.gov/vetdata.

Newby LK, LaPointe NM, Chen AY, Kramer JM, Hammill BG, DeLong ER, … Califf RM. (2006). Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. *Circulation*, *113*, 203-212.

Nguyen HT, Kirk JK, Arcury TA, Ip EP, Grzywacz JG, Saldana SJ, … Quandt SA. (2013). Cognitive function is a risk factor for health literacy in older adults with diabetes. *Diabetes Research and Clinical Practice*, *101*, 141-147.

Oake N, Jennings A, van Walraven C, & Forster AJ. (2009). Interactive voice response systems for improving delivery of ambulatory care. *American Journal of Managed Care*, *15*(6), 383-391.

Ortman, JM, Velkoff VA, & Hogan H. (2014). *An Aging Nation: The Older Population in the United States*, Current Population Reports, P25-1140. U.S. Census Bureau, Washington, DC.

Osborn CY, Paasche-Orlow MK, Bailey SC, & Wolf MS. (2011). The mechanisms linking health literacy to behavior and health status. *Am J Health Behav*, *35*(1), 118-128.

Osterberg L, & Blaschke T. (2005). Adherence to medication. *NEJM*, *353*, 487-497.

Paasche-Orlow MK, & Wolf MS. (2007). The causal pathways linking health literacy to health outcomes. *Am J Health Behav, 31*(Suppl 1), S19-S26.

Parashar S, Rumsfeld JS, Spertus JA, Reid KJ, Wenger NK, Krumholz HM, … Vaccarino V. (2006). Time course of depression and outcome of myocardial infarction. *Arch Intern Med, 166*, 2035-2043.

Parikh NS, Parker RM, Nurss JR, Baker DW, & Williams MV. (1996). Shame and health literacy: the unspoken connection. *Patient Educ Couns, 27*(1), 33-39.

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

Peterson AM, Takiya L, & Finley R. (2003). Meta-analysis of trials of interventions to improve medication adherence. *American Journal of Health-System Pharmacy*, *60*(7), 657-665

Petrilla AA, Benner JS, Battleman DS, Tierce JC, & Hazard EH. (2005). Evidence-based interventions to improve compliance with antihypertensive and lipid-lowering medications. *Int J Clin Pract, 59*, 1441-1451.

Phelan EA, Borson S, Grothaus L, Balch S, & Larson EB. (2012). Association of incident dementia with hospitalizations. *JAMA, 307*, 165-172.

Pignone M, DeWalt DA, Sheridan S, Berkman N, & Lohr KN. (2005). Interventions to Improve Health Outcomes for Patients with Low Literacy. *J Gen Intern Med*., *20*(2), 185-192.

Poon I, Lal LS, Ford ME, & Braun UK. (2009). Racial/ethnic disparities in medication use among veterans with hypertension and dementia: a national cohort study. *Ann Pharmacother, 43*, 185–193.

Rasmussen JN, Chong A, & Alter DA. (2007). Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA, 297*, 177–186.

Ravelo A, Wagner TH, Phibbs CS, Bhandari A, Chen S, & Barnett PG. (2003). Prevalence and costs of chronic conditions in the VA health care system. *Med Care Res Rev, 60*(Suppl), 146S-167S.

Risser J, Jacobson TA, & Kripalani S. (2007). Development and psychometric evaluation of the Self-efficacy for Appropriate Medication Use Scale (SEAMS) in low-literacy patients with chronic disease. *J Nurs Meas, 15*(3), 203-219.

Robertson D, & Keller C. (1992). Relationships among health beliefs, self-efficacy, and exercise adherence in patients with coronary artery disease. *Heart Lung, 21*, 56-63.

Rogers ES, Wallace LS, & Weiss BD. (2006). Misperceptions of medical understanding in low-literacy patients: implications for cancer prevention. *Cancer Control*, *13*(3), 225-229.

Roter DL, Hall JA, Merisca R, Nordstrom B, Cretin D, & Svarstad B. (1998). Effectiveness of interventions to improve patient compliance: a meta-analysis. *Med Care*, 36, 1138-1161.

Safeer RS, Cooke CE, & Keenan J. (2006). The impact of health literacy on cardiovascular disease. *Vascular Health and Risk Management, 2*, 457-464.

Sarkar U, Ali S, & Whooley MA. (2007). Self-efficacy and health status in patients with coronary heart disease: Findings from the Heart and Soul Study. *Psychosom Med, 69*, 306-312.

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

Schroeder K, Fahey T, & Ebrahim S. (2004). How can we improve adherence to blood pressure-lowering medication in ambulatory care? Systematic review of randomized controlled trials. *Arch Intern Med, 164*, 722-732.

Senst BL, Achusim LE, Genest RP, Cosentino LA, Ford CC, Little JA, … Bates DW. (2001). Practical approach to determining costs and frequency of adverse drug events in a health care network. *Am J Health Syst Pharm*, *58*, 1126-1132.

Shah ND, Dunlay SM, Ting HH, Montori VM, Thomas RJ, Wagie AE, & Roger VL. (2009). Long-term medication adherence after myocardial infarction: experience of a community. *Am J Med, 122,* 961e.7-961.e12.

Sikka R, Xia F, & Aubert RE. (2005). Estimating medication persistency using administrative claim data. *Am J Manag Care*, *11*, 449-457.

Simpson RJ. (2006). Challenges for improving medication adherence. *JAMA, 296*(21), 2614-2616.

Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, & Johnson JA. (2006). A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ*, *333*(7557), doi:10.1136/bmj.38875.675486.55.

Skala JA, Freedland KE, & Carney RM. (2005). Heart Disease. Cambridge, MA: Hogrefe & Huber Publishers.

Smith SC Jr, Benjamin EJ, Bonow, RO, Braun LT, Creager MA, Franklin BA, … Preventive Cardiovascular Nurses Association. (2011). AHA/ACCF secondary prevention and risk reduction therapy for patients with atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation, 124*, 2458-2473.

Sokol MC, McGuigan KA, Verbrugge RR, & Epstein RS. (2005). Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care, 43*, 521-530.

Spertus JA, Kettlekamp R, Vance C, Decker C, Jones PG, Rumsfeld JS, ... Cohen DJ. (2006). Prevalence, predictors and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement. *Circulation*, *113*, 2803-2809.

Substance Abuse and Mental Health Services Administration, Office of Applied Studies. (2008). The NSDUH Report. Major Depressive Episode and Treatment for Depression among Veterans Aged 21 to 39. Rockville, MD.

Substance Abuse and Mental Health Services Administration. (2013). Results from the 2012 National Survey on Drug Use and Health: Mental Health Findings, NSDUH Series H-47, HHS Publication No. (SMA) 13-4805. Rockville, MD: Substance Abuse and Mental Health Services Administration.

Sudore RL, Yaffe K, Satterfield MD, Harris TB, Mehta KM, Simonsick EM, … Schillinger D. (2006). Limited literacy and mortality in the elderly. *Journal of General Internal Medicine*, *21*, 806-812.

Tariq SH, Tumosa N, Chibnall JT, Perry MH 3rd, & Morley JE. (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. *Am J Geriatr Psychiatry*, *14*, 900-910.

Thombs BD, Bass, EB, & Ford DE. (2006). Prevalence of depression in survivors of acute myocardial infarction. *J Gen Intern Med, 21*, 30-38.

Thombs BD, Bass EB, Ford DE, Stewart KJ, Tsilidis KK, Patel U, … Ziegelstein RC. (2006). Prevalence of depression in survivors of acute myocardial infarction. *J Gen Intern Med*, *21*, 30-38.

Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, … Wagner DR. (2012). Third universal definition of myocardial infarction. *J Am Coll Cardiol, 60,*(16), 1581-1598.

Thygesen K, Alpert JS, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial infarction. (2007). Universal definition of myocardial infarction. *Eur Heart J*, *20,* 2525-2538.

Unni E, & Farris KB. (2011). Determinants of different types of medication non-adherence in cholesterol lowering and asthma maintenance medications: A theoretical approach. *Patient Educ Couns, 83*(3), 382-390.

U.S. Department of Health and Human Services. (2000). Healthy People 2010: Understanding and Improving Health. 2nd ed. Washington, DC: U.S. Government Printing Office.

U.S. Department of Veteran Affairs. Department of Defense. (2009). *VA/DoD Clinical Practice Guideline for Management of Major Depressive Disorder (MDD).* Washington, DC.

U.S. Department of Veterans Affairs. One in Ten Older Vets is Depressed. Retrieved from http://www.va.gov/health/NewsFeatures/20110624a.asp.

VA Health Services Research and Development. (2005). Combined Monitoring Board Guidelines. Available at: vaww.hsrd.research.va.gov/for_researchers/resources/CMB_guidelines.pdf

Vincent AS, Roebuck-Spencer TM, & Cernich A. (2014). Cognitive changes and dementia risk after traumatic brain injury: Implications for aging military personnel. *Alzheimer's & Dementia*, *10*, S174-S187.

Wang PS, Bohn RL, Knight E, Glynn RJ, Mogun H, & Avorn J. (2002). Noncompliance with antihypertensive medications: The impact of depressive symptoms and psychosocial factors. *J Gen Intern Med, 17*, 504-511.

Wei L, Wang J, Thompson P, Wong S, Struthers AD, & MacDonald TM. (2002). Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow-up study. *Heart*, *88*, 229-233.

White, S, and Dillow, S. (2005). *Key Concepts and Features of the 2003 National Assessment of Adult Literacy* (NCES 2006-471). U.S. Department of Education. Washington, DC: National Center for Education Statistics.

Whooley MA. (2006). Depression and cardiovascular disease. *JAMA*, *295*, 2874-2881.

Whooley MA, de Jonge P, Vittinghoff E, Otte C, Moos R, Carney RM, … Feldman MD. (2008). Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA, 300*, 2379-2388.

Williams MV, Baker DW, Honig EG, Lee TM, & Nowlan A. (1998). Inadequate literacy is a barrier to asthma knowledge and self care. *Chest, 114*, 1008-1015.

Williams MV, Baker DW, Parker RM, & Nurss JR. (1998). Relationship of functional health literacy to patients' knowledge of their chronic disease: a study of patients with hypertension and diabetes. *Arch Intern Med, 158*, 166-172.

Wolf MS, Curtis LM, Wilson EA, Revelle W, Waite KR, Smith SG, … Baker DW. (2012). Literacy, cognitive function, and health: results of the LitCog study. *J Gen Intern Med*, *27*(10), 1300-1307.

Wolf MS, Davis TC, Osborn CY, Skripkauskas S, Bennett CL, & Makoul G. (2007). Literacy, self-efficacy, and HIV medication adherence. *Patient Educ Couns*, *65*(2), 253-260.

Wolf MS, David TC, Tilson HH, Bass PF, & Parker RM. (2006). Misunderstanding of prescription drug warning labels among patients with low literacy. *Am J Health Syst Pharm, 63*(11), 1048-1055.

World Health Organization (WHO). (2003). *Adherence to Long Term Therapies: Evidence for Action*. Geneva: WHO.

Wray LO, Wade M, Beehler GP, Hershey LA, & Vair CL. (2013). A program to improve detection of undiagnosed dementia in primary care and its association with healthcare utilization. *Am J Geriatr Pscychiatry,* Advance online publication. doi: 10.1016/j.jagp.2013.04.018.

Wu J, Lennie TA, Dekker RL, Biddle MJ, & Moser DK. (2013). Medication adherence, depressive symptoms, and cardiac event-free survival in patients with heart failure. *J Cardia Fail*, *19*, 317-324.

Yaffe K, Hoang TD, Byers AL, Barnes DE, & Friedl KE. (2014). Lifestyle and health-related risk factors and risk of cognitive aging among older veterans. *Alzheimer's & Dementia, 10*, S1111-S121.

Yan AT, Yan RT, Tan M, Huynh T, Soghrati K, Brunner LJ, … Canadian ACS Registries Investigators. (2007). Optimal medication therapy at discharge in patients with acute coronary syndromes: temporal changes, characteristics, and 1-year outcome. *Am Heart J, 154*, 1108-1115.

Youmans SL, & Schillinger D. (2003). Functional health literacy and medication use: the pharmacist's role. *Ann Pharmacother, 37*, 1726-1729.

Ziegelstein RC, Fauerbach JA, Stevens SS, Romanelli J, Richter DP, & Bush DE. (2000). Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Arch Intern Med*, *160*, 1818-1823.

APPENDIX A

RAPID ESTIMATE OF ADULT LITERACY IN MEDICINE, REVISED (REALM-R)

INSTRUCTIONS FOR USE

The REALM-R is a word recognition test consisting of 11 items used to identify people at risk for poor literacy skills (Bass et al, 2003). Words that appear in this test are:

Fat	**Osteoporosis**	**Anemia**	**Colitis**
Flu	**Allergic**	**Fatigue**	**Constipation**
Pill	**Jaundice**	**Directed**	

Fat, Flu, and Pill are not scored and are positioned at the beginning of the REALM-R to decrease test anxiety and enhance confidence.

SPECIAL CONSIDERATIONS WHEN USING THE REALM-R

1. **Examiner Sensitivity**
   Many adults with low literacy skills will attempt to hide their deficiency. Ensure that you approach each person with respect and compassion. You may need to provide encouragement and reassurance. Many people with low literacy feel ashamed. Be sensitive.

2. **Visual Acuity**
   If the person wears glasses, ask them to wear the glasses for the test. The word list should be set in 18-point font.

3. **Pronunciation**
   Dictionary pronunciation is the scoring standard.

4. **Dialect, Accent, or Articulation Problems**
   Count a word as correct if it is pronounced correctly and no additions or deletions have been made to the beginning or ending of the word. For example, a person who says “jaundiced” would not receive credit for the word “jaundice”; “directs” would not receive credit for the word “directed”. Words pronounced with a dialect or accent should be counted as correct, provided there are no additions or deletions to the word. Particular attention should be paid to persons who use English as a second language.

5. **Limitations of the REALM-R**
   The REALM-R can only be used for persons who read English; it has not been validated in other languages.

ADMINISTRATION

1. Print the list in 18-point font or greater

2. Introduce the REALM-R to the person. The words “read” and “test” should be avoided when introducing and administering the REALM-R. The following statement can be used to introduce the REALM-R:

   > “Sometimes in the health care system, medical words are used that many people are not familiar with. I would like to get an idea of what medical words you are familiar with.”

3. Give the person the list of the REALM-R words. Point to the first word and ask the person to read the 11 words out loud. Be sensitive to dialect, accent, and articulation problems.

4. If the person takes more than five seconds on a word, they should be encouraged to move on to the next word (e.g., say “Let’s try the next word.”) If the person begins to miss every word or appears to be struggling or frustrated, tell them, “Just look down the list and say the words you know.”

SCORING

Use the REALM-R Examiner Record to record the outcome of the test. The words Fat Flu and Pill are not scored. Count as an error any word that is not attempted or is mispronounced. Place a check mark (“✓”) next to each word the person pronounces correctly, and an “X” next to each work the person does not attempt or mispronounces. Those with a score of 6 or less should be considered to be at risk for poor health literacy.

REALM-R WORD LIST

Fat

Flu

Pill

Allergic

Jaundice

Anemia

Fatigue

Directed

Colitis

Constipation

Osteoporosis

REALM-R EXAMINER RECORD

Fat

Flu

Pill

Allergic _____

Jaundice _____

Anemia _____

Fatigue _____

Directed _____

Colitis _____

Constipation _____

Osteoporosis _____

Fat, Flu, and Pill are not scored.

Self-efficacy for Appropriate Medication Use Scale (SEAMS)

SEAMS Scale

1) How confident are you that you will keep all your medical appointments as scheduled?
2) How confident are you that you will be able to take all or most of your medicines as directed?

How confident are you that you can take your medicines correctly…

3) When you take several different medicines each day.
4) When you take medicines more than once a day.
5) When you are away from home.
6) When you have a busy day planned.
7) When they cause some side effects.
8) When no one reminds you to take the medicine.
9) When the schedule to take the medicine is not convenient.
10) When your normal routine gets messed up.
11) When you are not sure how to take the medicine.
12) When you are not sure what time of day to take your medicine.
13) When you are feeling sick (you know, like having a cold or the flu).
14) When you are feeling fine.
15) When you get a refill of your old medicines and some of the pills look different than usual.
16) When a doctor changes your medicines.

How confident are you that you can carry out the following tasks…

17) Get refills for your medicines before you run out.
18) Fill your prescriptions whatever they cost.
19) Make taking your medicines part of your routine.
20) Always remember to take your medicines.
21) Take your medicines for the rest of your life.

All questions are scored on a 1-3 point scale, with 1 = Not confident; 2 = Somewhat confident; 3 = Very confident.

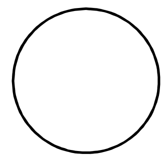
This is the original scale. The reduced 13-question version includes only items 3-13, 15, and 16. Items 1, 2, 14 and 17-21 were omitted after psychometric testing.

VAMC
SLUMS Examination

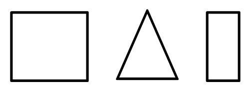
Name______________________________ Age________________________________

Is patient alert?____________________ Level of education________________________

__/1 1 1. What day of the week is it?
__/1 1 2. What is the year?
__/1 1 3. What state are we in?
4. Please remember these five objects. I will ask you for what they are later.
Apple Pen Tie House Car
5. You have $100 and you go to the store and buy a dozen apples for $3 and a tricycle for $20.
1 How much did you spend?
__/3 2 How much do you have left?
6. Please name as many animals as you can in one minute.
__/3 0 0-4 animals 1 5-9 animals 2 10-14 animals 3 15+ animals
__/5 7. What were the five objects I asked you to remember? 1 point for each one correct.
8. I am going to give you a series of numbers and I would like you to give them to me backwards. For example, if I say 42, you would say 24.
0 87 1 649 1 8537
__/4 9. This is a clock face. Please put in the hour markers and the time at Ten minutes to eleven o'clock.



2 Hour markers okay
2 Time correct
__/2 1 10. Please place an X in the triangle.
1 Which of the above figures is largest?



11. I am going to tell you a story. Please listen carefully because afterwards, I'm going to ask you some questions about it.
Jill was a very successful stock broker. She made a lot of money on the stock market. She then met Jack, a devastatingly handsome man. She married him and had three children. They lived in Chicago. She then stopped work and stayed at home to bring up her children. When they were teenagers, she went back to work. She and Jack lived happily ever after.

__/8 2 What was the female's name? 2 What work did she do?
2 When did she go back to work? 2 What state did she live in?

_____ TOTAL SCORE

	SCORING	
HIGH SCHOOL EDUCATION		LESS THAN HIGH SCHOOL EDUCATION
27-30	Normal	25-30
21-26	MNCD*	20-24
1-20	Dementia	1-19

*Mild neurocognitive disorder

PATIENT HEALTH QUESTIONNAIRE PHQ-9

NAME: ____ **DATE:** _____________

Over the *last 2 weeks*, how often have you been bothered by any of the following problems?
(*use "✓" to indicate your answer*)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling asleep or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3
add columns:		+	+	

(*Healthcare professional: For interpretation of TOTAL, Please refer to accompanying scoring card.)* **TOTAL:** ______________________

10. If you checked off *any* problems, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all	_____
	Somewhat difficult	_____
	Very difficult	_____
	Extremely difficult	_____

Fold back this page before administering this questionnaire

INSTRUCTIONS FOR USE

For doctor or healthcare professional use only

PHQ-9 QUICK DEPRESSION ASSESSMENT

For initial diagnosis:

1. Patient completed PHQ-9 Quick Depression Assessment on accompanying tear-off pad.
2. If there are at least 4 ✓s in the blue highlighted section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.
3. ***Consider Major Depressive Disorder***
   - If there are at least 5 ✓s the blue highlighted section (one of which corresponds to Question #1 or #2)
   - ***Consider Other Depressive Disorder***
   - If there are 2 to 4 ✓s the blue highlighted section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician and a definitive diagnosis made on clinical grounds, taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient. Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (e.g., every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ✓s by column. For every ✓:

Several days = 1	More than half the days = 2	Nearly every day = 3

3. Add together column scores to get TOTAL score.
4. Refer to the accompanying PHQ-9 Scoring Card to interpret the TOTAL score.
5. Results may be included in patients' files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

PHQ-9 SCORING CARD FOR SEVERITY DETERMINATION

For healthcare professional use only

Scoring – add up all checked boxes on PHQ-9

For every ✓: Not at all = 0; Several days = 1

More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
0-4	None
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression