PROFILING PATIENTS WITH HEART FAILURE AND TESTING A

MOTIVATIONAL INTERVIEWING INTERVENTION TO IMPROVE HEART

FAILURE SELF-CARE

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DEDICATION

To my parents, who have lovingly and faithfully supported me in every endeavor. Dad, you gave me the confidence to go after my dreams and Mom, you serve as an example of a woman who can do anything she sets her mind to.

To my children, Caleb and Micah, who bring energy, joy and perspective to each day.

To my husband, Tim, for walking with me on this journey, being a faithful partner and my biggest advocate.

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ABSTRACT

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Background: Heart failure (HF) is the fastest growing cardiovascular syndrome in the United States and the most common reason for hospitalization of Medicare recipients. HF is prevalent, costly to society and complex to manage. The purpose of this body of work was to strengthen the evidence base for self-care by studying understudied aspects of HF self-care maintenance.

Methods/Results: This body of work entails four discrete studies. The first study identified modifiable predictors of patients who are at risk of consuming a diet higher in sodium than recommended by the 2010 Heart Failure Society of America guidelines. The second study identified two unique patterns of sodium intake, "very high" (mean 4.5 g/day) and "generally adherent" (mean 2.4 g/day). Predictors of the *very high* sodium intake group were being obese, having diabetes mellitus and less than 65 years old. The third study identified unique patterns of inflammation and myocardial stress in a sample

of patients with HF from the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION) clinical trial. Predictors of the worst biomarker pattern were identified and exercise was protective for being in the worst biomarker pattern. In response to these studies, the Motivational Interviewing Tailored Interventions for Heart Failure patients (MITI-HF) randomized controlled trial was designed and conducted to test the efficacy of a tailored motivational interviewing approach to improve self-care, physical HF symptoms and quality of life in patients with HF. Motivational interviewing was a successful approach for improving self-care maintenance, but there were no differences between groups for self-care management, self-care confidence, physical HF symptoms or quality of life.

Conclusions: In the context of the rising prevalence of HF within an environment of increasing cost-conscious appropriation of healthcare resources, this body of work provides evidence for targeting self-care interventions to patients who are at highest risk of poor outcomes. It also provides evidence that motivational interviewing is a successful approach for improving self-care maintenance behaviors, specifically eating a lower sodium diet and exercising.

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CHAPTER I: INTRODUCTION

Background and significance

Heart failure (HF) is a cardiovascular syndrome that affects more than 5.1 million Americans over the age of 20.[1] Currently, HF is the fastest growing cardiovascular condition in the United States.[2] Three primary risk factors of HF include age, hypertension and coronary heart disease. Hypertension and coronary heart disease currently affect approximately 77.9 and 15.4 million Americans over the age of 20 respectively.[1] Forecasts project that by 2030, 41.4% of all US adults will have hypertension.[1] Increasing prevalence of coronary heart disease coincides with a decrease in mortality of coronary heart disease, (annual death rate declined 40.3% and the actual number of deaths declined 27.1% from 1999-2009).[3] The decline in mortality from coronary heart disease results in a greater population at risk of developing HF, due to the fact that people are living longer with damaged myocardium. In addition, HF is a common endpoint for other prevalent cardiovascular and extra-cardiovascular diseases including: cardiac valve disorders, cardiomyopathy, diabetes mellitus, renal failure and obesity.[4-7] The combined impact of these factors results in a projected 46% increase in HF prevalence from 2012 to 2030 resulting in more than 8 million people with HF.[1]

Managing a single complex medical condition such as HF was estimated to cost $32 billion in the United States (U.S.) in 2012 and costs are estimated to increase 127% to 69.7 billion between 2012 and 2030.[2] A large proportion of treatment costs are attributed to over one million annual hospitalizations in the U.S.,[8,9] of which 90% are

potentially preventable.[10] HF is the most common reason for the hospitalization of

Medicare recipients.[9] In total, heart disease accounted for almost 2 million discharges in

2010 (among Medicare beneficiaries) with an average length of stay of 4.8 days and an

average cost of $11,132 per hospitalization at discharge.[11] Thirty-day readmission rates

are reported to be as high as 27% [9] and more than one third are readmitted within 90

days.[9,10] Overall, HF hospitalization rate declined from 1998-2008, but at a lower rate for

black men than for other demographic groups.[1]

One avenue for cost savings is to reduce unnecessary hospitalizations. The costs

incurred by Medicare for what may be preventable readmissions are estimated to be

about $17 billion or 20% of Medicare's hospital payments.[10] Due to this high cost

burden, the Centers for Medicare and Medicaid Services have taken a tough stance to

reduce HF readmissions. As part of the Affordable Care Act, the Hospital Readmission

Reduction Program has reduced payments to hospitals if patients with HF are admitted at

the same or a different hospital within 30-days of a previous hospital admission.[12]

Patients with HF frequently are readmitted to the hospital because they experience

exacerbations in their symptoms caused by cardiac dysfunction, generally left or right

ventricular hypertrophy, which cause neurohormonal and circulatory abnormalities, and

manifest as symptoms such as fluid retention, shortness of breath and fatigue on

exertion.[13] HF is a complex syndrome to manage because clinical symptoms vary

considerably between patients and during the course of the disease. Depending on the

severity and degree of vigilance in management, recurrent bouts of acute exacerbations

are common. If patients survive an acute exacerbation they are at high risk of

rehospitalization.[14,15] To reduce the economic and social burden of HF and improve patient outcomes, better management strategies that incorporate optimized medical therapy in concert with effective self-care are critical.[14-17]

Conceptual Model

The concept of "self-care" in HF refers to the practices in which patients engage to maintain their own health and the decision-making process around managing signs or symptoms.[18-20] In recent work by Riegel and colleagues, they provide evidence that self-care decisions are guided by a naturalistic decision making process.[21] Naturalistic decision making is defined as real-world decision making which takes into account multiple competing factors, limited time, uncertainty, high stakes, vague goals, unstable conditions and other unknowns.[22] Self-care decision making is affected by situation awareness with mental simulation of a plausible course of action and evaluation of that outcome in addition to past experience, characteristics of the decision and personal goals.[21] The naturalistic decision making process is particularly relevant in the context of HF because it is a chronic condition that requires constant decision-making around health practices and symptom management in order to maintain hemodynamic stability.[20] Self-care is measured most commonly in research with two instruments, the European Heart Failure Self-Care Behavior Scale[23] and the Self-Care of Heart Failure Index.[24]

Self-care entails two core components, choosing positive health practices ('self-care maintenance') and making decisions around the management of symptoms signs and symptoms ('self-care management').[18-20] The foundation of self-care is self-care maintenance, as illustrated in The Situation Specific Theory of Heart Failure Self-care[19]

(Figure 1.1). Self-care management builds on routine self-care maintenance practices starting with symptom monitoring and ending with critical decision-making and follow-up. As such, symptom monitoring is a bridge between self-care maintenance and management. Recognizing symptoms is a necessary pre-cursor to being able to gauge symptom importance, implement treatment and evaluate the response.

Figure 1.1: The Situation Specific Theory of Heart Failure Self Care

Self-care maintenance

Self-care maintenance involves performing positive health practices, such as medication adherence, consuming a low-sodium diet, staying physically active, monitoring daily weight and other symptoms, keeping medical appointments, avoiding tobacco and limiting alcohol consumption.[20] Arguably the most critical daily self-care behavior is medication adherence—no other treatment is equally able to modify the physiological cascade associated with HF.[20] Two of the most understudied aspects of self-care maintenance include eating a low sodium diet and doing routine exercise. In this

body of work, a particular focus will be given to these two self-care maintenance behaviors.

Low-sodium diet

Consuming a low sodium diet is one of the most frequently recommended self-care behaviors; however, it is estimated that only 22-55% of HF patients adhere to a low-sodium diet.[25-27] The rationale for moderate sodium restriction is that in general, sodium promotes fluid retention, higher ventricular filling pressures and symptoms of congestion, all of which put patients with HF at higher risk for acute decompensation and hospitalization.[25,28-31] The guidelines for HF are consistent in recommending a low-sodium diet,[13,32-36] though they differ in terms of their specificity—from general moderation[32] to 2-3 g/day and further restriction for severe HF.[13] All of the guidelines are based on expert opinion, or level C evidence, not clinical trial data.

Exercise

Patients with HF are encouraged to exercise because physiologically, regular exercise dilates coronary and peripheral skeletal vessels,[37] stimulates angiogenesis,[38] and causes reductions in peripheral hypoxia,[39] local inflammation,[40] and resting heart rate.[41] Results from smaller studies demonstrate that sustained exercise therapy improved myocardial contractility, diastolic filling, myocardial perfusion, and endothelial dysfunction.[37,39,42-45] Despite this wide range of benefits, few patients with HF regularly engage in exercise.[46,47] One of the reasons why few patients with HF routinely exercise is

that safety of exercise was not established until the results of the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial were reported in 2008. Previously, health providers did not routinely recommend exercise.

The purpose of HF-ACTION was to determine whether aerobic exercise could reduce all-cause mortality, all-cause hospitalization and improve quality of life. HF-ACTION included 2,331 patients who were randomized to an exercise or control group for 30 months.[48,49] Though there was no difference between the two study groups in all-cause mortality or all-cause hospitalizations in the primary analysis, there was a difference in health status between the exercise training and control groups.[50] The study reported in Chapter IV is based on a sub-sample of data from HF-ACTION.

Self-care management

Self-care management is a more complex process than self-care maintenance because it requires critical decision-making and follow-up action. Four steps to the self-care management process have been specified. The first step entails recognizing early signs and symptoms. Though the recognition of symptoms may seem straightforward, it is not easy for many patients with HF to detect changes in their symptoms—including even large increases in body weight due to fluid retention.[51] Many patients with HF have other co-morbid conditions so symptoms such as breathlessness or fatigue are often attributed to asthma, chronic obstructive pulmonary disease, lack of physical activity, over-exertion or aging.[52] If symptoms are not routinely monitored and recorded then recognizing subtle changes that occur over time can be difficult. The second self-care management step entails deciding that a change in symptoms requires a response,

followed by taking action. Finally, patients need to be able to evaluate whether their response to the symptom was effective.[20]

Factors affecting self-care

There are multiple social, psychological, and physical factors that affect a patient's ability to perform and maintain HF self-care. For instance, social support from family members, especially spouses, children and close friends, is instrumental in influencing adherence to prescribed medications.[20,53-55] Depression is also associated with delays in seeking medical care[56] and is one of the main psychological factors that affect self-care in HF.[54] Depression is highly prevalent among both inpatients (50%) and outpatients (11-25%) with HF.[57] People who are depressed are less likely to engage in health practices such as smoking cessation or regular exercise.[58] Physically, general cognitive impairment is estimated to affect 25% of patients with HF, including impairment of executive function, memory, language, mental speed and attention.[59,60] Physiologically, cognitive impairment in HF can be caused by impaired cerebral vessel reactivity, microembolisms[61] and chronic hypoperfusion.[61,62]As such, cognitive impairment adversely affects self-care.[61,63,64] In addition, age and HF severity are associated with reduced cerebral blood flow due to abnormalities in the heart-brain vascular loop.[62] HF is also associated with white-matter infarcts and reduced gray-matter volume,[65] both of which impact memory, psychomotor speed and executive function,[66] which are critical for adequate self-care. Knowledge of how people with cognitive impairment perform self-care is limited by the fact that they are excluded from many

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studies, due to ethical issues around informed consent, problems with follow-up, dropout and adherence to a protocol. Social support, depression and cognitive impairment are just three factors among many that influence a patient's ability to maintain HF self-care.

Self-care and Clinical Outcomes

Self-care is considered an evidence-based recommendation for preventing health outcomes (ie: hospitalizations) and improving patient-oriented outcomes (ie: quality of life). Systematic literature reviews by McAlister and colleagues and Jovicic and colleagues report a decrease in HF hospitalization and all-cause re-hospitalization among patients who engage in self-care.[67,68] A major limitation of this early work is that self-care was not actually measured; it was assumed to be the mechanism by which event-risk was reduced. In the Heart Failure Adherence and Retention Trial (HART) trial (n=902), self-management counseling plus HF education was compared with HF education alone for the primary end point of death or HF hospitalization.[69] There was no difference in the primary outcome between the two groups, suggesting that self-management counseling did not reduce death or HF hospitalization in patients with mild to moderate HF.[70] Most recently, Dracup and colleagues reported the results of the Rural Education to Improve Outcomes in HF clinical trial. Once again, there were no differences in the clinical outcomes of hospitalization and cardiac death between patients randomized to the education intervention and control groups.[71] The association between self-care and patient-reported measures of health status and quality of life is also unclear, primarily due to conceptual and methodological weaknesses in self-care intervention studies.[72,73] In a

review of 21 interventions on the benefits of self-care on quality of life, some demonstrated improved quality of life in response to self-care interventions and others reported no effect.[72] A positive association between HF self-care and health status was found when both self-care management and self-care confidence were high.[74] While it is believed that self-care improves both clinical and patient-oriented outcomes, more research is needed to determine what dose and type of self-care interventions are needed to improve these outcomes. Evidence of improvement in health outcomes could impress patients with HF and clinicians of the critical role that self-care can have on both duration and quality of life.

The relationship between self-care behaviors and specific biomarkers of inflammation and neurohormonal activation has been reported in a cross-sectional study of 168 symptomatic patients with HF.[75] A one-point increase in the self-care management scale of the Self Care of HF Index was associated with a 12.7% reduction in levels of N-terminal pro-B-type natriuretic peptide and soluble tumor necrosis factor receptor type 1, which are associated with higher risk of hospitalization and death.[75] Lee and colleagues have proposed that oxidative stress may be reduced through better volume homeostasis, which decreases mechanical stress and ventricular wall stretch.[20,75] That is, being attuned to early symptoms of congestion and responding promptly with effective self-care management techniques may promote fluid volume homeostasis.[75-77]

In a review article on HF self-care, Riegel and colleagues support the development of personalized, or tailored, interventions to address barriers, improve self-efficacy and focus on key self-care maintenance and management skills.[20] In the context

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of complex long-term conditions like HF, the rationale for using a tailored approach is that it may motivate individual patients and increase the likelihood that they will actively implement self-care maintenance or management behaviors.[78] Tailoring is a form of individualization or personalization, which attempts to increase motivation by developing a customized plan that addresses relevant preferences and needs. Tailored approaches to cardiovascular disease prevention may involve the assessment of genetic variants, biomarkers and imaging modalities,[2] as well as specific interventions and educational materials. Bennett and colleagues implemented tailored educational content to personal health beliefs and behaviors and found it improved self-care in patients with HF.[79] Tailored interventions are designed to take into consideration specific characteristics and desired outcomes of individuals using a combination of strategies and information based on individual assessment.[80] Theoretically, tailoring may enhance the impact of a health message by altering attention and influencing how a message is processed by enhancing cognitive preconditions for effortful processing.[81] Whether a tailored intervention will provide superior improvement in self-care and quality of life is addressed in this body of work.

Purpose and specific aims

The primary purpose of this body of work was to strengthen the evidence base for self-care by studying specific HF self-care maintenance behaviors. The secondary purpose was to test the efficacy of a tailored motivational interviewing (MI) approach to improve self-care, quality of life, physical HF symptoms and clinical outcomes.

The first aim was to identify patterns and predictors of high sodium intake. The hypothesis was that interventions that promote a low-sodium diet should be targeted to patients with HF who are most likely to consume high quantities of sodium. To address the first aim, two quantitative analyses were performed. As reported in Chapter II, predictors of higher than recommended sodium intake were identified using a mixed effect logistic analysis from a longitudinal dataset of 280 patients with HF. Secondly, as reported in Chapter III, two distinct patterns of sodium intake were identified using an alternative growth mixture modeling analysis. Conceptually, both of these studies address the self-care maintenance skill of maintaining a low-sodium diet.

Table 1.1 Aim 1: Patterns and predictors of high sodium intake

Aim	Title of paper for how aim was addressed
1) Identify predictors of high sodium intake. *Hypothesis:* Identifying predictors of high sodium intake informs who should be targeted with low-sodium diet interventions.	Chapter II: Identifying predictors of higher than recommended sodium intake in HF patients using a mixed effect logistic analysis of longitudinal data Chapter III: Using growth mixture modeling to identify subgroups of sodium adherence in adults with HF
2) Identify distinct biomarker patterns and identify predictors of the worst biomarker pattern. *Hypothesis:* Common and distinct patterns of biomarkers of inflammation and myocardial stress can be identified. Predictors of these patterns can also be identified and subsequently used to target high-risk patients.	Chapter IV: Identifying biomarker patterns and predictors of inflammation and myocardial stress

3) Design and implement Motivational Interviewing Tailored Intervention (MITI-HF) to improve HF self-care.	Chapter V: Motivational interviewing tailored interventions for heart failure (MITI-HF): design and methods
Hypothesis: Participants in the motivational interviewing group will have higher self-care outcome scores, quality of life and physical symptoms burden compared to the usual care group.	Chapter VI: Motivational interviewing tailored interventions for heart failure (MITI-HF): self-care, physical HF symptoms and quality of life

The second aim was to identify common and distinct patterns of change in serum biomarkers of inflammation and myocardial stress and quantify the influence of exercise therapy on patterns of change in a community-based sample of patients with HF. Currently, little is known about which *a priori* factors predict biologic patterns characterized by inflammation and myocardial stress in patients with HF. As reported in Chapter III, three distinct patterns of inflammation and myocardial stress were identified and predictors of the worst biomarker pattern are reported. Conceptually, this study supports the self-care maintenance behavior of exercise as a mechanism for slowing the progression of HF.

The third aim, reported in Chapters V and VI, was to test the efficacy of MI to improve self-care behaviors, physical HF symptoms and quality of life in patients recently discharged from a HF hospitalization. Differences between the study groups were tested and reported for statistical and clinical improvement from baseline to 90-days in self-care maintenance, self-care management, self-care confidence, physical HF symptoms and quality of life. This study supports using a tailored motivational interviewing approach to improve heart failure self-care maintenance.

Summary

This dissertation explores multiple bio-behavioral methods for profiling patients with HF who are most vulnerable to poor self-care, physiologic and clinical outcomes. This work specifically addresses characteristics of patients who are at higher risk of consuming a high-sodium diet and predictors of worse patterns of inflammation and myocardial stress, both of which can be used to target interventions to the most vulnerable patients with HF. This work also tests whether a tailored motivational interviewing intervention is able to improve self-care behaviors, physical HF symptoms and quality of life and in a pilot randomized controlled trial. Finally, this body of work concludes with overall themes and recommendations for future research and clinical practice.

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CHAPTER II: IDENTIFYING PREDICTORS OF HIGHER THAN RECOMMENDED SODIUM INTAKE IN PATIENTS WITH HEART FAILURE: A MIXED EFFECT ANALYSIS OF LONGITUDINAL DATA

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Abstract

Background: A low-sodium diet is a core component of heart failure self-care, but patients have difficulty following the diet.

Aim: The aim of this study was to identify predictors of higher than recommended sodium excretion among patients with heart failure.

Methods: The World Health Organization Five Dimensions of Adherence model was used to guide analysis of existing data collected from a prospective, longitudinal study of 280 community-dwelling adults with previously or currently symptomatic heart failure. Sodium excretion was measured objectively using 24-hour urine sodium measured at three time points over six months. A mixed effect logistic model identified predictors of higher than recommended sodium excretion.

Results: The adjusted odds of higher sodium excretion were 2.90, (95% confidence interval (CI): 1.15-4.25, p<0.001) for patients who were obese; 2.80 (95% CI: 1.33-5.89, p=0.007) for patients with diabetes; and 2.22 (95% CI: 1.09-4.53, p=0.028) for patients who were cognitively intact.

Conclusion: Three factors were associated with excess sodium excretion, and two, obesity and diabetes, are modifiable by changing dietary food patterns.

Introduction

Heart failure is a major public health concern because it is associated with high

morbidity, mortality and cost. Self-care is recognized as a means of improving these

outcomes.[1] Consuming a low-sodium diet is one of the most frequently recommended

self-care behaviors; [2-5] however, it is estimated that only 22-55% of patients with heart

failure are adherent to a low-sodium diet.[6-8] The rationale for not consuming excessive

sodium is that it can lead to fluid retention, higher ventricular filling pressures and

symptoms of congestion[9]—all of which put patients with heart failure at risk for acute

decompensation and hospitalization.[10, 11]

The general recommendation for all adults in the United States is to consume less

than 2,300 milligrams (mg) of sodium a day; however, the average American consumes

approximately 3,400 mg of sodium per day.[12] Sodium is one of the primary cations in

extracellular fluid. By influencing the shifting of water between body compartments, it

plays an important role in maintaining body fluid tonicity,[13] blood volume and pressure.

The Heart Failure Society of America (HFSA) guidelines recommend that patients with

symptoms of heart failure restrict daily sodium intake to 2,000-3,000 mg/day.[6] The most

recent 2013 American Heart Association (AHA) Guideline for the Management of Heart

Failure recommends sodium restriction (< 3000 mg/day) for patients with stage C and D

heart failure.[14]

Patients with heart failure face a number of barriers to effectively quantifying

sodium intake and maintaining a low-sodium diet. A major barrier is that many patients

do not find low sodium foods palatable and consequently never adjust to the taste of low

sodium foods and change their eating habits.[15] A lack of knowledge about how to identify high sodium foods, even when labeled, is also a barrier for patients.[15-18] Few restaurants offer low-sodium options, which decreases dining out opportunities for socialization with friends.[15-17] Overall, there are multiple barriers that can impede patients with heart failure from consistently following a low-sodium diet.

The aim of this study was to identify socio-demographic and clinical characteristics that predict higher than HFSA recommended sodium intake, estimated by urinary sodium excretion, using longitudinal data of patients with heart failure. For the purposes of this study, we assumed that sodium excretion was a reflection of sodium consumption. The World Health Organization (WHO) Five Dimensions of Adherence model was used to identify factors potentially associated with poor dietary adherence.[19] This holistic model acknowledges the multi-dimensionality of adherence including social and economic conditions, the health care system, as well as condition-, therapy- and patient-related factors.[19] Previously, this model has been used to guide the assessment of medication adherence in patients with heart failure.[20]

Methods

Study population

This study was a secondary analysis of data collected in an observational prospective cohort study of 280 community-dwelling adults with previously or currently symptomatic heart failure who were followed over a six-month time period. This study was in compliance with the Declaration of Helsinki.[21] Institutional Review Board approval was obtained from all three sites and all participants gave written informed

consent. The parent study was conducted to investigate the relationship between excessive daytime sleepiness and heart failure self-care. The detailed methodology of this study has been reported elsewhere. [22] In brief, this was a prospective cohort study with patients assigned to one of four cohorts based on excessive daytime sleepiness and cognitive decline. Multiple heart failure self-care behaviors were measured including eating a low sodium diet, which was assessed with 24-hour urine sodium specimens at three time-points (enrollment, 3- and 6-months). Patients with heart failure were prospectively enrolled from three outpatient settings, two in Pennsylvania and one in Delaware, between 2007 and 2010. The basic eligibility criteria for participation included: (1) chronic heart failure with prior or current symptoms, (2) ability to read and speak English, and (3) sufficiently able to complete questionnaires and study procedures (i.e. adequate cognition, English fluency, ability to read). Patients were ineligible to participate in the study if they had dementia, as measured by the Telephone Interview for Cognitive Status[23] along with other criteria specified in the parent study. [22] Most participants in this study were followed in specialty heart failure clinics and were on standard medical therapy. The usual care provided by heart failure specialty clinics was not augmented in this observational study.

Variables and Measures

Clinical information (e.g., etiology and type of heart failure, left ventricular ejection fraction (LVEF), and comorbid illnesses) was abstracted from the medical record by a registered nurse at each of the three enrollment sites. These nurses were familiar with the unique electronic medical record systems in their own setting. Each nurse

received extensive training to assure consistency of data collection. The principal investigator assured the fidelity of the data collection protocol at each site and was available for questions throughout the study period.

Comorbidities (including diabetes) were scored with the Charlson Comorbidity Index, a commonly used measure,[24] directly from the medical record. In this sample, all patients had a score of at least one because they all had heart failure. Validity was demonstrated by the instrument authors when comorbidity scores (categorized as low, medium, and high) predicted risk of ten-year mortality, complications, health care resource use, length-of-hospital-stay, discharge disposition and cost.[24-27]

New York Heart Association (NYHA) functional class was scored Class I-IV by a single board certified cardiologist using data obtained from a standardized interview.[28] Body mass index (BMI) was calculated based on patients weight at the baseline visit and self-reported height. Detailed information on participants' medications, with doses, was collected at each data collection period. Sociodemographic characteristics were self-reported.

Cognition was measured with a battery of neuropsychological tests administered in person by trained research assistants. The number of tests on which participants scored below their age-based norm was used as an indicator of cognitive status. Any participant who scored more than 1.5 standard deviations beyond the range of normal on at least two of the paper-and-pencil tests was considered to have mild cognitive decline. For analysis, the cognition variable was dichotomized to indicate those with or without cognitive

impairment. The details of the neurocognitive battery and methodology for categorizing cognitive status are reported in detail in the parent study.[22]

In this study, dietary sodium intake was approximated using urine sodium excretion. Sodium is under tight homeostatic control and is only lost from the body as sweat (20-80 mmol/day), stool (5-10 mmol/day) or urine (1-500 mmol/day).[29] Patients with heart failure do not typically engage in strenuous physical activity; therefore do not lose sodium from heavy perspiration. Variations in sodium excretion are primarily due to variations in recent sodium intake.[30] In this study, we made the assumption that the 24-hour urinary sodium excretion samples reflected dietary sodium intake across the study period, consistent with previous studies.[10, 31, 32] The 24-hour urine collection method has been validated by urine recovery of oral doses of para-amino benzoic acid [33-35] and the collection procedures followed in the parent study were consistent with recommendations for collection by the Institute of Medicine.[36]

Based on criteria set forth by the 2010 HFSA practice guidelines and published papers, urine sodium in mmoles was converted to mg (mg= mmole*22.99).[5, 10] The urine sodium binary outcome in this study was created using 3,000 mg/day 24-hour urine sodium cut point for patients in NYHA Class I/II and a 2,000 mg/day 24-hour cut point for patients in NYHA Class III/IV. Expected dietary sodium categories were compared between participants whose dietary sodium excretion was within recommended levels versus those in higher than recommended levels.

Procedures

Data were collected at baseline, three, and six months by research assistants during home visits. Training for urine specimen collection was provided for the patient and family member, if available, at the baseline data collection interval. Prior to each subsequent urine collection, patients were telephoned to remind them and reinforce training for the procedure. Patients were given urine containers, collection devices, verbal and written instructions (with pictures) specifying when they should start and finish collecting the urine specimen. Participants were instructed to start the collection at 0800, discard that specimen, and collect the final specimen at 0800 on the following day. Prior to the patient collecting each urine specimen, the research assistant inquired about changes in the medication regimen. If the participant had experienced a recent medication change the collection was delayed for three days starting from the date the medication was changed. Participants recorded when their urine sodium collection started and finished. A courier picked up the specimens from the participant's homes after the 24-hour sample was completed.

The central laboratory at the Hospital of the University of Pennsylvania analyzed the urine samples to determine the amount of sodium in each specimen using the ion-selective electrode method (Beckman LX® 20 Chemistry Analyzer, Beckman Coulter, Inc., Fullerton, CA).

Statistical Analysis

Descriptive statistics were used to calculate frequencies with percentages and means with standard deviations for the total sample, urine sodium in grams per day, and sodium consumption. Chi-square and Kruskal-Wallis tests were used to compare baseline

characteristics of binary, categorical and ordinal variables between groups. For the purposes of between group comparisons, the doses for patients on loop diuretics (n =183) were converted to furosemide equivalents using the following formula: furosemide 80 mg = torsemide 40 mg = bumetanide 2 mg.[37] The other participants on diuretics (n = 8) were prescribed hydrochlorothiazide and compared separately. This method has been used in other studies.[10]

Over the three points of data collection, data on the urine sodium excretion were missing overall in 23% of the participants (193/840 samples), 19% at baseline, 29% at 3-months and 23% at 6-months. Multiple imputations were performed for urinary sodium excretion and body mass index (BMI) data to account for missing time-varying covariates.[38-40] Multiple imputation is a principled, likelihood based method using statistical modeling to impute data using the method of chained equations.[41] In short, this method creates ten copies of the data, as recommended by Rubin.[40] The multiple imputations were based on baseline age, gender, etiology of heart failure, cognitive status and LVEF and complete data for time-varying covariates, including NYHA class, BMI and urine sodium excretion. Each dataset was then analyzed separately. [42] Estimates of the parameters of interest were averaged across all the datasets to give a single, final estimate. [42, 43] After imputation, data were checked to confirm reasonable values. Standard errors and 95% confidence intervals were estimated by calculating within and between components of variance using the method of Rubin.[40]

To determine predictors of higher than recommended sodium intake, a mixed effect logistic model with a random intercept was tested for each patient. Adjusted odds

ratios, 95% confidence intervals and p-values are presented for statistically significant predictors of higher than recommended sodium intake fit on the imputed data.[44] The selection of model covariates was based on four of the five dimensions of adherence from the WHO conceptual model: condition, therapy, patient-related factors and social and economic conditions as well as statistical association with the outcome variable, urine sodium excretion. The final twelve covariates included in the multivariable regression models are presented in **Table 2.1**.[45]

Table 2.1: World Health Organization five dimensions of adherence model

Dimension of adherence	*Variables used in this study*
Social/economic factors	race, income, highest level of education
Therapy-related factors	diuretic (loop or thiazide)
Patient-related factors	gender, age, body mass index, cognitive status
Condition-related factors	heart failure type (diastolic or systolic), diabetes, hypertension, etiology (ischemic or non-ischemic)
Health-system factors	*Not available in this study*

Two sensitivity analyses were conducted. First, mixed effect logistic estimates were compared between the complete case and imputed data models. Estimates based on imputed data were more conservative in terms of effect sizes and had narrower confidence intervals. This was expected because confidence intervals and model variance depend on the amount of missing data, sample size and number of imputed datasets.[41, 46] Second, estimates from the mixed effects logistic models were confirmed with generalized estimating equations models with robust standard errors. Data are not shown for these two sensitivity analyses because there were no significant differences between the models. All data analyses were performed using Stata v. 11.2.[47]

Results

This sample of patients with heart failure had a mean age of 62 years (standard deviation (SD): 12), was predominantly male (64%), functionally compromised (77% in NYHA class III or IV) with a mean left ventricular ejection fraction of 35 (SD: 17). Over one-third of the sample had diabetes. Among participants with diabetes 60% were also obese. Over two thirds of the sample had hypertension, and about 20% had chronic obstructive pulmonary disease. Sample demographic and clinical characteristics are shown in **Table 2.2**. The urine sodium levels were relatively normally distributed so mean and standard errors are presented. The majority of the sample was prescribed furosemide or an equivalent loop diuretic.

Table 2.2 Demographic, social and clinical characteristics of patients and 24-hour urine sodium urine samples: overall and by higher and lower sodium excretion levels at baseline (N=280)

Variables	Total	%	Mean UrNa grams/day (SE)	Na+ guidelines Within or Higher		p-value
Age						
<65 years	165	41	3.08 (0.03)	48	63	**0.022**
>=65 years	115	59	2.61 (0.03)	52	37	
Gender						
Male	180	64	3.23 (0.24)	61	66	0.425
Female	100	36	2.81 (0.03)	39	34	
Race						
Black/Other	105	38	2.95 (0.02)	33	37	0.597
White	175	62	3.30 (0.04)	67	63	
Income						
More than needed	98	35	2.75 (0.03)	38	33	0.269
Enough for needs	137	49	3.21 (0.03)	51	48	
Less than needed	45	16	3.35 (0.05)	11	19	
NYHA functional class						
Class I+II	66	23	3.03 (0.04)	33	17	**0.009**
Class III	164	59	3.02 (0.03)	49	68	
Class IV	50	18	3.28 (0.06)	18	15	
Diuretic use*						
Furosemide equ. (mg/day) n=183	183		3.07 (0.15)	72	69	0.703
<= 40 mg/day	91	50	2.97 (0.14)			

>40 and <=120 mg/day	63	34	3.33 (0.27)			
>120 mg/day	29	16	3.01 (0.27)			
Hydrochlorothiazide (mg/day)	8	3	3.30 (0.53)	1	3	0.400
HF etiology (n=279) †						
Ischemic HF	102	36	3.11 (0.03)	35	38	0.625
Non-ischemic HF	177	64	3.05 (0.03)	66	61	
BMI (n=279) †						
Normal (18-24)	74	26	2.39 (0.03)	38	18	**0.001**
Overweight (25-29)	73	26	2.86 (0.05)	27	27	
Obese (30+)	133	48	3.53 (0.02)	35	55	
Highest level of education						
Less than high school	27	10	2.65 (0.07)	11	7	0.271
High school graduate	102	36	3.05 (0.03)	39	35	
More than high school	151	54	3.12 (0.03)	50	58	
Type of heart failure						
Systolic	194	69	3.00 (0.02)	76	69	0.475
Diastolic or mixed	86	31	3.19 (0.05)	24	31	
Charlson Co-morbidity						
Low	149	53	2.96 (0.04)	56	50	0.268
Moderate	101	36	3.13 (0.06)	37	35	
High	30	11	3.26 (0.09)	7	15	
Diabetes						
Yes	107	38	3.57 (0.05)	23	47	**0.001**
No	173	62	2.72 (0.04)	77	53	
Hypertension						
Yes	181	65	3.06 (0.02)	65	63	0.729
No	99	35	3.07 (0.03)	35	37	
COPD						
Yes	222	79	2.53 (0.06)	73	81	0.129
No	58	21	3.20 (0.03)	27	19	
Cognition						**0.004**
Cognitively impaired	107	39	2.90 (0.02)	47	28	
Not cognitively impaired	165	61	3.14 (0.03)	53	72	

*Diuretic use: This only includes information on patients who were on diuretic medications. The proportions are only for those prescribed furosemide (n=183), not the entire population sample. †Sample size for variables with missing values. Abbreviations: SE=standard error, Na+=sodium, UrNa=urine sodium, NYHA=New York Heart Association, COPD=chronic obstructive pulmonary disorder

The median and interquartile range values for urine sodium excretion on the complete cases at all three time points were 2,770 mg (1,750 – 3,950 mg) at baseline, 2,630 mg (1,690 – 4,000 mg) at 3-months and 2,780 mg (1,900 – 3,790 mg) at 12-months. There was no trend in sodium excretion across time that would suggest that participants modified their diets in anticipation of these measurements. We found no difference in the pattern of observed values for participants with missing data and those with complete observations.

Table 2.3 Factors associated with higher sodium excretion (n=280)

Variables	Adjusted OR	95% CI		p-value
Cognition				
Cognitively impaired	1.00	Reference		__
Cognitively intact	2.22	1.09	4.53	0.028
Body mass index				
Normal (18-24)	1.00	Reference		__
Overweight (25-29)	1.79	0.75	4.25	0.187
Obese (30+)	2.90	1.15	4.25	<0.001
Diabetes				
No	1.00	Reference		__
Yes	2.80	1.33	5.89	0.007
Gender				
Female	1.00	Reference		__
Male	1.16	0.54	2.51	0.703
Age				
>=65 years	1.00	Reference		__
<65 years	1.95	0.97	3.90	0.059
Hypertension	0.51	0.25	1.04	0.068
Income	1.11	0.67	1.84	0.696
Diuretic use	1.05	0.48	2.33	0.897
Heart failure etiology	0.72	0.31	1.67	0.438
Type of heart failure	1.24	0.78	1.98	0.351
Education	1.14	0.67	1.96	0.607
Race	1.17	0.57	2.42	0.663

Abbreviations: OR: odds ratio, CI: confidence interval

In the final model identifying patient characteristics associated with higher than recommended sodium intake **(Table 2.3)**, patients with heart failure who were obese

(BMI>30) had nearly three times higher adjusted odds of consuming more than recommended sodium intake compared to patients with a normal body weight (BMI<25). The adjusted odds of sodium intake above recommended level were over two times higher in patients who were cognitively intact compared to patients with some cognitive impairment. Patients with heart failure and diabetes had almost three times the adjusted odds of consuming more than the recommended sodium intake.

Discussion

The purpose of the study was to identify characteristics of patients with heart failure who had higher than recommended 24-hour urine sodium excretion. In this study, we used 24-hour sodium excretion as an estimate of dietary sodium intake, or adherence to sodium guidelines. Considering possible predictors drawn from the WHO adherence model, the three most important predictors of higher sodium excretion were patient- and condition-related factors. Patients with heart failure who were obese or had diabetes and those who were cognitively intact were more likely to excrete higher amounts of sodium.

The association between higher sodium and obesity is most likely explained by both direct and indirect effects.[32, 48] One explanation for the relationship between obesity and higher sodium consumption is that high-calorie foods often contain high sodium.[49] Increased dietary sodium intake is directly correlated with increased calorie consumption.[31, 50] According to the Salted Food Addictive Hypothesis, salted foods act in the brain like an opiate agonist, producing a hedonistic reward, which becomes associated with foods being judged as "delicious" or "flavorful."[48] Withdrawal of salty foods acts like an opiate receptor withdrawal and causes perceived "cravings" for salted foods.[48]

Over time, daily consumption of salted foods can produce an addiction, which escalates and can stimulate overeating.[51]

The association between high sodium intake and obesity has also been found in rat animal models[52] and has a physiological explanation: chronic salt overload induces adipocyte hypertrophy, which enhances insulin sensitivity for glucose uptake and insulin-induced glucose metabolism.[52] Song and colleagues report a direct effect between sodium intake and risk of being overweight in humans, after adjusting for energy, water and soda consumption;[32] however their study sample did not include patients with heart failure, hypertension or diabetes. The relationship between obesity and sodium consumption is consistent with results of our previous study in which we found that patients with heart failure who were overweight had a four-fold increased odds of consuming more than 3,000 mg of sodium per day.[53]

Other lifestyle factors may help explain the relationship between obesity and sodium consumption. Processed and packaged foods are naturally high in sodium because sodium is a natural preservative that increases the shelf life of foods. Patients with heart failure often feel fatigued and may have less energy to dedicate to the purchase and preparation of low-sodium food. Originally, we thought that purchasing fresh produce and meat may be prohibitively expensive for patients on fixed or limited incomes; however, income was not a statistically significant predictor of higher sodium excretion. Another important question is whether the guidelines should recommend varying amounts of sodium intake for people with heart failure with different body weight and other clinical characteristics. According to Gupta and colleagues (2012) there is still

uncertainty as to whether dietary sodium intake recommendations should be individualized. [9]

Diabetes was a strong predictor of higher than recommended sodium intake. This may be explained by the fact that any form of kidney disease in which tubular reabsorption of filtered sodium does not match the filtered load plus dietary intake can cause renal sodium wasting (ie: hyperfiltration occurring in earlier stages of diabetic nephropathy).[13] The finding that diabetes is a predictor of higher sodium intake is consistent with a previous analysis in which patients with diabetes were four times as likely to consume more than 4 grams of sodium per day over time.[53] This finding may be explained by the association between diabetes and obesity, in which case diabetes is acting as a marker of obesity.

In the literature, associations between mild cognitive impairment and heart failure self-care behaviors are mixed.[1, 54, 55] Mild cognitive impairment has been associated with worse self-care management [56, 57] probably because of an inability to perform the complex decision-making required to manage signs and symptoms. An association between cognitive impairment and poorer self-care maintenance such as eating a low sodium diet has not been reported. In a study by Cameron and colleagues, the majority of patients (73%) had unrecognized or sub-clinical cognitive impairment and were as likely to engage in health promoting behaviors, such as daily weighing, as those without cognitive impairment.[57] Dickson and colleagues reported that poorer cognition was associated with better self-care behaviors among patients with heart failure in a mixed-methods study.[58] It is important to note that these prior studies focused on the subjective

assessment of multiple self-care behaviors and not exclusively on dietary sodium. Further, there were considerable differences across studies in the methods of measuring cognition that may, in part, explain differences in study findings.[58]

While it may be assumed that patients with mild cognitive impairment will not be able to follow a low-sodium diet that was not the case in this study. Patients who were cognitively intact had more than double the odds of consuming higher than recommended sodium levels compared to patients with cognitive impairment. This seemingly counter-intuitive finding may be explained by the fact that patients with cognitive impairment often have caregivers who make and provide their meals. Patients who are cognitively intact may be more self-reliant in making dietary decisions. This finding could also be explained by the rigidity that is associated with cognitive impairment.[59, 60] Rigidity refers to the tendency to form and repeat particular behaviors; eating the same foods is one form of rigidity. We cannot confirm either of these hypotheses because we did not collect data on caregivers or rigidity associated with specific dietary choices in this study.

Many patients with heart failure struggle to consume levels of sodium that are considered moderate. In a study of adults with heart failure from the Southern United States, only 33% of individuals consumed 2000 mg/day or less with the wide range of 522 to 9251 mg/day.[61] Likewise, based on 24-hour urinary sodium excretion levels, another study reported that 34% of the sample was compliant with recommendations to consume less than 3000 mg/day and only 15% consumed less than 2000 mg/day.[10]

Recently sodium restriction for patients with heart failure has been questioned due to wide variation in the study protocols, study samples, fluid intake, measurement of

sodium intake and compliance.[14] Some studies have even questioned any sodium restriction;[62, 63] however, this was largely due to a very rigid definition of sodium intake (80 mmol/day).[62] Paterna and colleagues recommend a normal sodium diet, defined as 120 mmol/day (about 2800 mg/day) [62, 63] which is consistent with the recommendation of < 3g a day for patients with Class C and D HF.[14] Overall, the message across these studies and a recent review by Gupta and colleagues is consistent— high sodium intake is not optimal for patients with heart failure because excessive sodium intake is associated with fluid retention; however, the lower-dose range of sodium intake needs to be better defined, and possibly individualized to patients in future studies.[9]

Strengths and Limitations

One of the strengths of this study was the repeated measures of sodium excretion on the same individuals over a six-month period. Multivariate statistical methods were used for these repeated measures to account for the correlation of measures within an individual, which reduced measurement error and individual variability. The use of longitudinal data in this study also provided a clearer picture of how well patients followed a low-sodium diet over an extended period of time, instead of one point in time. Another strength of the study is that we used robust and transparent imputation methods to address potential bias from incomplete data.[38, 40]

The study also had several limitations including the fact that this was a secondary analysis of a dataset that did not include measures of sodium intake. Data from carefully controlled studies show that at least 7 days of direct measurement of sodium intake and excretion in the urine are needed to achieve correlations of 0.8,[64] which implies that food

records and urine excretion provide complementary information about sodium intake. The relationship between sodium intake and excretion is analogous to fasting blood glucose and hemoglobin A1c in diabetic patients. These two measures provide similar, but different, information about dietary adherence in patients with diabetes. In this study, our intention was not to precisely estimate sodium intake over the previous 24 hrs, but to estimate general adherence to dietary recommendations. For our purposes, 24-hour sodium excretion was the best available marker of dietary sodium consumption.

Another limitation of this study was that patients in this sample were on loop diuretics, which enhance urinary excretion of sodium by inhibiting tubular reabsorption at the thick ascending limb of the Loop of Henle, in the nephron.[13] Arcand and colleagues (2010), found no statistically significant relationship between 24-hour urine sodium excretion and sodium intake from food records in patients with heart failure on a loop diuretic; however, they reported significant correlations for non-heart failure cardiac patients and for patients with heart failure who were not prescribed a loop diuretic.[65] While informative, limitations of the Arcand study were that it used a cross-sectional, correlational design in a young, relatively small sample of patients with heart failure in which other relevant variables that may explain the differences in sodium excretion were not controlled. Though there may be some imprecision from using urinary sodium excretion as a measure of dietary sodium intake for patients on loop diuretics, it is still considered the best measure for patients with heart failure.[10, 31, 66] In addition, we statistically controlled for diuretic use.

There are inherent limitations to a secondary data analysis, including the fact that this study was limited by the demographics and size of the original sample. For example this sample was younger than most other community dwelling samples of patients with heart failure so the results may not be generalizable to older adults with heart failure. There may be additional predictors of higher sodium intake that were not measured in the parent study, such as fluid intake, and thus could not be controlled for. In addition, while it was a strength that we used four of the five dimensions of adherence in the WHO model, the dimensions were not measured comprehensively. For instance, due to the sample size, we were restricted to including only variables that were both conceptually consistent with the WHO dimension as well as statistically associated with sodium excretion in the final model. Some dimensions may not have been fully captured by the variables selected.

Conclusion

Patients with heart failure who are cognitively intact, those who have diabetes or are obese are at risk for consuming more sodium than recommended. The 2013 Report of the AHA Guideline for the Management of Heart Failure recommends reasonable sodium restriction for patients with symptomatic HF to reduce congestive symptoms[14] and the HFSA guidelines recommend that all patients with heart failure be provided with dietary instruction.[5] Sodium dietary instructions should be contextualized within a longer conversation with patients about their general sodium intake. Further research may support identifying higher risk patients and intervening to help them decrease their

sodium intake. Ultimately, interventions around dietary sodium intake may help decrease their risk of decompensation and re-hospitalization.[11, 67]

Implications for Practice

- Patients who have diabetes, are obese or are cognitively intact might be at risk for consuming more sodium than recommended.

- Further research should identify patients and intervene to help them reduce high sodium consumption with tailored dietary interventions.

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CHAPTER III: USING GROWTH MIXTURE MOELING TO IDENTIFY CLASSES

OF SODIUM ADHERENCE IN ADULTS WITH HEART FAILURE

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Abstract

Background: The prevention of fluid retention is important to reduce hospitalizations in patients with heart failure. Following a low-sodium diet helps to reduce fluid retention. Objective: The primary objective of this study was to use growth mixture modeling to identify distinct classes of sodium adherence—characterized by shared growth trajectories of objectively measured dietary sodium. The secondary objective was to identify patient-level determinants of the nonadherent trajectory.

Methods: This was a secondary analysis of data collected from a prospective longitudinal study of 279 community-dwelling adults with previously or currently symptomatic heart failure. Growth mixture modeling was used to identify distinct trajectories of change in 24-hour urinary sodium excretion measured at three time points over six months. Logistic modeling was used to predict membership in observed trajectories.

Results: The sample was predominantly male (64%), mean age 62 years, functionally compromised (59% NYHA class III), with non-ischemic HF etiology. Two distinct trajectories of sodium intake were identified and labeled adherent (66%) and non-adherent (34%) to low-sodium diet recommendations. Three predictors of the non-adherent trajectory were identified, confirming our prior mixed-effect analysis. Compared with normal weight patients (BMI <25), being overweight and obese was

associated with a 4-fold incremental increase in the likelihood of being in the non-adherent trajectory (odds ratio (OR): 4.63, 95% confidence interval (CI): 1.66-12.91, p<0.002). Being less than 65 years of age (OR: 4.66, 95% CI: 1.04-20.81, p=0.044) or having diabetes (OR: 4.15, 95% CI: 1.29-13.40, p=0.016) were both associated with over four times the odds of being in the non-adherent urine sodium trajectory compared with people who were over 65 or without diabetes, respectively.

Conclusions: Two distinct trajectories of sodium intake were identified in patients with heart failure. The non-adherent trajectory was characterized by an elevated pattern of dietary sodium intake shown by others to be associated with adverse outcomes in heart failure. Predictors of the non-adherent trajectory included higher body mass index, younger age and diabetes.

Introduction

Adherence to a low-sodium diet is an important self-care behavior for patients

with heart failure (HF). Excess sodium intake promotes higher ventricular filling

pressures, pulmonary congestion, clinical symptoms of fluid retention, and puts patients

with HF at high risk for acute decompensation and hospitalizations. [1] As such, adherence

to a low-sodium diet is a key factor in reducing hospitalizations[2] and one of the most

frequently recommended self-care behaviors. [3-6] Both the 2012 European Society of

Cardiology and 2009 American College of Cardiology/American Heart Association

guidelines recommend less than 2 g/day of dietary sodium. [7,8] Likewise, the Heart Failure

Society of America recommends that all patients with clinical symptoms of HF restrict

sodium to 2-3 g/day. [6] It is estimated, however, that only about 22-55% of HF patients

are adherent to a low-sodium diet. [9-12]

Adherence, as defined by the World Health Organization (WHO), is a

multidimensional phenomenon, determined by multiple dimensions related to social and

economic conditions, the health care system in addition to condition, therapy or patient-

related factors.[13] Like medication adherence in this patient population, adherence to a low

sodium diet is influenced by a number of factors.[14] Although several factors have been

associated with non-adherence to a low-sodium diet in the adult population with HF,

there are limitations to these research findings. Most prior studies on 24-hour urine

sodium excretion are cross-sectional in design and conducted with small samples.

Deterministic methods, including mixed effects modeling have previously been used to

identify patient-level factors associated with high sodium intake using an *a priori*

determined cutoff of adherence.[15] This study builds on that analysis by applying a growth mixture modeling methodology to identify the "most likely" trajectory membership and quantify uncertainty in trajectory membership over time.

The specific aim of this study was to use growth mixture modeling to identify distinct patterns of change in 24-hour urine sodium excretion, as a proxy for dietary sodium intake, over six months of observation. The secondary aim was to build on a previous mixed effects analysis[15] and examine patient-level determinants of observed trajectories of urine sodium.

Methods

Design and Study population

The methodology of this study has been previously reported in detail. [14] In brief, this was a prospective, observational study of the association between excessive daytime sleepiness and HF self-care among 279 community-dwelling adults with chronic HF. The participants were enrolled from three outpatient settings in Philadelphia, Pennsylvania and Newark, Delaware between 2007 and 2010. Most of the participants were followed in specialty HF clinics and most were on optimal medical therapy. Given the observational nature of this study, the usual care provided by HF specialty clinics was not augmented. Participants did not receive supplemental HF self-care education outside of what was provided as part of routine care.

Inclusion criteria for the study specified adults with previously or currently symptomatic HF confirmed by echocardiographic and clinical evidence. [14] The

participants needed to be able to actively participate in the study, so inclusion criteria specified that patients must be able to read and speak English and have sufficient cognition and health literacy to complete the questionnaires. Otherwise eligible individuals were excluded if they lived in a long-term care setting and were not responsible for their own self-care, including preparing and making choices about food. People were also excluded if they had renal failure requiring dialysis, imminent plans to move out of the area, a history of drug or alcohol abuse within the past year or an imminently terminal illness. People with major depressive illness were also excluded because self-care behaviors are influenced by major depression. [16] This study was in compliance with the Declaration of Helsinki. [17] Institutional Review Board approval was obtained from all three sites and all participants gave written informed consent. Data were collected at baseline, 3-and 6-months by research assistants during home visits. Institutional Review Board approval was obtained for this secondary analysis.

Measurement of dietary sodium

A 24-hour urine sodium collection is considered a reliable and valid estimate of sodium intake [18,19] and has been used as an objective measure of sodium intake in other studies with patients with HF. [1,20] Sodium is under tight homeostatic control. If individuals do not perspire heavily, urine sodium accounts for approximately 95% to 98% of daily dietary sodium intake. [21] Variations in 24-hour urine sodium are primarily attributed to changes in sodium intake over the previous 24 hours.[22] Daily urine sodium levels are estimated to fluctuate only about 11%. [23] Validation for 24-hour urine

collection has been performed by urine recovery of oral doses of para-amino benzoic acid.[19,23,24]

The methodology for collecting and measuring dietary sodium intake has been reported elsewhere [15] and is summarized here. Dietary sodium intake was estimated using three 24-hour urine sodium levels measured at enrollment, and at three and six months after enrollment. The procedure for the collection and quantification of the 24-hour urine samples is summarized here. At the time of enrollment, participants and their family members were given training for the specimen collection. Participants were provided with all necessary supplies including: urine containers, collection devices, verbal and written instructions (with pictures) specifying when they should start and finish collecting the specimen. Prior to each urine collection, patients were given a reminder call and training for the procedure was reinforced by the research assistant. Participants self-reported the start and stop time of the urine collection. If the recorded time was less than 22 hours or greater than 26 hours it was considered inaccurate and excluded from the analysis. Specimens were collected from participant's homes by a courier service shortly after the 24-hour sample was complete.[15]

Urine sodium analyses were completed at the central laboratory at the Hospital of the University of Pennsylvania using the ion-selective electrode method (Beckman LX[®] 20 Chemistry Analyzer, Beckman Coulter, Inc., Fullerton, CA) to determine the amount of sodium in the urine specimens. A normal urinary sodium level is 40 to 120 mEq/L/day. [11] In order to compare urine excretion with the recommended diet of 2-3 g/day sodium intake, [6] urine sodium excretion in millimoles was converted to g (g=

mmol* .02299) to estimate dietary sodium intake. As a quality assurance measure, urinary creatinine was measured concurrently. Normal urinary creatinine is $1 \pm 10\%$ g [25] so any samples with creatinine levels <0.9 g in 24 hours were considered incomplete.[26]

Statistical Analysis

Standard descriptive (proportions, means and standard deviations), unadjusted odds ratios and *t* tests were used to describe the sample and compare trajectories. Latent growth mixture modeling was used to identify distinct trajectories of urinary sodium using data from three time points.

Latent class growth modeling is used to examine patterns in longitudinal data with repeated measures to identify classes or subgroups within a population. Unique trajectories or pathways differentiate classes from one another. Using repeated measures to identify subgroups within a population has been used across multiple disciplines. Latent class growth mixture analysis also has been used across multiple disciplines to identify trajectories of development; [27] nighttime continence;[28] physical aggression in young boys;[29] the natural history of prostate disease;[30] depression recovery profiles[31] and preventative interventions for reducing classroom violence. [32] It has also been used extensively in the substance abuse literature to identify trajectories and predictors of high-risk behavior.[33-44] Within the heart failure literature, it has been used to identify patterns of cognitive change,[45] as well as patterns of medication nonadherence. [46]

The purpose of growth mixture modeling is to identify homogenous subgroups within larger heterogeneous populations and represent unobserved heterogeneity among subjects in a sample. Finite mixture random effects are used to represent the departure of

individuals' latent growth parameters from the population mean growth parameter. [32,47] Class membership of an individual cannot be measured directly; however, it can be inferred based on membership in a specific trajectory.[48] According to Wang and colleagues growth mixture modeling can be described as having three steps. The first step is analogous to random effects modeling which specifies individual-level observed data as a sum of fixed effects, random effects and measurement errors at each observation point. [48] The second step represents the distribution of class-specific random effects and covariate effects on class-specific mean growth trajectories. The third step includes the covariate effects on class membership using regression models. [48]

Growth mixture modeling has many benefits over alternative methods, as reviewed by Preacher.[49] Growth mixture modeling can model changes in factors over time as random effects, allow for variations between individuals and subgroups (instead of individuals and the population average as in mixed-effect modeling) and judge comparative fit between iterative models with various statistics; the focus of growth mixture modeling is on capturing inter-and-intra-individual differences over time.[50] Conventional deterministic approaches minimize within group and maximize between-group variance. In contrast, growth mixture modeling employs a model-based approach to calculate the probability of membership in each trajectory, identify "most likely" trajectory membership, and quantifies uncertainty in trajectory membership. In this article the terms subgroups and classes are used synonymously to describe people who share a specific growth trajectory.

Growth mixture modeling was performed using MPlus v.6.12 (Los Angeles, CA).

Model fit between 2 to 4 trajectories were compared (k vs k-1 trajectories) using the Lo-

Mendell-Rubin adjusted likelihood ratio test (p<0.05), parametric bootstrapped likelihood

ratio test (p<0.05), Bayesian Information Criteria (BIC), convergence (entropy closest to

1.0), the proportion of the sample in each trajectory (not less than 5%), and average

posterior probabilities (closest 1.0). [50,51] Predictors of observed trajectories of dietary

sodium were quantified using logistic regression modeling in MPlus. Unadjusted and

multivariate odds ratios (OR) and 95% confidence intervals (CI) were calculated for each

model factor, taking into account our method of multiple imputation, described below.

The following ten determinants of non-adherence were tested based on the five

dimensions of adherence posed by the WHO.[52] Four of the five WHO adherence

dimensions were included in this analysis. The fifth factor was not included because data

on the health care system was not available for this secondary data analysis. Patient

related factors included gender, age and BMI. Social and economic factors included race,

income and highest level of education. Condition related factors included New York

Heart Association (NYHA) functional class, HF type (diastolic or systolic), etiology of

HF and diabetes as a comorbidity. Therapy related included diuretic use.

Robust Handling of Missing Data

In an effort to reduce bias, a principled method of multiple imputation[53] was

performed to account for missing urine sodium excretion values (23% of the sample had

at least one missing value). Data were imputed using the method of chained equations

(Stata v. 11.2). [54-56] The method of chained equations is a contemporary technique that

imputes missing data based on multiple covariates in the dataset (i.e. a full information method of imputation). The latent class variable was fit on imputed data in Mplus v.6.12. Multiple sensitivity analyses were performed to examine potential differences in the significance and effect size of predictors of urine sodium trajectories comparing complete case with imputed data samples. There were no differences in the predictors identified in the models except for the size of the confidence intervals; thus, for economy of presentation, only the final analysis using imputed data is shown here.

Results

The overall demographic and clinical characteristics of the sample population overall at baseline are presented in **Table 3.1**. This sample of adults (n=279) with HF was predominantly male (64%), had a mean age of 62, non-ischemic HF etiology and was functionally compromised (59% NYHA class III). The unadjusted odds ratios for the analysis are presented in **Table 3.2**. The covariates that had a statistically significant unadjusted association with the non-adherent trajectory were diabetes (p=0.008), income (p=0.031) and BMI (p<0.001).

Modeling of three and four trajectories resulted in poor model fit and small trajectories (*data not shown*). Entropy for the two-class model was 0.752 and there were high average posterior probabilities of membership in both trajectories (94% and 91%), indicating very limited uncertainty in trajectory membership. Based on the observed characteristics, we labeled the first and largest trajectory "adherent" (n=178, 66%) and second trajectory "non-adherent" (n=91, 34%).

Table 3.1: Characteristics of the overall sample at baseline (n=279)

	Overall n (%)		**Overall n (%)**
Age		Diuretic	
< 65 years	165 (59)	Yes	225 (81)
>=65 years	114 (41)	No	54 (19)
Gender		Cognitive Impairment* (n=271)	
Male	179 (64)	Yes	107 (40)
Female	100 (36)	No	164 (61)
Race		Heart failure type	
Black/Other	104 (38)	Diastolic/Mixed	86 (31)
White	175 (63)	Systolic	193 (69)
Income		Body mass index * (n=278)	
More than needed	98 (35)	Normal	74 (26)
Enough to meet needs	137 (49)	Overweight	73 (26)
Less than needed	44 (16)	Obese	131 (47)
NYHA functional class		Highest level of education	
Class I+II	65 (23)	Less than high school	27 (10)
Class III	164 (59)	High school graduate	102 (37)
Class IV	50 (18)	More than high school	150 (54)
Heart failure etiology		Diabetes	
Ischemic HF	102 (37)	Yes	171 (61)
Non-ischemic HF	177 (63)	No	108 (39)
Hypertension		COPD	
Yes	180 (65)	Yes	58 (21)
No	99 (35)	No	221 (79)

NYHA = New York Heart Association, COPD = Chronic obstructive pulmonary disease
*Variables containing missing data

Table 3.2: Unadjusted odds of membership in the non-adherent urine sodium trajectory (n=279)

	Unadjusted Odds Ratio	95% CI	p-value
Gender			
Female		(reference)	
Male	1.51	0.57-4.03	>0.2
Body Mass Index			
Normal		(reference)	
Overweight	5.27	2.23-13.06	<0.001
Age			
>=65 years		(reference)	
< 65 years	4.80	0.45-51.80	0.20
Diabetes			
No		(reference)	
Yes	3.71	1.41-9.80	0.008
Race			
White		(reference)	
Black/Other	2.60	0.97-7.00	0.059
Income	2.07	1.07-4.02	0.031
NYHA Functional Class	1.27	0.69-2.37	>0.20
Heart failure etiology	1.57	0.37-6.68	>0.20
Heart failure type	2.68	0.89-8.03	0.078
Diuretic	3.58	0.35-36.62	>0.20
Cognitive Impairment *n=271	1.00	0.44-2.27	>0.20
LVEF *n=278	0.99	0.97- 1.00	0.089

CI = confidence intervals, NYHA = New York Heart Association, LVEF = Left Ventricular Ejection Fraction, *Variables containing missing data

As displayed in the **Figure 3.1** there was heterogeneity within each trajectory, as demonstrated by the error bars, which indicate two standard deviations around each mean urine sodium level at each point in time. Paired t-tests demonstrate statistically significant differences between the two trajectories at each time point (p<0.001). Those in the adherent group started off at baseline with a mean sodium consumption of 2.42 g/day (standard deviation (SD) ±0.19, 95% CI: 2.39-2.45) versus 4.41 g/day (SD: ±0.34, 95% CI: 4.33-4.48) in the non-adherent trajectory (t=61.68, p<0.001). At three months, the

mean difference between the two trajectories was 2.16 g/day (SE: 0.36, t=59.99, p<0.001) and by six months was 1.98 g/day (SE: ±0.03, t=62.56, p<0.001). Within the adherent and non-adherent trajectories there were no differences from baseline to 6 months (SE: ±0.02, t= -1.39, p=0.166 and SE: ±0.05, t= -0.47, p=0.640), indicating that there were limited changes in dietary sodium intake over time.

Figure 3.1: Trajectories of adherence to a low-sodium diet
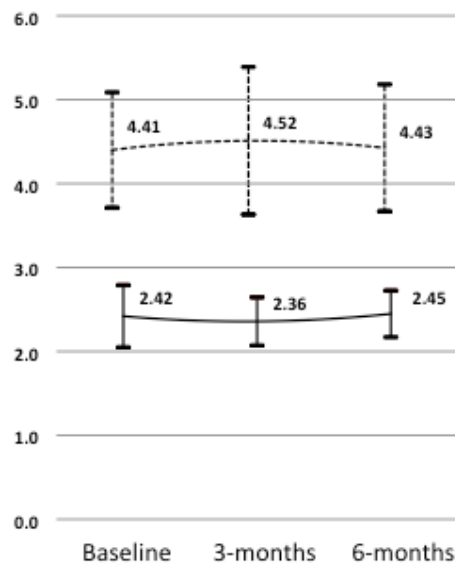
Based on the WHO model, predictors of membership in the non-adherence trajectory were identified. The conceptual model was also supported using data driven statistical approaches including univariate associations. Compared with normal weight patients (BMI <25), being overweight and obese was associated with a 4-fold incremental increase in the likelihood of being in the non-adherent trajectory (OR: 4.63, 95% CI: 1.66-12.91, p<0.002). Being less than 65 years of age (OR: 4.66, 95% CI: 1.04-20.81, p=0.044) or having diabetes (OR: 4.15, 95% CI: 1.29-13.40, p=0.016) were both associated with over four times the odds of being in the non-adherent urine sodium

trajectory compared with people who are over 65 or do not have diabetes, respectively. There were no significant differences in the odds of being in the non-adherent trajectory based on gender, cognition, diuretic use, income level, education, race, HF etiology, HF type or NYHA functional status.

Discussion

The primary aim of this study was to identify trajectories of sodium adherence in a sample of community dwelling HF patients and two groups were identified. Based on the more liberal Heart Failure Society of America sodium recommendations of 3g/day sodium intake, [6] one trajectory was labeled "adherent" and the other "non-adherent" to a low sodium diet. Both groups were consistently adherent or non-adherent over six months of follow-up. That is, there was no change in the level of adherence or non-adherence over time.

To the best of our knowledge, this is the first study that describes adherence to a low-sodium diet using a growth mixture approach; however, this method has been applied to medication adherence in this study sample. [46] The predictors of the non-adherence to a low sodium diet were being overweight or obese, age less than 65 years and having diabetes. These results that obesity and diabetes predict higher sodium consumption are consistent with an analysis that employed a mixed-effect analytic approach;[15] however, in this study we also identified younger age as a risk factor for being non-adherent to a sodium restricted diet.

HF patients who were overweight or obese, age less than 65 years or have diabetes were identified as being more likely to have trouble following a restricted

sodium diet and may need more focused, tailored self-care interventions.[57] One approach to tailoring self-care interventions that we are testing in a pilot randomized control study is a tailored motivational interviewing and skill-building approach to improving self-care behaviors including adherence to a low-sodium diet.

The finding that being obese is strongly associated with greater odds of being non-adherent to a restricted sodium diet implies that these patients may be consuming more food and by default more sodium, or that they are specifically consuming more foods that are higher in sodium. This finding is consistent with the Intersalt international study of electrolyte excretion and blood pressure, in which investigators reported a positive correlation between BMI and sodium excretion.[19] They proposed that overweight individuals consuming higher sodium intake most likely explains this finding.[58] In contrast, Chung et al [20] found no differences in BMI between people who self-reported being adherent or non-adherent to low-sodium guidelines. The approach in our study is different than that used by Chung and colleagues in that we did not apply a 2,000 mg cutoff for sodium adherence. Instead, we identified distinct and naturally occurring trajectories of urinary sodium excretion that happened to track with current dietary sodium recommendations. Moreover, the current study was longitudinal in design. Thus, methodological differences may explain our incongruent findings.

Other authors studying sodium adherence in the HF population have not reported our finding of an association between younger age and non-adherence to a low sodium diet. In studies of adherence to self-maintenance behaviors, an association between age and adherence to medication has been reported. Several studies report that younger

patients are more adherent to taking medication [59,60] while others found no consistent

difference in medication adherence by age. [61-63] In this specific sample, we found no

difference in overall medication adherence by age. [64] The association with younger age

and the non-adherent trajectory could be that younger patients with HF may also be more

newly diagnosed and not yet adept in the skills of identifying and avoiding hidden

sodium in foods. Patients with HF who are over 65 years may be living that long because

they have been more stringent with the self-maintenance behavior of eating a low salt

diet.

The finding that diabetes is a strong predictor of the non-adherence to a low

sodium diet is most likely explained by overconsumption of sodium, rather than a

physiologic mechanism. In fact, in the diabetic state of hyperinsulinemia, sodium

reabsorption is enhanced in the nephron segments of the kidney. [65-68] Clinically, patients

with both HF and diabetes may struggle to closely monitor both their sugar and their

sodium intake. There may receive conflicting messages from multiple providers about

nutritional priorities. The implications of this finding may be that interventions are

needed to specifically address the dietary complexities of managing both HF and diabetes

in this patient population.

Several factors that we anticipated would predict sodium adherence did not reach

statistical significance, including higher income and education. We expected that people

who reported having inadequate income would potentially be more likely to be non-

adherent to a low sodium diet because low-sodium food is more expensive and time

consuming to prepare than processed, higher-sodium foods; however, there were no

differences between people who reported more income than needed, enough to meet needs or less than needed. Several investigators have suggested that people with more years of education would be more adherent with medication; [62,69] however, education has not been found to be associated with sodium adherence. In this study, we found no differences in sodium adherence based on education. The lack of association between years of education and adherence to low-sodium diet is consistent with the propositions of the WHO adherence model,[13] which suggests that higher education in and of itself does not necessarily lead to higher health literacy or behavior change. In this specific study, poor health literacy was an exclusion criterion. As an observational study, there was also no intervention tested, limiting our ability to comment on behavior change.

There are probably many other barriers to following a low-sodium diet that are more important than knowledge. For instance, an identified barrier for patients is the perception that foods will taste bland and unappealing without added salt.[57] This barrier has been addressed by clinicians who promote flavoring with salt substitutes, using low-sodium cook books and allowing taste buds to adapt to lower-sodium foods.[70] Other contextual barriers identified in a qualitative descriptive study of older women with hypertension and HF include eating alone with no motivation to cook healthy meals. These women also identified that healthcare providers need to provide more education on a low-sodium diet, as well as large-print informational materials.[71] A study by De Brito-Ashurt (2011) identified barriers to dietary sodium restriction in people of Bangladeshi origin with chronic renal disease living the UK.[72] Though the disease and patient population are different from this study population, the barriers, including deeply rooted

dietary beliefs, attitudes and culturally established taste for salt,[72-74] are likely to be universal across patient populations.

Other authors found low-sodium diet adherence rates to be about 28% or 29%.[11,12] The findings from this study offer a different perspective from that of population-average adherence. What we can say is that 66% of the sample fit the adherent profile to sodium recommendations and 34% fit the non-adherent profile. These numbers cannot be compared with other population averages or direct calculations of sodium adherence. This non-deterministic approach offers advantages to understanding how non-adherence can be examined and provides a list of useful predictors that are relevant to clinicians for tailoring self-care interventions and education.

Strengths and Limitations

The primary strength of this study is the use of growth mixture modeling, which enables moving away from quantifying the overall population average to examining and quantifying heterogeneity and identifying distinct subgroups. Another strength of this research is that it includes longitudinal data collected at three time points, on a relatively large group of community dwelling stable patients with HF. Many other studies that have examined sodium adherence included only one, 24-hour urine collection in small sample sizes. With an even larger sample size, we may have been able to identify more latent categories of adherence and more predictors of trajectory membership. Further research is needed to determine if the two classes identified in this study will hold across multiple populations of patients with HF. In other words, are these predictors consistent and generalizable to different populations of patients with HF, or localized findings? The

primary limitation of this dataset was that originally 23% of the total sample had missing

outcome data; however, this was accounted for, at least in part, by contemporary and

robust imputation techniques.

Conclusion

Two distinct trajectories of sodium intake were identified. The non-adherent

trajectory identifies a distinct pattern of dietary sodium intake that is not consistent with

current sodium guidelines. Identified predictors (overweight or obese, less than 65, or

having diabetes) can be used by clinicians to target interventions to patients who are most

likely to struggle with eating a lower sodium diet. Results can also be used to tailor

interventions and patient education programs to the highest risk groups. They can also be

incorporated into HF management programs. Future studies identifying the specific

barriers within these patient populations are also warranted so that the specific barriers

can be targeted with interventions.

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CHAPTER IV: IDENTIFYING BIOMARKER PATTERNS AND PREDICTORS OF INFLAMMATION AND MYOCARDIAL STRESS

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Abstract

Background: Regular exercise is recommended to improve physical function in patients with heart failure (HF). Exercise is known to decrease inflammation and thought to decrease myocardial stress. Studies of N-terminal pro b-type natriuretic (NT-proBNP) and high-sensitivity C-reactive protein (hsCRP) have been mixed in patients with HF. A multi-marker analysis may help identify distinct subgroups of HF patients who respond to exercise. The primary study objective was to identify common and distinct patterns of change in serum biomarkers of hsCRP and NT-proBNP and quantify the influence of exercise therapy on the patterns of change.

Methods and Results: NT-proBNP and hsCRP were assessed in a random sample of 320 participants from the biomarker sub-study of the HF-ACTION study, a randomized clinical trial of exercise training versus usual care in patients with stable and chronic HF. Growth mixture modeling was used to identify unique biomarker patterns measured over 12-months. Three statistically independent and clinically meaningful biomarker patterns of NTproBNP and hsCRP were identified. The largest "lowest and improving," pattern (61%) had the lowest levels of NT-proBNP and hsCRP at baseline, with declines over time. The second "elevated and stable" pattern (34%) had higher hs-CRP and consistent NT-proBNP over time. The smallest and most deleterious "elevated and worsening" pattern (5%) had the highest levels of NT-proBNP and increasing hsCRP ($p<0.001$) over time. Participants randomized to the exercise intervention were much less likely to have the *elevated/worsening* pattern of NT-proBNP and hsCRP (relative risk ratio: 0.23, CI: 0.06-0.92, $p=0.037$).

Conclusions: Exercise therapy was protective for reducing the frequency of membership

in the worst pattern, indicating that exercise may help slow the progression of HF.

Introduction

Exercise therapy is considered a safe non-pharmacological intervention to improve functional capacity[1] and clinical outcomes[2] for adults with heart failure. Moderate exercise routines (3 to 7 metabolic equivalent hours per week) are associated with a decreased risk of clinical events.[3] Physiologically in patients with heart failure, exercise training improves myocardial contractility, perfusion, endothelial dysfunction,[4,5] angiogenesis,[6] and coronary and peripheral skeletal vessel dilation.[7] A challenge to the broad implementation of exercise training in heart failure is physiologic heterogeneity in response to exercise. That is, some patients respond to exercise therapy with reductions in peripheral hypoxia,[8] local inflammation[9] and resting heart rate,[10] while others do not. Accordingly, the primary aim of this study was to identify common and distinct patterns of change in serum biomarkers of systemic inflammation and myocardial stress among adults with stable heart failure who participated in an exercise trial. The secondary aim of this study was to identify socio-demographic and clinical predictors of the most unfavorable patterns of change in biomarkers of systemic inflammation and myocardial stress. We hypothesized that exercise therapy would be associated with more favorable patterns of change in biomarkers over time.

Methods

Study population

This was a secondary data analysis of a random selection of 320 participants from the complete cases of the biomarker sub-study of Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) randomized control trial.

The full study design has been published previously.[2,11] Briefly, HF-ACTION was a multicenter, randomized control trial designed to examine long-term safety and efficacy of aerobic exercise training in a large sample of medically stable, chronic outpatients with heart failure. Enrollment criteria included reduced left ventricular ejection fraction (LVEF) of 35% or less, New York Heart Association (NYHA) class II to IV and willingness to undergo exercise training. Patients were excluded if they could not exercise, were already habitual exercisers or had a cardiovascular event in the preceding 6 weeks. Participants were randomized from 82 centers within the United States, Canada and France from 2003-2007 to a usual care or aerobic exercise-training group. The intervention entailed 36 supervised sessions followed by home-based training.

All participants were to perform a maximal exercise test with gas exchange measurements on a treadmill, using the modified Naughton protocol, or a cycle ergometer, using a 10-Watt/min ramp protocol.[12] Functional exercise capacity was measured at baseline by peak oxygen consumption (peak VO_2).[11] Blood samples were collected from a peripheral vein into EDTA-containing tubes, centrifuged immediately and stored at $-70°C$.[11] All samples were obtained on the same day but prior to exercise testing at the baseline, 3-month, and 12-month visits.[13] Assays for all biomarkers were performed using commercially available assays (Roche Diagnostics, Inc.) at the Duke University central core laboratory.[13] Socio-demographic and clinical history characteristics were self-reported at baseline and patients completed the EuroQol-5D (EQ-5D) as a measure of baseline health status.[11]

The HF-ACTION randomized control trial was approved by all relevant

institutional review boards at the participating centers and the coordinating center.[11] This study was also approved by institutional review boards at the University of Pennsylvania and Duke University.

Biomarker measures

High-sensitivity C-reactive protein (hsCRP) (mg/L) was selected as a marker of inflammation because it is associated with heart failure severity.[14,15] N-terminal pro b-type natriuretic (NT-proBNP) (pg/mL) was selected as a marker of myocardial stress and hemodynamic congestion because it is released in response to ventricular dilation, hypertrophy and wall tension[16] and increases with the severity of ventricular dysfunction.[17] NT-proBNP is also used routinely in the clinical management of patients with heart failure and is an indicator of heart failure progression.[13,18,19] In addition, standard, reproducible and cost-effective assays are available for both biomarkers, making them useful for prognostication.[20,21] Both assays were also available in the HF-ACTION repository. Troponin was initially considered for this analysis, but was not included because there were concerns about the analytic sensitivity and lack of variability (zero-inflation) of the assay.

Statistical Analysis

In the preliminary analysis, descriptive statistics of frequency, central tendency and dispersion over time were used to describe hsCRP and NT-proBNP independently. Mean values of ln(hsCRP) and ln(NT-proBNP) values were compared between the exercise training and usual care groups using analysis of covariance (ANCOVA), controlling for baseline biomarker values and treatment allocation. Heterogeneity within

each biomarker was further examined using histograms, box-, dot- and spaghetti-plots. Consistent with previous HF-ACTION publications,[13,22] raw values of NT-proBNP and hsCRP were log-transformed to approximate normality.

The primary aim of this study was to identify common and distinct patterns of change in ln(hsCRP) and ln(NT-proBNP). We chose to use growth mixture modeling to facilitate a multi-marker, multi-mechanism analysis of the serum biomarkers of systemic inflammation and myocardial stress.[23-26] Though traditionally biomarkers have been considered individually,[16] multi-marker strategies are now recommended to improve risk stratification and prediction in chronic heart failure.[16,27,28]

Figure 4.1 Conceptual Model
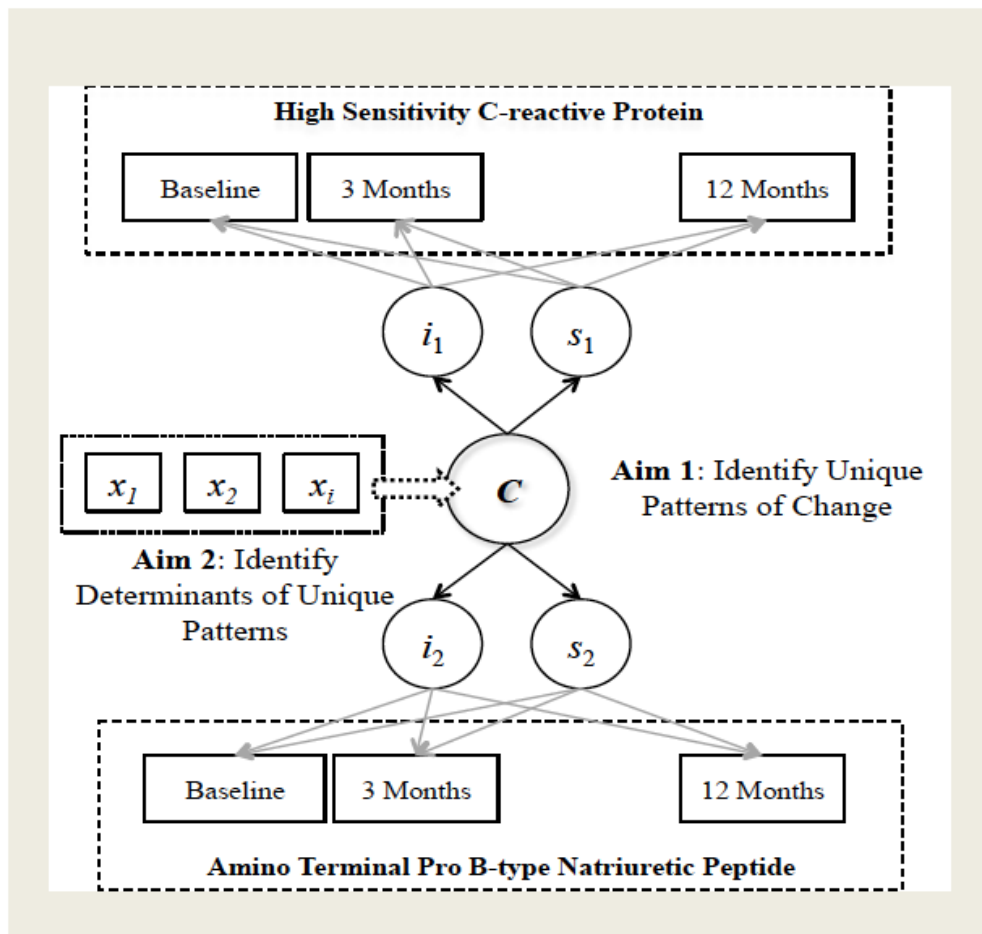
Growth mixture modeling is a model-based naturalistic approach used to identify distinct and common patterns of change over time within one or more measures **(Figure 4.1)**. Growth mixture modeling allows for the identification of previously unobserved patterns of change that have unique means, variances and homogeneous within-pattern growth. The benefits of this modeling approach specific to this study are that multiple patterns can be identified, missing data are handled with full-information maximum likelihood estimation, and patterns are not reliant on equally spaced time intervals.[29] Model selection was guided by the procedures explained by Ram and colleagues[29] and detailed in **Table 4.1**.

Table 4.1: Model fit criteria for latent class models

1	The Lo-Mendell-Rubin adjusted likelihood ratio test (p<0.05), indicating additive information from models with *k* vs. *k*-1 patterns of change
2	Parametric bootstrapped likelihood ratio test (p<0.05), indicating additive information from models with *k* vs. *k*-1 patterns of change
3	Bayesian Information Criteria and Akaike information criterion, with smaller numbers indicating better comparative fit
4	Convergence (model entropy closer to 1.0)
5	The proportion of the sample in each pattern of change (not less than 5% of the sample)
6	Posterior probabilities (average probability of belonging in "most likely" pattern of change closet to 1.0)

Individual growth mixture models for ln(NT-proBNP) and ln(hsCRP) were identified and integrated into a single biomarker latent class model, which was characterized by three distinct biomarker patterns. Baseline characteristics of the patterns were described using medians (interquartile ranges) or means (SD) and frequencies

(proportions) where appropriate. Comparisons of characteristics among the biomarker patterns were made using χ^2 analysis or one-way analysis of variance depending on levels of measurement.

The second aim of the study was to identify socio-demographic and clinical predictors of the individual unfavorable biomarker patterns of change. A model comparison approach[30] was applied throughout the model building process starting with covariates associated in bi-variate analyses with the outcome variable (p<0.05). Next, *a priori* factors were added and factors associated with the outcome using a forward (starting with an empty model) and backwards (starting with a full model) stepwise selection approach were added. Variables were eliminated conservatively in a sequential approach if they had a p-value over 0.20. Factors that were considered in the models but were not significant and did not contribute to the robustness of the model were removed. The covariates included in the final model were the following 17 variables: randomization to the exercise intervention or usual care, gender, race, age, heart failure etiology, baseline creatinine, baseline peak VO_2, body mass index (BMI), pain and anxiety (assessed with the EQ-5D), diabetes, hypertension, taking a loop diuretic, implantation of a pacemaker, bi-ventricular pacer or implantable cardioverter-defibrillator, treatment with an angiotensin-converting-enzyme inhibitor (ACE) or angiotensin II receptor blocker (ARB). BMI was evaluated as a categorical variable and continuous linear, quadratic and log transformed variable. The continuous linear form of the variable was included in the model because neither the quadratic nor the log transformed continuous variables were statistically significant.

Multinomial and logistic regression were used to identify predictors of observed

patterns and relative risk ratios (RRR), odds ratios (OR) and 95% confidence intervals (CI) were quantified and reported. Level of significance was set to p<0.05. Model fit was compared among multiple models using a χ^2 likelihood ratio test, pseudo R^2, AIC, and BIC tests as well as post-estimation fit statistics. StataMP v11.2 (College Station, Texas) was used for descriptive and comparative statistics, multinomial regression and logistic regression models. All mixture modeling was completed using Mplus (version v.7.0, Los Angeles, CA). ANCOVA models that used the baseline biomarker value as the single covariate were used to test for differences between the usual care and intervention groups' mean ln(NTproBNP) and ln(hsCRP) values at baseline, 3-and 12-months, respectively.

Results

Baseline characteristics for this study cohort are reported in **Table 2**. Overall, the median age was 58 years, the majority of the sample was male (73%), NYHA class II (71%) with a median left ventricular ejection fraction (LVEF) of 24. Just over one-third of participants had a history of diabetes (34%) or previous myocardial infarction (39%) and approximately two-thirds had hypertension (60%). The vast majority of participants in this study were treated with evidence-based therapies, including over 95% on an ACE or ARB. Almost 50% of the sample was on a statin medication and almost 14% had an implanted biventricular pacemaker.

Table 4.2: Baseline demographic and clinical characteristics by biomarker patterns of change at baseline n=320

Variables (%, median/IQR)	Overall N=320	Lowest/improving n=197	Elevated/stable n=108	Elevated/ worsening n=15	p-value
Treatment group, no (%)					0.29
Usual care	157 (49)	92 (47)	55 (51)	10 (67)	
Exercise training	163 (51)	105 (53)	53 (49)	5 (33)	
Age, median (IQR)	58 (51, 67)	59 (51, 69)	57 (52, 65)	57 (43, 64)	0.15
Female sex (%)	86 (27)	48 (24)	36 (33)	2 (13)	0.12
Race n=315 (%)					0.76
Black or Other	112 (36)	66 (34)	41 (38)	5 (33)	
White	203 (64)	127 (66)	66 (62)	10 (67)	
New York Heart Association class (%)					0.15
II	226 (71)	145 (74)	69 (64)	12 (80)	
III/IV	94 (29)	52 (26)	39 (36)	3 (20)	
Ischemic etiology of heart failure (%)	167 (52)	96 (49)	63 (58)	8 (53)	0.27
Diabetes mellitus (%)	108 (34)	69 (35)	33 (31)	6 (40)	0.64
Previous Myocardial Infarction (%)	126 (39)	80 (41)	40 (37)	6 (40)	0.83
Hypertension (%)	194 (60)	113 (57)	74 (69)	7 (47)	0.09
Atrial fibrillation or atrial flutter (%)	64 (20)	36 (18)	23 (21)	5 (33)	0.34
Clinical values, median (IQR)					
Left ventricular ejection fraction	24 (21, 30)	25 (21, 30)	25 (20, 30)	24 (18, 29)	0.50
Systolic blood pressure, mm Hg	112 (102, 130)	113 (102, 130)	110 (99, 130)	112 (100, 122)	0.71
Diastolic blood pressure, mm Hg	70 (61, 80)	70 (60, 80)	70 (62, 78)	68 (60, 74)	0.81

Sodium at baseline, mEq/L	139 (138,141)	140 (138, 141)	139 (138, 141)	139 (136, 140)	0.33
Creatinine at baseline, mg/dL, n=294	1.2 (1.0, 1.5)	1.1 (1.0, 1.4)	1.2 (1.0, 1.5)	1.2 (0.9, 1.6)	0.13
BUN, mg/dL, n=292	20 (15, 27)	19 (15, 25)	22 (15, 31)	22 (15, 27)	0.23
Beck Depression Index II, n=318	8 (4, 15)	7 (4, 15)	8 (4, 15)	13 (5, 7)	0.16
Baseline use of medications and devices (%)					
ACE inhibitor or ARB	305 (95)	189 (96)	102 (94)	14 (93)	0.78
B-blocker	299 (93)	183 (93)	101 (94)	15 (100)	0.56
Loop diuretic	241 (75)	135 (69)	94 (87)	12 (80)	0.001*
Statin	156 (49)	98 (50)	50 (46)	8 (53)	0.79
Implantable cardioverter-defibrillator	118 (37)	63 (32)	48 (44)	7 (47)	0.07
Pacer	61 (19)	33 (17)	24 (22)	4 (27)	0.39
Biventricular pacemaker	44 (14)	20 (10)	20 (19)	4 (27)	0.042*
Functional measures (median, IQR)					
Peak oxygen consumption, mL/kg/min	15.2 (12.2, 17.8)	15.6 (13.1, 18.2)	13.4 (11.3, 16.9)	14.5 (12.8, 16.9)	0.002*
Body mass index, kg/m^2,	30 (26, 35)	29 (25, 33)	32 (28, 38)	20 (26, 35)	<0.001*
Six minute walk test, m (n=312)	384.0 (314.9, 440.2)	384.8 (320.0, 441.9)	384.0 (306.6, 438.9)	356.0 (306.0, 423.7)	0.40
EuroQol-5D (%)					
Question 4: Pain/Discomfort (n=317)					0.22
No pain or discomfort	149 (47)	102 (52)	41 (39)	6 (40)	
Moderate pain	161 (51)	90 (46)	62 (59)	9 (60)	
Extreme pain	7 (2.2)	4 (2.0)	3 (28)	0 (0)	

Question 5: Anxiety (n=318)					0.54
Not anxious	187 (59)	118 (61)	62 (57)	7 (47)	
Moderately/Extremely anxious	131 (41)	77 (39)	46 (43)	8 (53)	

Data are complete for all 320 participants unless otherwise indicated, p-values indicate difference in mean values across biomarker subgroups for continuous variables. Abbreviations: IQR: interquartile range; BUN: blood urea nitrogen; ACE: angiotensin-converting-enzyme; ARB: angiotensin II receptor blocker *p-values are significant (<0.05) between the biomarker patterns

Baseline socio-demographic and clinical characteristics were compared

between the original parent cohort and this subgroup. In general, the subpopulation

was representative of the parent cohort, but there were significant differences in the

proportions of patients in NYHA class II at baseline in the sample versus total

population (71% versus 63%, p=0.008). There were no statistically significant

differences between the means in the usual care and intervention groups for ln(NT-

proBNP) between baseline and 3 months (p=0.499) or baseline and 12 months

(p=0.471). There were also no differences in ln(hsCRP) from baseline to 3 months

(p=0.168) or baseline to 12 months (p=0.193) between the usual care and intervention

groups **(Figure 4.2).** Thus, growth mixture modeling was used to further identify and

describe potential underlying patterns.

Figure 4.2 HsCRP and NT-proBNP for exercise training and usual care groups
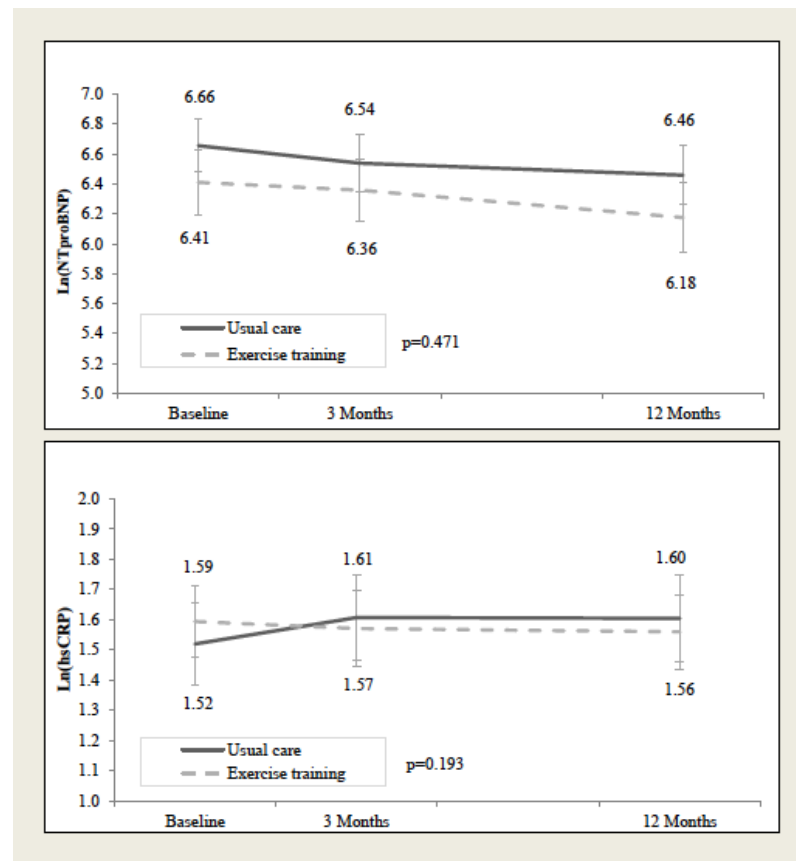
Identification of Multiple Patterns of Change in Biomarkers Over Time

Three statistically independent and clinically meaningful biomarker patterns of

NTproBNP and hsCRP were identified (model entropy: 0.79, Lo-Mendell Rubin test p-

value=0.016) **(Figure 4.3)**. Based on the observed characteristics of NT-proBNP and

hsCRP, the first pattern of change (n=197 [61%]; average posterior probability = 0.923)

was labeled "*lowest/ improving*." That is, patients classified in the *lowest/improving*

pattern had the lowest levels of NT-proBNP and hsCRP at baseline, and there were

significant declines in both NT-proBNP (p=0.006) and hsCRP (p<0.001) over the course

of 12-months. The second pattern of change (n=108 [34%]; average posterior probability

= 0.872) was labeled *"elevated/stable."* Patients classified in the *elevated/stable* pattern

had higher hsCRP (p<0.001) and similar NT-proBNP levels (p=0.885) compared with the

lowest/improving pattern at baseline. In the *elevated/stable* pattern, there were slight

improvements in hsCRP over the 12-month follow-up period (p=0.017). The third and

smallest pattern of change (n=15 [5%]; average posterior probability was 0.900) was

labeled *"elevated/worsening"* because patients fitting this pattern had the highest levels

of NT-proBNP at baseline that did not change over time (p=0.827), and hsCRP increased

significantly over 12 months (p<0.001).

Figure 4.3 Bio-marker patterns
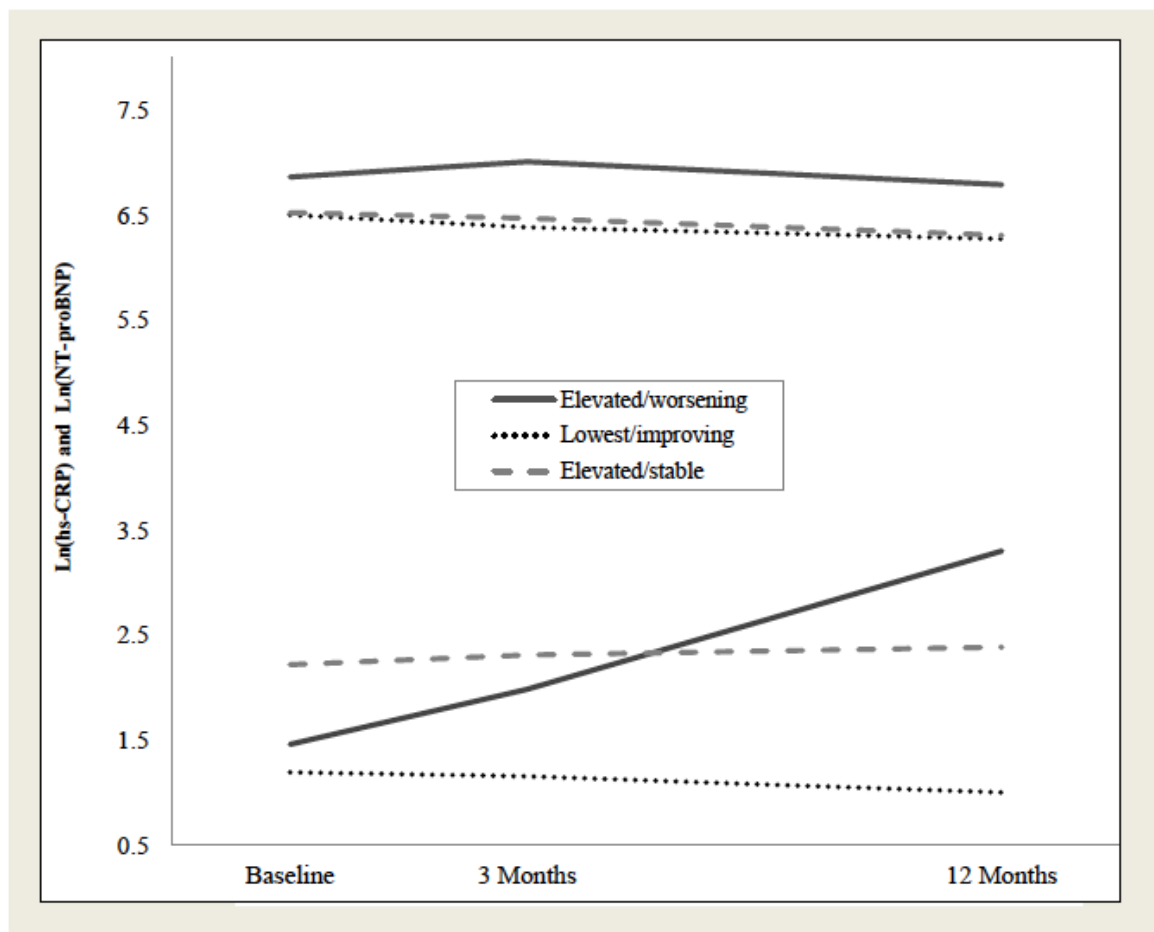
Identification of Biomarker Pattern Determinants

Determinants of the *elevated/stable* and *elevated/worsening* biomarker patterns from the multinomial regression are presented in **Table 4.3**, (model χ^2=90.71, p<0.001, pseudo R^2=19.51%). Participants randomized to the exercise therapy intervention were 77% less likely (RRR: 0.23, p=0.037) to be in the *elevated/worsening* compared to *lowest/improving* pattern. The risk of being in the *elevated/worsening* pattern was also almost six times higher (RRR: 5.84, p=0.033) for participants who had a bi-ventricular pacemaker prior to baseline, and over 1.5 times (RRR: 1.68, p=0.005) higher for each unit increase in serum creatinine at baseline. The absolute difference in mean creatinine at baseline was 0.5 higher in the *elevated/worsening* compared to the *lowest/improving* pattern.

Table 4.3: Multinomial regression model predicting elevated/stable and elevated/worsening patterns of change

Variable	Relative Risk Ratio	95% Confidence Interval	p-value
*Predictors of the elevated/stable pattern			
Exercise group	0.53	0.29-0.99	0.045
Loop diuretics	3.00	1.29-7.00	0.010
Hypertension	2.52	1.28-4.96	0.008
Ischemic etiology	2.22	1.08-4.51	0.028
Pain	1.80	0.99-3.26	0.054
Body mass index, kg/m^2	1.08	1.02-1.13	0.005
Peak Vo2, mL/kg/min	0.92	0.85-1.00	0.057
Diabetes	0.44	0.23-0.86	0.017

†Predictors of the elevated/worsening pattern			
Exercise group	0.23	0.06-0.92	0.037
Bi-ventricular pacer	5.84	1.16- 29.5	0.033
Baseline creatinine	1.68	1.17-2.42	0.005

* These results compare the elevated/stable to lowest/improving pattern
† These results compare the elevated/worsening to lowest/improving pattern

Participants in the exercise intervention group were 47% less likely (RRR: 0.53, p=0.045) to be in the *elevated/stable* compared to *lowest/improving* biomarker pattern. Participants with diabetes were also less likely to be in the *elevated/stable* pattern (p=0.017). Participants who were taking a loop diuretic had three times the risk (RRR: 3.0, p=0.010) of being in the *elevated/stable*, compared to *lowest and improving* pattern. Likewise, participants had over double the risk of being in the *elevated/stable* pattern if they had hypertension (RRR: 2.52, p=0.008) or heart failure of ischemic etiology (RRR: 2.22, p=0.028). Each additional unit of BMI was associated with an 8% increase (RRR: 1.08, p=0.005) in the likelihood of being in the *elevated/stable* pattern.

The results of the logistic model, which combined the *elevated/stable* and *elevated/worsening* and compared them with the *lowest/improving* pattern, were consistent with the multinomial results (**Table 4.4**). Once again, being in the exercise group provided a 51% protective effect (OR: 0.49, p=0.018) compared to the usual care group for not being in the *combined elevated/worsening* pattern. Consistent with the previous model, participants with diabetes were less likely to be associated with the worse biomarker pattern (p=0.026). The odds of being in the *combined elevated/worsening* pattern were over two times higher for patients with heart failure of

ischemic etiology (OR: 2.13, p=0.030), hypertension (RR: 2.05, p=0.028) or for those on loop diuretics (OR: 2.38, p=0.026). The odds of being in the *combined elevated/worsening* pattern were also 8% higher for each unit increase in BMI (OR: 1.08, p=0.003). The variables in the model offer fair prognostication for the *combined elevated/worsening* pattern (area under the curve: 0.78).

Table 4.4: Predictors of the combined elevated/worsening compared to lowest/improving pattern

Variable	Odds Ratio	95% Confidence Interval	p-value
Exercise group	0.49	0.27-0.89	0.018
Ischemic etiology	2.13	1.08-4.24	0.030
Loop diuretic	2.38	1.11-5.11	0.026
Hypertension	2.05	1.08-3.89	0.028
Body mass index	1.08	1.03-1.13	0.003
Diabetes	0.48	0.25-0.91	0.026

Discussion

Using the growth mixture modeling, we identified a deleterious biomarker pattern characterized by elevated myocardial stress and inflammation and a favorable pattern characterized by lower myocardial stress and decreasing inflammation over 12-months. Exercise therapy was protective for not having the *elevated/worsening* pattern of change in biomarkers over time. This finding supports the potential for exercise therapy to contribute to slowing or preventing the progression of heart failure.[31]

The finding that there are no mean differences in mean ln(NT-proBNP) or ln(hsCRP) over time between the exercise and usual care group are consistent with the study by Ahmad and colleagues that used a sample of 928 participants from the HF-ACTION study.[22] Ahmad and colleagues reported that exercise training (measured by volume of exercise) was not associated with numerical decreases in NT-proBNP and hsCRP from baseline to 3-months.[22] In an effort to further explain the relationship between these biomarkers (NT-proBNP and hsCRP) and exercise therapy, this study used growth mixture modeling to identify distinct multi-marker biomarker patterns. This methodology is especially relevant for a heterogeneous heart failure population, where being able to identify distinct sub-groups (or patterns) is clinically informative. When NT-proBNP and hsCRP were combined into distinct multi-marker patterns, we identified an *elevated/worsening* pattern with rising hsCRP over 12-months. The characteristics of this pattern may partially explain why there was not a statistically significant mean reduction in hsCRP in the exercise therapy group compared to usual care. The study findings reported here are consistent with results from the Cardiovascular Health Study (CHS), in which deFilippi and colleagues reported a protective effect of moderate physical activity on the risk of developing heart failure, neurohormonal activation (measured by NT-proBNP) and cardiac injury (measured by Troponin T).[32]

One predictor of the *elevated/worsening* pattern of change was having a bi-ventricular pacemaker. More participants with a bi-ventricular pacer were also classified as NYHA III/IV, indicating that having a bi-ventricular pacer may be a proxy for heart failure severity. Higher baseline creatinine was also associated with over a one-and-a-half fold risk of having the *elevated/worsening* pattern. Worsening renal function is defined as

absolute creatinine elevation of 0.1 to 0.5 mg/dL.[33] The difference between the

lowest/improving and *elevated/worsening* was 0.5 mg/dL, which is a clinically

meaningful difference because of the association with 6-month mortality, readmission

and functional decline.[33] This finding is consistent the Breathing Not Properly study

where there was a weak but significant correlation between estimated glomerular

filtration rate (eGFR) and BNP.[34] Likewise, in a study reported by Anwaruddin and

colleagues, lower eGFR was associated with higher proBNP.[35] The relationship between

renal function and natriuretic peptides is complex and may be explained by elevated

intravascular volume, atrial pressure, systemic pressure or by ventricular mass.[36]

When comparing the *elevated/stable pattern*, in which there was an elevation in

hsCRP, but not NT-proBNP, with the *lowest/improving* pattern, once again, participants

randomized to the exercise therapy intervention were much less likely to have the

deleterious biomarker pattern. Hypertension was associated with a two and a half fold

risk of being in the *elevated/stable* compared to *lowest/improving* pattern, along with

other measures of severity—being on a loop diuretic or having heart failure of ischemic

etiology. Many patients with reduced renal function also have hypertension, which can

cause left ventricular hypertrophy and elevated natriuretic peptides.[36] Hypertension and

hsCRP have also been associated in other studies due to shared mechanisms of oxidative

stress and endothelial dysfunction.[37] Specifically, hsCRP is known to attenuate nitric

oxide production and decrease endothelial nitric oxide synthase expression leading to

vasoconstriction and atherothrombosis.[20] The association between elevated hsCRP and

hypertension is consistent across multiple racial and ethnic groups.[38,39]

Higher BMI was also associated with the *elevated/stable* biomarker pattern. The inverse relationship between BMI and NT-proBNP has been reported in many other studies,[40-44] explaining why obesity was associated with the *elevated/stable* and not the most unfavorable pattern—*elevated/worsening*. One theory for this inverse association is that there is increased clearance of NT-proBNP by type C natriuretic peptide receptors on adipocytes.[45] In obese patients, natriuretic peptides are still routinely used for diagnostic purposes, but at lower cutoff levels.[43]

Diabetes was also associated with a 56% lower risk of being in the *elevated/stable* compared to *lowest/improving* biomarker pattern. This may be explained by a higher proportion of diabetic patients being on a statin medication compared to non-diabetics (59% versus 43%). Statins are associated with reduced hsCRP in diabetic patients.[46] The apparently protective effect of diabetes may be due to chance, or it might be related to the fact that diabetic participants were less likely than non-diabetic participants to have ischemic etiology (44% versus 56%). However, controlling for statin use and ischemic vs. non-ischemic etiology in post-hoc models did not change the strength of the relationship between diabetes and the risk of having the hazardous patterns of change in these biomarkers. More research is needed to further explore associations among diabetes and other comorbidities in heart failure and the systemic inflammatory and myocardial stress responses to exercise.

Strengths and Limitations

The growth mixture modeling analytic approach was a major strength of this study because it allowed for the identification of previously unobserved biomarker

patterns of change. As such, it is a useful analytic tool for helping to explain the heterogeneity in response to exercise therapy that is common among patients with heart failure. Another strength of this study was that it built off the results of the Ahmad study,[22] demonstrating how different types of biomarker analyses can help to explain how exercise may be able to slow or prevent the progression of heart failure.[31]

One potential limitation of this study is its generalizability because it was conducted on a random sample of the biomarker sub-study with near-complete data. This random sample is representative of the larger HF-ACTION trial population. Though it is unlikely that our results were solely a function of sample selection, it is possible that if this analysis were done on in the entire dataset that the results would be different. The relative risk reduction reported in this study should be interpreted with caution because the *elevated/worsening* pattern was relatively small and the overall sample size of the study was modest. Although we successfully identified statistically distinct biomarker subgroups and corresponding predictors, further testing in a larger sample may increase the precision of the estimates. Given that the measure of exercise was randomization to the exercise intervention, rather than quantity, it is likely that the protective effect of exercise would be stronger if adherence were accounted for. The final limitation is that the exercise therapy group tended to have lower NT-proBNP at baseline, though this difference was not statistically significant (p=0.083). This slight imbalance at randomization is unlikely to account for the protective effect of exercise therapy reported in this study.

In summary, these study results indicate that exercise therapy may prevent worsening inflammation and myocardial stress in patients with stable heart failure and help counteract the pathophysiological processes of the heart failure progression through multiple biologic mechanisms. These results contribute to the body of knowledge on exercise as a preventative and therapeutic intervention for patients with heart failure.

There are many related avenues for future research around exercise and heart failure, including further elucidation of mechanisms of benefit, identifying which biomarkers are modified by exercise, quantifying the dose of exercise needed to achieve a benefit, and identifying ways to engage heart failure patients in exercise.[31] There is also a strong need to identify different exercise regimens for patients with heart failure and prevalent comorbid conditions such as type 2 diabetes. In the future, multi-marker biomarker analyses of exercise interventions may also be able to clarify which patients can be expected to benefit from exercise by demonstrating the mechanism by which exercise slows the progression of heart failure.[31]

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CHAPTER V: MOTIVATIONAL INTERVIEWING TAILORED INTERVENTIONS FOR HEART FAILURE (MITI-HF): STUDY DESIGN AND METHODS

(To Be Submitted to *Contemporary Clinical Trials*)

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Statement of Author Contributions: Ruth Masterson Creber was the lead author on this article. She and Barbara Riegel DNSc, RN were a co-Principal Investigators (PI) of the MITI-HF randomized controlled trial. Both co-PIs were responsible for the study design, protocol development, study implementation and data collection. Ruth Masterson Creber analyzed the study data and drafted this article. Barbara Riegel DNSc, RN was the senior author and Investigator of the study. Megan Patey and Marissa DeCesaris were both research assistants on MITI-HF. They collected data and provided edits to the manuscript. Wendy Hiller Gee from Krames Staywell developed the Krames Staywell patient education materials and provided edits to the article. Victoria Dickson, PhD RN from New York University School of Nursing, helped design the study protocol and provided critical edits to the article.

Abstract

Lack of engagement in self-care is common among patients needing to follow a complex treatment regimen, especially patients with heart failure who are affected by comorbidity, disability, and the side effects of poly-pharmacy. In response, clinical practice guidelines recommend using behavioral approaches to engage patients in self-care. The efficacy of motivational interviewing to improve self-care in patients with heart failure remains understudied. We are conducting a brief, nurse-led motivational interviewing randomized controlled trial to address behavioral and motivational issues related to heart failure self-care. Participants who are randomized to the intervention group receive both home and phone-based motivational interviewing sessions over 90 days. Participants in the control group receive care as usual. The purpose of the study is to test the efficacy of a MI intervention on self-care, physical HF symptoms and quality of life. This article presents the study design and methods and plans for statistical analysis for Motivational Interviewing Tailored Interventions for Heart Failure (MITI-HF). Study findings will contribute to the literature on the efficacy of motivational interviewing to promote heart failure self-care.

Introduction

Heart failure is a cardiovascular syndrome affecting more than 5.1 million Americans. It is growing in prevalence with 670,000 new cases diagnosed each year,[1] especially among patients older than 80 years.[2] The management of heart failure is complex because it often occurs in the context of multiple comorbid conditions.[2] Each comorbid condition requires specific self-care, making prioritization a persistent challenge. One method that has been efficacious for decreasing symptom prevalence and preventing re-hospitalization is the promotion of self-care.[3] Initiating effective self-care for early signs and symptoms of heart failure may help patients have a better quality of life[3] and delay the onset of an acute decompensation.[4,5]

Self-care for patients with heart failure has been defined as a naturalistic decision-making process comprised of both self-care maintenance and self-care management.[6,7] Self-care maintenance involves choosing positive health practices that may help to prevent an acute exacerbation (e.g. taking medication as prescribed, consuming a low-salt diet, staying physically active, and monitoring daily weight). Self-care management builds on these routine behaviors and includes critical decision-making and follow-up actions around managing signs and symptoms when they occur (e.g., taking an extra diuretic for shortness of breath).[6-8] Heart failure self-care must be adapted to the individual because each person has his or her own symptom experience and functional disability.

Early evidence from a mixed-methods pilot study[9] suggested that a motivational interviewing (MI) intervention was beneficial for adults with heart failure by improving

their self-care.[9] Riegel and colleagues reported that the effectiveness of the intervention was due to the MI approach.[9] Building upon these earlier findings, MITI-HF was designed improve heart failure self-care maintenance behaviors using MI.

The article describes the study design and research methods used to evaluate the intervention (Clinicaltrials.gov ID MITI-HF_EGKMF). We designed Motivational Interviewing Tailored Interventions for Heart Failure (MITI-HF) to examine the feasibility and efficacy of a MI intervention to improve patients' self-care. The primary aim of the study is to test the feasibility and preliminary efficacy of MITI-HF for its impacts on heart failure self-care over 90 days. The secondary aim is to examine the impact of MITI-HF on secondary outcomes of physical HF symptoms and quality of life over 90 days.

Background

To improve self-care, this study uses a tailored MI approach. Traditionally, patient education programs focus on disseminating didactic information. Information alone is rarely sufficient to influence symptom management behaviors,[10-12] especially in the case of heart failure where there are often competing co-morbidities including diabetes mellitus (38%), hypertension (73%), kidney disease (45.9%) and obesity (46.8%),[2] in addition to chronic obstructive pulmonary disease, depression, and cognitive impairment.[13-15] Overall, educational approaches for improving heart failure self-care have been developed and tested with little impact on heart failure outcomes.[16-18]

Tailored interventions are designed to address the individual characteristics of persons within a sample.[19] Conceptually, this is similar to the Lauver *et al* definition of

individual-centered interventions, which addresses either characteristics and experiences or individuals' goals or preferences.[20] In this case, the intervention is targeted to hospitalized patients with chronic heart failure and then tailored specifically to patient's goals and to match individuals' unique self-care maintenance or management needs. We postulated that a tailored MI approach would help patients with heart failure address behaviors that are problematic by increasing internal motivation to engage in specific self-care behaviors chosen by the patient.

MI is grounded in client-centered counseling, cognitive-behavioral therapy, and social cognitive therapy.[21] MI also incorporates the Transtheoretical Model of Behavior Change, which assesses a patient's readiness to change behavior and develops strategies to move toward taking action to change behavior.[22] MI integrates the concepts of relationship building from humanistic therapy[23] with active strategies oriented towards stages of change.[22] The main characteristics of motivational interviewing are: expressing empathy, developing discrepancy, rolling with resistance, and supporting self-efficacy.[24] The interviewer maintains a nonjudgmental approach and allows the patient to determine the need for behavioral change, rather than offering unsolicited advice on the need for change. The interviewer only explores ways to implement change once the patient expresses the desire and confidence to change. The goal of MI is to help individuals work through inherent ambivalence present in problematic or unhealthy behaviors,[24,25] and to help them verbally express their own reasons for or against change using a nonjudgmental, empathetic and encouraging tone.[26] MI can help people identify how their current behaviors conflict with their ability to achieve personal health goals, especially in the context of low readiness to change.[26]

MI was initially developed for the treatment of substance abuse.[27-29] Due to its strong theoretical base and empirical support, MI is now used for patients with a wide variety of unhealthy behaviors including illicit drug abuse, eating disorders, asthma, HIV risk behavior, and gambling.[30] It is also used for cardiovascular diseases, including heart failure in acute and outpatient settings.[9,31-33] Brodie and colleagues used MI to increase physical activity among older adults with heart failure,[31] as well as general and disease specific quality of life.[32] MI has specifically been used to improve heart failure self-care in small pilot studies;[9,34] however, larger studies are needed to build the body of evidence and confirm the preliminary albeit promising results of these small pilot trials.

Theoretical Frameworks

The Situation Specific Theory of Heart Failure Self-care[6] is used as the guiding theoretical framework for the study. The Model for Tailoring Behavioral Interventions[19] was used to plan, implement and evaluate the tailored intervention, and MI is the mechanism for delivery.

Intervention development

The Model for Tailoring Behavioral Interventions[19] was used to develop and test the tailored intervention. The Model for Tailoring Behavioral Interventions has five steps: 1) understanding, 2) assessing, 3) planning, 4) implementing and 5) evaluating. The first step in designing the tailored intervention was selecting the individual characteristics on which the intervention would be tailored.[19] In this study tailoring was based on physical, mental, and behavioral health characteristics. Physically, all participants in the study have had a recent hospitalization for acute decompensation of heart failure. Behavioral

decision-making is at the heart of self-care so participants' self-care scores were assessed using the Self-Care of Heart Failure Index (SCHFI) v 6.2.[7,35] The intervention was planned based on areas that patients were deficient in according to the SCHFI as well as their self-defined goals. For example, if a patient's goal was: *"to be able to attend my grandson's football games this fall,"* the nurse tailors the intervention to specific physical activity needs. Implementation includes conducting a randomized controlled trial. The study outcomes are common across individuals despite the fact that each intervention is tailored to participants' unique goals and areas that they self-defined as needing growth.

Usual care

All participants are enrolled from the hospital and both the intervention and the control groups receive patient education materials in the hospital. Patient education sheets were designed by Krames StayWell for a 6th grade or below literacy level, according to the Fog Index **(Table 5.1)**.[36] The photographic images in the materials are commensurate with the demographics and culture of the study population. For instance, the "Busting Barriers" sheet pictures three generations of African American males to reinforce the benefits of social and familial support. All of the educational sheets targeted goal behavior changes through participant interaction, such as writing down the names of support people who would help them see habits that might block their progress toward change. Individuals randomized to the UC did not receive any other intervention.

Table 5.1 Patient Education Materials

Patient Education Sheet	Educational content areas
Busting Self-Care Barriers	Helps patients to identify possible challenges to self-care in order to prevent them from becoming barriers; recommendations include being active, reducing salt, limiting fluid, taking an extra water pill, and calling a healthcare provider.
Breaking Down Your Barriers	Describes how to take steps to improve self-care, identify support people, and identify benefits of self-care behaviors.
Dealing with Heart Failure Symptoms	Helps patients record baseline information such as weight, walking distance, and amount of stairs able to climb before becoming short of breath.
Watch for Changes	After baseline information has been identified, this is a worksheet describes how to monitor symptom changes. It also offers tips for limiting salt and fluids.
Stay Active to Help Your Heart	Focuses on how to incorporate activity into a daily routine, including how to choose an activity and warning signs of overexertion.
Adding Activity to Your Day	Includes tips for making activity part of your day, and for how to keep it fun by walking with friends or reading a book while on an exercise bike.
My Heart Failure Symptom Chart	This chart is for recording daily weight, change from baseline weight and changes in symptoms.
My Symptom Action Plan	This worksheet is for recording action plans for different scenarios of worsening heart failure symptoms, including swelling, increased shortness of breath, and weight gain of 2 or more pounds in 1 day.

Motivational Interviewing Intervention

Heart failure specialist nurses provide the MI intervention. The nurses conduct one home-based MI intervention session followed up by three MI phone calls over 90 days. The intervention begins with a conversation about the participant's self-identified goals. During the home intervention, the nurses focus on self-care areas that the

participant identifies as high priority. During that visit the participant sets specific goals, which the nurses follow up with and reinforce over the follow-up phone calls. Based on our prior work with motivational interviewing, we anticipate that one 60-minute session and three to four follow-up phone calls scheduled over the following few months are adequate to deliver this intervention.[9]

Interventionist Training

Before starting the study, the bachelor or masters degree prepared nurse interventionists received two full days of training covering detailed aspects of MI theory and heart failure-specific self-care techniques and skills. The principal investigators and an expert in MI supervised both training days. The nurses practiced the techniques of MI through numerous role-play scenarios with one another and the facilitators.

Treatment Fidelity

Treatment fidelity is monitored throughout the intervention by recording all of the intervention sessions. All audiotaped intervention sessions are transcribed, and analyzed to assess treatment fidelity, a methodological strategy used to monitor and enhance the reliability and validity of the intervention.[37] Prior to implementation of the protocol, a standardized rubric was developed based on the intervention manual to score adherence to the study protocol including the use of the principles of MI. This provided a mechanism for providing corrective feedback to the interventionists regarding deviations from the study protocol. Each audio recording is reviewed to determine the proportion of the intervention elements covered by the nurse interventionist using a checklist. In addition to ongoing feedback with the interventionists, a psychologist trained in MI also

reviews random transcripts and provides feedback to the interventionists on the quality of MI as well as adherence to the protocol.

Study Design

MITI-HF is a prospective, single blinded, pilot feasibility randomized single-site trial. The target sample size is 65 participants; however, to account for an estimated 35% attrition rate, the target number for recruitment is 100 participants. The target sample size was calculated based on a 2:1 randomization scheme (intervention: control) with 90% power (5% alpha) to detect a difference of 80% versus 50% (intervention and control group) of scoring over 70 on the SCHFI, which is the cut-off for adequate self-care[35] at three months. The power analysis was performed using G*Power [38] and confirmed with PASS.[39]

Procedures

To achieve balance in the study arms, randomization is performed using minimization,[40] stratifying participants on NYHA class and gender. Randomization to the intervention or usual care group occurs after the informed consent form is signed and a cardiologist scored New York Heart Association (NYHA) Functional Class interview **(Figure 5.1)**.

Figure 5.1: MITI-HF flow chart

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                    ┌─────────────────────────────┐
                    │ Identify potential participant│
                    └──────────────┬──────────────┘
                                   ↓
                    ┌─────────────────────────────┐
                    │   Present study opportunity to│
                    │      potential participant    │
                    └──────────────┬──────────────┘
                                   ↓
                    ┌─────────────────────────────┐
                    │  If agree, obtain informed consent│
                    └──────────────┬──────────────┘
                                   ↓
                    ┌─────────────────────────────┐
                    │   Screen for health literacy &│
                    │           cognition           │
                    └──────────────┬──────────────┘
                                   ↓
                    ┌─────────────────────────────┐
                    │  If eligible, complete NYHA,  │
                    │ SCHFI, Med Record Review.     │
                    │  Provide patient education    │
                    │         worksheets.           │
                    └──────────────┬──────────────┘
                                   ↓
                        ┌──────────────────┐
                   ┌────│  Randomization   │────┐
                   │    └──────────────────┘    │
                   ↓                            ↓
          ┌─────────────────┐         ┌─────────────────┐
          │  MI Intervention │         │    Usual Care    │
          └────────┬────────┘         └────────┬────────┘
                   ↓                            ↓
    ┌───────────────────────────┐   ┌───────────────────────────┐
    │ 2 week post-hospital phone │   │ 2 week post-hospital phone │
    │  call to complete KCCQ,    │   │  call to complete KCCQ,    │
    │  HFSPS, Socio-demographics │   │  HFSPS, Socio-demographics │
    └─────────────┬─────────────┘   └─────────────┬─────────────┘
                  ↓                                 ↓
    ┌───────────────────────────┐                  │
    │ Home intervention and      │                  │
    │ follow-up phone calls      │                  │
    └─────────────┬─────────────┘                  ↓
                  ↓                  ┌───────────────────────────┐
    ┌───────────────────────────┐   │ 90 day phone call to       │
    │ 90 day phone call to       │   │ complete KCCQ, HFSPS,      │
    │ complete KCCQ, HFSPS,      │   │ SCHFI, Hospitalizations    │
    │ SCHFI, Hospitalizations &  │   │ and Medical Events         │
    │ Medical Events, Intervention│  └───────────────────────────┘
    │ satisfaction survey        │
    └───────────────────────────┘
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Data Collection

Medical history, including comorbidities and heart failure characteristics, are obtained from patients' electronic medical records. Kansas City Cardiomyopathy Questionnaire (KCCQ) and Heart Failure Somatic Perception Scale (HFSPS) data are collected at baseline approximately two weeks after hospital discharge via phone call by research assistants blinded to study group. Over time, we realized that the 6-item screening tool for cognition was not adequate to pick up some cases of severe cognitive impairment. In response, a second screening was put in place two weeks after discharge and before the baseline questionnaires were completed. If participants had no recollection of the study, or signing the informed consent during the baseline call, they were excluded from the study on the grounds that they had cognitive impairment severe enough to meet exclusion criteria. Research assistants collect follow-up data at 90 days on the SCHFI, KCCQ, HFSPS and self-reported clinical events.

Sample

Adults with heart failure are enrolled into the MITI-HF study from two urban inpatient cardiology units. To be included, participants have to: 1) be hospitalized with a primary or secondary diagnosis of heart failure, 2) be able to read and speak English, 3) be 18 years of age or older 4) live in a setting where they can independently engage in self-care, 5) live within 30 miles from the university hospital 6) have at least adequate health literacy, 7) have symptomatic HF (NYHA II-IV) and 8) be willing to participate. Exclusion criteria included: 1) being on a Milrinone drip, 2) being on a list for an implanted ventricular assist device or heart transplant, 3) pregnancy, 4) psychosis and 5)

cognitive impairment with the inability to participate in the intervention or complete the study instruments. Study enrollment took place from January 2012 to December 2013.

Ethics

The institutional review board at the affiliated University approved the study protocol. Written informed consent and Health Insurance Portability and Accountability Act authorization are obtained from all interested participants. All research assistants are trained in HIPAA confidentiality and the protection of human research subjects. All procedures are in accordance with the Declaration of Helsinki.[41]

Measurement of Variables

Self-care is measured using the SCHFI v. 6.2, a 22-item, interviewer-administered instrument that quantifies HF patients' self- care maintenance, self-care management, and self-care confidence (self-efficacy).[7,35] Each scale score ranges from 0 to 100; higher scores indicate better self-care. Quality of life is measured with the KCCQ, which has 23 items that can be quantified into five subscales: physical limitations, symptoms, quality of life, social interference, and self-efficacy. Each domain-specific subscale and the overall clinical summary score range from 0 to 100.[42] Higher scores indicate better quality of life. Acute physical symptom recognition is measured with the HFSPS. Scores are calculated by summing responses; higher values reflect worse physical symptom distress.

Data Analyses

Standard descriptive statistics of frequency, central tendency, and dispersion will be used to describe all measures of the study at baseline. Comparisons of socio demographic and clinical characteristics between the intervention and usual care groups at baseline will be reported using Student's t, Pearson χ^2 analysis or ANOVA where appropriate. Differences between groups in improvements in self-care will be quantified using t-tests without assuming equal variance; Cohen's d is calculated as a standardized index of effect size. Repeated measures tests are used within subjects. Analyses will be conducted using StataSE (College Station, Texas) using intention-to-treat. Effect sizes will be calculated with G Power. [38]

Conclusion

This article describes the development and implementation of MITI-HF, a tailored MI intervention to support heart failure self-care. The significance of this study is that it tests an innovative, MI intervention that has high potential to be integrated into transitional care discharge planning services. We anticipate that using this MI approach can help patients with heart failure focus on their internal motivation to change in a non-confrontational, patient-centered, collaborative way. It also affirms their ability to practice competent self-care relevant to their personal health goals. Future articles will present the results of the study and implications for heart failure research and clinical practice.

Acknowledgments

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CHAPTER VI: **M**OTIVATIONAL **I**NTERVIEWING **T**AILORED **I**NTERVENTIONS

FOR **H**EART **F**AILURE (MITI-HF): RANDOMIZED CONTROLLED TRIAL

(To Be Submitted to *American Heart Journal*)

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Abstract

Background: Self-care has been shown to decrease symptom prevalence, improve quality of life, delay the onset of acute decompensation and prevent hospitalization for patients with heart failure (HF). The efficacy of using motivational interviewing (MI) to improve self-care is unknown.

Methods and Results: We conducted a randomized controlled trial to test the comparative efficacy of a tailored MI intervention versus usual care in improving HF self-care behaviors, physical HF symptoms and quality of life. The intervention consisted of a single home visit and 3-4 follow-up phone calls by a nurse over 90 days. A total of 67 participants completed the study (mean age 62 ± 12.8 years), of which 54% were Black, 30% were female, 84% had class III/IV symptoms, and 63% were educated at a high school level or less. Both the intervention and usual care groups had significant improvements in self-care maintenance and confidence (*all* $p<0.01$); the intervention group also had a significant improvement in self-care management ($p<0.01$). However, participants in the intervention group had a 9-point greater improvement in self-care maintenance compared with the usual care group ($p=0.026$) at 90 days. There were no differences between the groups in self-care management, confidence, physical HF symptoms or quality of life at 90 days.

Conclusions: Patients with HF who received the MI intervention had statistically significant and clinically meaningful improvements in self-care maintenance over 90 days that exceeded that of usual care. Overall, MI is an effective approach for improving self-care maintenance.

Introduction

Heart failure (HF) affects more than 5.1 million Americans[1] and costs the United

States $39.2 billion annually.[2] HF is currently the most common reason for the

hospitalization of Medicare recipients.[3-6] The costs for preventable readmissions are

estimated to be about $17 billion or 20% of Medicare's hospital payments.[7] Patients with

HF are frequently admitted to the hospital because they experience exacerbations in

symptoms with fluid retention, shortness of breath, and fatigue on exertion.[8] Considering

the increasing prevalence, cost and social burden to patients and their families,

interventions that incorporate self-care with effective medical therapy are critical to

optimize patient health and improve patient outcomes.[9-11]

Self-care has the potential to reduce hospitalizations and improve quality of life.

Several studies have examined the impact of self-care education on patient-oriented and

clinical outcomes including self-care behaviors,[12] self-efficacy,[13] quality of life,[13-16]

physical activity,[17] health status,[18] hospitalizations,[19,20] mortality,[16] myocardial stress,[21]

and systemic inflammation.[22] Overall, there has been an apparent lack of effectiveness of

self-care education on clinical outcomes. One reason is that patients face a number of

prohibitive barriers to mastering self-care skills and knowledge, including cognitive

impairment, excessive daytime sleepiness, low-health literacy,[23-25] and poor motivation.[26]

Motivational interviewing (MI) has been proposed as a client-centered strategy to engage

patients in self-care,[12,27] and improve self-efficacy and readiness to change.

The purpose of this randomized controlled trial (Motivational Interviewing

Tailored Interventions for Heart Failure [MITI-HF]) was to test a tailored MI intervention

designed to improve self-care compared to usual care. The primary study outcome was change in self-care maintenance (i.e. daily behaviors like taking prescribed medications, restricting fluid and dietary sodium intake, participating in health-seeking behaviors, and monitoring for HF symptoms). The main hypothesis was that HF patients enrolled in the group receiving a uniquely tailored MI intervention would improve in self-care after 90 days. Secondary outcomes included physical HF symptoms and quality of life.

Methods

Study design

MITI-HF was a prospective, single-blinded, pilot randomized controlled trial. The University's Institutional Review Board approved the study, which actively enrolled participants from January 2012 to December 2013. Detailed description of study methods including participant eligibility, recruitment procedures and data collection have been registered (Clinicaltrials.gov MITI-HF_EGKMF), reported in a study design paper[28] and are summarized here. The target recruitment size was 100 participants, a sample size calculated to provide 90% power (5% alpha) to detect a difference of 80% versus 50% (intervention and control group) likelihood of scoring over 70 on the Self-Care of Heart Failure Index (SCHFI) v.6.2 at 90 days. The power analysis was performed using G*Power [29] and confirmed with PASS.[30]

Participants

One hundred participants were randomized to receive the MITI-HF intervention or usual care after a HF-related hospitalization. The study inclusion and exclusion criteria

are shown in **Table 6.1**. Potential participants were approached during an inpatient HF-

related hospitalization at a University affiliated urban hospital. All eligible patients were

screened for health literacy,[31] cognitive impairment (using a six-item screener derived

from the Mini Mental Status Exam (MMSE)),[32] baseline self-care (using the SCHFI

v.6.2),[33] and a standardized interview to assess New York Heart Association (NYHA)

functional class.[34] Those who met the inclusion criteria and agreed to participate provided

written informed consent. At the end of this visit, all participants received a set of

educational fliers related to identifying and addressing self-care barriers, dealing with

heart failure symptoms, maintaining a lower sodium diet and an active lifestyle.

Participants were then randomized by minimization[35] to one of two intervention groups

with a 2:1 randomization ratio stratified by NYHA functional class and gender.[36]

Table 6.1. Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
1. Hospitalized with a primary or secondary diagnosis of HF	1. Current treatment with milrinone
2. Able to read and speak English	2. On a list for an implanted VAD or heart transplant
3. 18 years of age or older	3. Pregnancy
4. Living in a setting to independently engage in self-care	4. Psychosis
5. Living within 30 miles from the University Hospital	5. Cognitive impairment- the inability to pass the six-item screener or complete study instruments
6. Have at least adequate health literacy	6. Inability to provide informed consent
7. Symptomatic HF (NYHA I-IV)	

Abbreviations: HF: heart failure, NYHA: New York Heart Association, VAD: ventricular assist device

       Baseline data were collected approximately two weeks after hospital discharge. A

research assistant (blinded to study group allocation) called participants to obtain socio-

demographic information and to administer the baseline Kansas City Cardiomyopathy

Questionnaire (KCCQ) and Heart Failure Somatic Perception Scale (HFSPS).

Approximately 90 days after completion of the intervention, participants were called to complete the follow-up questionnaires (SCHFI, KCCQ, HFSPS). If the first follow-up call was unsuccessful, the research assistant would try every 3 to 5 days for up to 60 days. If there was no contact with the participant after 60 days from the expected follow-up date, the participant was considered lost to follow-up.

Intervention Description

As described in detail elsewhere,[28] participants assigned to the intervention group received a MI tailored intervention that included a home-based MI intervention and 3-4 follow-up phone calls over the course of 90 days. Participants assigned to the usual care group continued with their usual care without further intervention. We chose this model of delivery for the intervention based on the Situation Specific Theory of Self-Care theoretical framework and our previous research.[12] During the home visit the nurse worked with the participant using a MI approach to identify specific client-centered goals related to HF self-care. Together they developed a client-directed plan for accomplishing the goals, which were reinforced in the follow-up phone calls. A case study details how the nurse used the MI intervention to increase patient motivation and develop a plan for incorporating self-care behaviors into the daily routine of one participant.[37]

Study Measures and Outcomes

Self-care. Self-care was measured using the SCHFI v. 6.2, which is a 22-item, interviewer-administered instrument that quantifies self-care maintenance, self-care management, and self-care confidence (self-efficacy) for patients with HF.[33,38] The SCHFI was written for a sixth grade reading level and takes approximately 5 to10

minutes to complete. Scores on each scale were standardized to range from 0 to 100—

higher scores indicate better self-care. A score of 70 or greater in each self-care scale

score is considered adequate and an improvement of 8 points is considered a clinically

significant improvement.[33] Cronbach's α is not recommended as a measure of reliability

for these scales because both self-care maintenance and self-care management scales are

multidimensional.[39] Using more appropriate coefficients, for the self-care maintenance

scale, the reliability coefficients ranged from 0.75 to 0.83, depending on which

coefficient was used. For self-care management, reliability coefficients ranged from 0.66

to 0.77. Self-care confidence is unidimensional and the various reliability coefficients,

including Cronbach's alpha, ranged from 0.84 to 0.90.[39] In a recent exploratory factor

analysis, the comparative fit index construct validity scores were: 0.92 for self-care

maintenance; 0.95 for self-care management and 0.99 for self-care confidence.[40]

Concurrent validity of the SCHFI v 6.2 has been demonstrated by comparing it to the

European Health Failure Self-care Behavior Scale (r= -0.65, p<0.001).[40]

Quality of life. Quality of life was measured with the KCCQ, which has 23 items

that can be quantified into five subscales: physical limitations, symptoms, quality of life,

social interference, and self-efficacy. Each domain-specific subscale and the overall

clinical summary score range from 0 to 100 (higher scores indicate better outcomes).[41] In

another population of patients with heart failure the internal consistency of the KCCQ is

reported as being high (Cronbach's α 0.92).[42] Tests of construct validity for the KCCQ

have strong associations with NYHA class, SF-36 and the six minute-walk-test.[41]

Acute Physical Heart Failure Symptoms. Acute physical HF symptoms were measured with the HFSPS. This scale asks how much participants were bothered by common symptoms of HF during the previous week. The responses to the 18-items range from 0 (I did not have this symptom) to 5 (extremely bothersome).[43] Scores were summed with higher values indicating worse physical symptom distress. The reported reliability of the HFSPS scale is 0.90.[44] Validity was demonstrated when the two domains, dyspnea and early/non-specific congestion were associated with survival at 180 and 365-days.[45]

Participant characteristics. Age, gender, comorbid conditions, prescribed medications, diagnostic lab tests, and echocardiogram results were obtained from the medical record. During baseline interviews research assistants obtained information on race/ethnicity, insurance status, years of education, perceived and general health from the participant. General health was measured by rating their health now compared to a year ago. Responses ranged from 1 (much worse) to 5 (much better) compared to a year ago. Participants were also asked about the quality of their social support and responses included fair, satisfactory, good or very good.

Traditional questions about income characteristics (sources, amounts received) have been wrought with a wide range of bias[46] and random error in both government surveys and other types of research.[47] So, income was measured with the question, "Financially, would you say you are: comfortable; have more than enough to make ends meet; have enough to make ends meet; or do not have enough to make ends meet?"

Data Analysis

Standard descriptive statistics were used to describe all study covariates at baseline. Independent sample *t*-tests were conducted for continuous variables and chi-squared tests for categorical variables. We assessed whether randomization achieved balance across study covariates between the two study groups for baseline demographic and clinical characteristics. We also measured whether there were any differences in participants who completed the study compared to those who were lost to follow-up (response bias). Gender specific analyses were completed to further explain differences between groups.

We used *t*-tests to assess for change in self-care maintenance and self-care confidence, physical HF symptoms and quality of life between baseline and 90 days within and across groups. We used chi-squared tests for differences in proportions to assess for improvement in self-care management because only a subset of participants was symptomatic and able to respond to these questions. Data analyses were conducted using StataSE 13.1 (College Station, Texas).

For the primary outcome (self-care maintenance) a model comparison approach[48] was applied throughout the model building process starting with covariates associated in bi-variate analyses with the outcome variable (p<0.05); then *a priori* factors were added. Factors that were considered in the models but were not significant and did not contribute to the robustness of the model were removed. The final model for predictors of change in self-care maintenance included the following eight variables: intervention group, general health, sleep apnea, financial status, coronary artery disease, gender, support quality, and

having a home health nurse. These eight variables were adjusted in the main analyses of group differences over time.

Results

The CONSORT diagram **(Figure 6.1)** reflects participants who were screened, enrolled, randomized and included in the analyses for both self-reported and objective outcomes between the two groups. A total of 100 participants were enrolled and 67 completed the study of self-reported outcomes. For these outcomes, including the primary outcome of self-care, the overall attrition rate was 33%, (13% in the usual care group and 42% in the intervention group) consistent with other studies of patients with HF.[49] There were no statistically significant differences in the socio-demographic or clinical characteristics of participants who completed versus did not provide self-reported follow-up data. There were also no statistically significant differences in the self-care, physical HF symptom or quality of life at baseline between those who completed and did not complete the study. Thus, the missing at random assumption was not violated.

Participants in the study had a mean age of 62 years and ranged in age from 23 to 86 years **(Table 6.2)**. This sample of adults was predominantly male (60%) and Black (>50%). This was a fairly low educated group with most having no more than a high school education. Many participants were unemployed or disabled, one-third reported financial distress, and three-quarters reported poor or fair health. Clinically, 30% had ischemic etiology and almost half had systolic HF with a reduced left ventricular ejection fraction (LVEF). Overall, participants in the study were functionally compromised (83.6% NYHA Class III or IV). Participants were also on numerous medications (12 SD

±5.5) and lived with multiple comorbidities (5.5, SD ± 2.8). In terms of support, most

people lived with another person and reported having good or very good support.

Figure 6.1 CONSORT diagram showing participant study flow
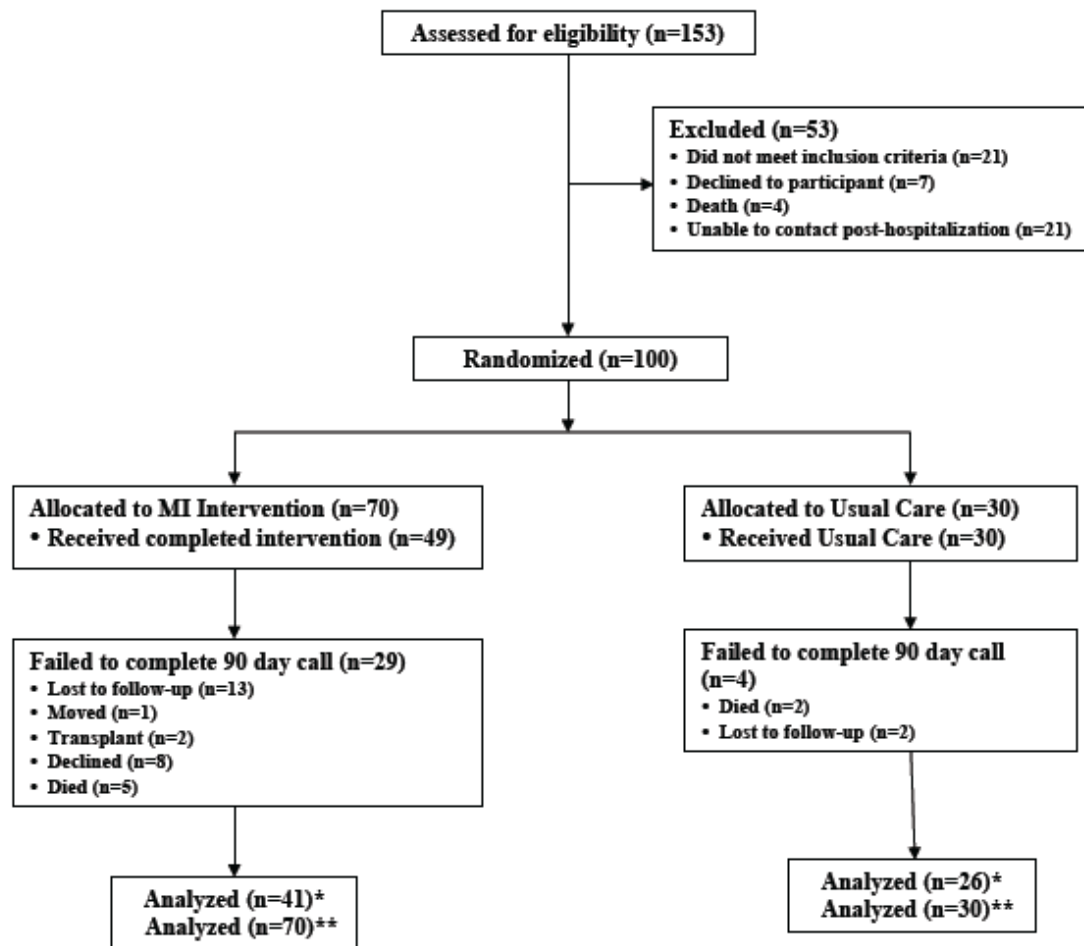
Table 6.2a. Baseline socio-demographic characteristics by randomization group

Variables	Randomization group (mean +/- SD or %)			
	Overall Total (N=67)	**Control** Total (N=26)	**Intervention** Total (N=41)	**p-value**
Age	62 (13.4)	63 (12.6)	60 (13.9)	0.397
Gender				0.130
Female	20 (29.9)	5 (19.3)	15 (36.6)	
Male	47 (70.2)	21 (80.8)	26 (63.4)	
Married/Partnered	31 (46.3)	15 (57.7)	16 (39.0)	0.135
Race				0.128
Black	36 (53.7)	17 (65.4)	19 (46.3)	
White	31 (46.3)	9 (34.6)	22 (53.7)	
Education				0.233
$\leq$High School	42 (62.7)	14 (53.9)	28 (68.3)	
College/Grad School	25 (37.3)	12 (46.2)	13 (31.7)	
Total years education	13 (2.3)	13 (2.2)	13 (2.4)	
Employment Status				0.834
Employed/Retired	32 (47.8)	12 (46.2)	20 (48.8)	
Unemployed/Disabled	35 (52.2)	14 (53.9)	21 (51.2)	
Financial Status				0.435
Comfortable/Enough	45 (67.2)	16 (61.5)	29 (70.7)	
Not enough	22 (32.8)	10 (38.5)	12 (29.3)	
Insurance Type				0.419
Government	50 (74.6)	18 (69.2)	32 (78.1)	
Commercial/HMO	17 (25.4)	8 (30.8)	9 (22.0)	
Health Perception				0.088
Poor/Fair	49 (73.1)	16 (61.5)	33 (80.5)	
Good/Very Good/Excellent	18 (26.9)	10 (38.5)	8 (19.5)	
Health in General				0.746
Worse/Same	37 (55.2)	15 (57.7)	22 (53.7)	
Better/Much Better	30 (44.8)	11 (42.3)	19 (46.3)	
Home Health Nurse	49 (73.1)	18 (69.2)	31 (75.6)	0.566
Provider Specialty				0.292
Medicine/Cardiology	16 (23.9)	8 (30.8)	8 (19.5)	
HF Specialist	51 (76.1)	18 (69.2)	33 (80.5)	
Lives with another	51 (76.1)	21 (80.8)	30 (73.2)	0.477
Support Quality				0.241

Fair/Satisfactory	11 (16.4)	6 (23.1)	5 (12.2)
Good/Very Good	56 (83.6)	20 (76.9)	36 (87.8)
Nurse Interventionist			0.902
Nurse 1	51 (76.1)	20 (76.9)	31 (75.6)
Nurse 2	16 (23.9)	6 (23.1)	10 (24.4)

Table 6.2b. Baseline Clinical Factors by Randomization Group

Variables	Randomization group (mean +/- SD or %)			p-value
	Overall Total (N=67)	Control Total (N=26)	Intervention Total (N=41)	
NYHA Functional Class				0.125
Class I/II	11 (16.4)	2 (7.7)	9 (22.0)	
Class III/IV	56 (83.6)	24 (92.3)	32 (78.1)	
HF Etiology				0.299
Ischemic	20 (29.9)	9 (34.6)	11 (26.8)	
Non-ischemic	31 (46.3)	9 (34.6)	22 (53.7)	
Other	16 (23.9)	8 (30.8)	8 (19.5)	
HF Type				0.478
Systolic	32 (47.8)	10 (38.5)	22 (53.7)	
Diastolic	13 (19.4)	6 (23.1)	7 (17.1)	
Mixed	22 (32.8)	10 (38.5)	12 (29.3)	
Ejection Fraction (%)	35 (16.8)	37 (16.5)	34 (17.2)	0.586
Total comorbidities	5.5 (2.8)	5.4 (3.5)	5.6 (2.4)	0.689
Pacemaker (any type)	21 (31.3)	8 (30.8)	13 (31.7)	0.936
Medications (total)	12 (5.5)	12 (5.6)	12 (5.6)	0.782
Beta Blocker	57 (85.1)	24 (92.3)	33 (80.5)	0.186
Ace Inhibitor	33 (49.3)	11 (42.3)	22 (53.7)	0.365
ARB	7 (10.5)	4 (15.4)	3 (7.3)	0.293
Statin	40 (59.7)	16 (61.5)	24 (58.5)	0.807
Diuretic	59 (88.1)	23 (88.5)	36 (87.8)	0.936
Baseline Lab Values				
Sodium	135.7 (15.6)	137.6 (2.8)	134.5 (19.9)	0.434
Hemoglobin	11.6 (1.9)	11.8 (1.8)	11.4 (1.9)	0.370
Creatinine	1.7 (1.3)	2.0 (1.9)	1.5 (1.3)	0.139
BUN	34.8 (29.0)	30.5 (23.8)	37.6 (31.9)	0.338

Abbreviations:HF: heart failure, NYHA: New York Heart Association, ARB: Angiotensin II Receptor Blockers, BUN:blood urea nitrogen, PE: Pulmonary Embolis, DVT: Deep vein thrombosis, CAD: coronary artery disease , COPD: chronic obstructive pulmonary disease, CV: cardiovascular disease

Self-care Outcomes

Overall, self-care maintenance (mean: 78.5, SD ±12.7) was adequate for the entire sample at 90 days **(Table 6.3)**. Within the intervention group, there was significant improvement in self-care maintenance (p<0.01) over 90 days. Within the usual care group there was also significant improvement in self-care maintenance (p<0.01). However, absolute change in self-care maintenance was greater in the intervention group compared to usual care (12.1 vs 19.7 points, Cohen's d= 0.44). Though the effect size was moderate, the difference between groups was not initially statistically significant. After adjusting for gender, general health, sleep apnea, financial status, coronary artery disease, support quality and having a home-care nurse, there was a statistically and clinically significant 8.9 point increase (95% CI: 1.0 -16.7) in the MI group compared to the usual care group (p=0.03) at 90 days.

Overall, at baseline, 6.0% of the sample was asymptomatic and thus unable to complete the self-care management scale (3.9% in the usual care group and 7.3% in the intervention group; p=0.56). At follow-up, 32.8% of the sample was asymptomatic, but there was no difference between the groups in achieving asymptomatic status (p=0.44). In the intervention group 90% improved in self-care management and in the usual care group 73% improved in self-care management (p=0.07).

In both groups self-care confidence improved more than 20 points (p<0.001) **(Table 6.3)**. There were no statistically significant differences in improvement in self-care confidence between the two study groups (p=0.31), although the absolute change in

self-care confidence was higher in the intervention compared to usual care group (26 vs 21 points, Cohen's d=0.26).

Physical HF symptoms, clinical summary score and quality of life

At baseline the mean score on the HFSPS, the measure of physical HF symptoms, was 19.9 (SD ± 19.4). At 90 days the mean HFSPS was 17.9 (SD ± 18.06) with no differences between (p=0.63) or within groups (MI: p=0.29; usual care: p=0.83). The mean score for men in the MI group decreased 7 points (95% CI: 0.58 to 13.50; p= 0.03) —indicating symptom improvement. There were no differences in the usual care group for men or for women in either group.

The mean KCCQ clinical summary score at baseline was 56.1 ±24.6 **(Table 3).** The within group change over 90 days was significant (p=0.01) although the mean change of 10.3 points between baseline and follow-up was not different between the groups (p=0.67).

Table 6.3. Self-care at Baseline and 90-days follow-up for participants in the usual care or Motivational Interviewing Groups

Variable	Intervention mean (SD)	Usual care, , mean (SD)	t-value (p)[c]
Self-care maintenance			
Baseline	59.9 (16.3)	64.7 (16.9)	1.2 (0.250)
90-days	79.6 (11.5)	76.8 (14.5)	-0.9 (0.383)
Absolute change	19.7 (16.0) [a]	12.1 (18.3) [a]	-1.8 (0.077)
Self-care management			
Baseline	50.1 (26.3)	56.7 (26.5)	1.0 (0.321)
90-days	48.4 (37.1) [b]	41.2 (38.1)	-0.8 (0.442)
Absolute change	1.7 (39.9)	15.6 (48.0)	-0.6 (0.564)
Self-care confidence			
Baseline	54.6 (22.2)	61.4 (18.5)	1.3 (0.204)
90-days	81.2 (18.0)	83.0 (16.3)	0.4 (0.690)
Absolute change	26.6 (20.8) [a]	21.6 (16.8) [a]	-1.0 (0.309)
KCCQ QOL			
Baseline	50.81 (29.27)	60.25 (28.01)	1.3 (0.196)
90-days	61.59 (26.67)	65.06 (28.48)	0.5 (0.614)
Absolute change	10.77 (28.15)	4.81 (21.37)	-0.9 (0.359)
KCCQ CSS			
Baseline	54.60 (24.49)	58.50 (25.12)	0.6 (0.531)
90-days	63.94 (24.82)	69.41 (23.89)	0.9 (0.382)
Absolute change	9.34 (23.91)	11.86 (20.86)	0.4 (0.665)
HFSPS Total Score			
Baseline	21.56 (19.23)	17.31 (19.65)	-0.9 (0.385)
90-days	18.76 (17.28)	16.58 (19.52)	-0.5 (0.634)
Absolute change	-2.81 (16.79)	-0.73 (17.14)	0.5 (0.627)

[a]: significant improvement (p<0.01) from baseline to 90-days by paired t-tests
[b]: N=41= because the follow-up score was not recorded for people who were asymptomatic at 90 days (n=26)
[c] p-values are for differences between group t-tests

    The combined mean KCCQ quality of life score for all participants was 54.5 (SD ± 29.0)

at baseline and 62.93 (SD ±27.2) at follow-up **(Table 6.3)**. The absolute change in quality of life

of 10.7 points from baseline to 90 days within the MI group was statistically significant (p=0.02)

compared to the change of 4.8 points in the usual care group (p=0.26) but the difference in quality

of life between groups was not significantly different (p=0.36) at 90 days. In a specific gender analysis, men within the MI group had an improvement of 12 points ±31.46 (p=0.05) in quality of life, while there were no significant differences for men in the usual care group or for women in either group.

Discussion

The results of this randomized controlled trial designed to test the efficacy of a MI intervention shows that using a MI approach improved self-care maintenance in this sample of adults with HF. Further, there was evidence of a trend in improved self-care management. These results support our earlier conclusion that motivating people with HF to take more control over their health with self-care can help them achieve optimal health outcomes.[50]

The finding that the MI intervention improved self-care maintenance is consistent with others who have used MI as a tool to improve physical activity in various patient populations living with chronic illness, including older adults with HF,[51] chronic obstructive pulmonary disease (COPD),[52] fibromyalgia[53] and chronic pain.[54,55] More specifically, MI is currently being tested to improve patient engagement and motivation for self-management in patients with COPD,[52] as a management strategy to sustain the clinical benefits of exercise for fibromyalgia[53] and to improve disability, pain intensity, (pain-specific) self-efficacy, motivation, and quality of life for people with chronic musculoskeletal pain.[55] Tse and colleagues also reported improved change scores for quality of life, self-efficacy, physical and psychological function and compliance with

exercise in a group receiving MI with a physical exercise intervention compared to a usual care group.[54]

In MITI-HF, quality of life improved in both study groups over 90 days; however, there were no statistically significant differences between groups. Brodie and colleagues also reported improvement in quality of life over 5 months after being in the MI physical activity intervention.[13] One of the reasons for the differences between MITI-HF and the Brodie study may be due to the use of different quality of life measurement tools. They used the Medical Outcomes Short Form-36 Health Survey and the Minnesota Living with Heart Failure questionnaire while we used the KCCQ in MITI-HF. The Brodie study also had a longer follow-up period. In addition, physical activity is known to improve quality of life[14] whereas in MITI-HF participants chose a variety of behavior changes, some of which are associated with a decrease in socialization options—including maintaining a low sodium diet—which may negatively impact quality of life. Beckie and colleagues also designed a study to promote healthy behavior change for women with coronary heart disease using MI and they reported improvement in global quality of life in the MI compared to usual care group.[56,57] Differences in study results between MITI-HF and the Beckie randomized controlled trial may be due to the fact that the Beckie study was powered to detect changes in quality of life (the sample size was much larger (n=225)). In addition, the intervention was much longer (6-months), more intensive (three, 60-min in-person MI sessions and 10 weeks of psychoeducational sessions) and gender-specific. The patient-population was also less sick than the MITI-HF sample of patients with HF. The quality of life measures in the two studies were also different. Beckie et al. used Multiple Discrepancies Theory and Self-Anchoring Striving Scale questionnaires to

measure quality of life compared to the KCCQ used in MITI-HF. It is also possible that in a functionally compromised population of patients with severe HF that there is a ceiling effect of how much quality of life can improve over time due to the impact of worsening of disease severity.

In MITI-HF, the MI intervention did not improve participant's self-care confidence (self-efficacy) over time compared with usual care. In contrast, there is early evidence from a study by Paradis and colleagues that reports improvement in self-efficacy using an MI approach in patients with HF.[58] In the Paradis study, patients received a similar dose of MI from a nurse (one face-to-face MI intervention followed up by two telephone conversations) and yet there was no improvement in self-care maintenance but there was improvement in self-care confidence over 1-month. Differences in study design between the two studies may explain the differences in self-care outcomes, including length of patient follow-up (30 versus 90 days) and at least one or two more follow-up MI phone calls in MITI-HF by the nurse.

MI has also been tested in other chronic disease patient populations to improve self-efficacy and clinical outcomes such as weight reduction in obese youth[59] and physical activity in aging adults.[60] In the Walpole study with obese youth, there were no statistically significant differences between the MI and social skills training groups for improvement in weight loss or self-efficacy; however, participants in both groups showed significant increases in self-efficacy and a trend of decreased body mass index z-scores.[59] Lilienthal and colleagues did a telephone-based MI intervention to increase physical activity and self-efficacy in aging adults.[60] The MI group reported higher self-efficacy for

physical activity at six months follow-up.[60] Once again, differences in the study results between MITI-HF and the Lilienthal study may be due to differences in disease severity between patient populations (those in MITI-HF study were much more functionally and physically compromised) and a longer follow-up period in the Lilienthal study (90 days versus 6 months).

Strengths/Limitations

Strengths of this study include minority participation (over 50%), with women well represented. One limitation was that objective measures of self-care behaviors (e.g. pedometer for exercise) were not used in this study. The largest limitation was the loss of participants to follow-up and specifically the difference in attrition for the self-reported outcomes between the usual care and MI group. One of the proposed reasons for differential dropout was that the MI group had at least 60% more points of contact than the usual care group, thus increasing opportunities for dropout.

Conclusions

MI is a successful approach for improving self-care maintenance for patients with HF. Future studies should consider using a MI approach to improve self-care.

Acknowledgments

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CH VII-SUMMARY AND CONCLUSIONS

Introduction

Patient outcomes related to heart failure (HF) continue to be poor, including high hospitalization rates, early death, exorbitant costs, intractable symptoms, and low quality of life (QOL).[1-4] To improve patient outcomes, better management strategies that incorporate optimized medical therapy with effective self-care are critical.[5-7] This body of work addressed several critical elements of HF self-care. The Situation Specific Theory of Heart Failure Self-Care was used to frame these studies.[8] This theory conceptualizes HF self-care as having two core components, choosing positive routine health practices ('self-care maintenance') and making decisions around the management of signs and symptoms of HF when they occur ('self-care management').[8,9]

The primary purpose of this body of work was to strengthen the evidence base for self-care by studying two understudied aspects of HF self-care maintenance—consuming a low-sodium diet and exercising. The secondary purpose was to test the efficacy of a tailored motivational interviewing (MI) approach to improve self-care, QOL, physical HF symptoms and clinical outcomes. The aims of these studies were to: 1) identify predictors of high sodium intake, 2) identify distinct biomarker patterns and predictors of worst biomarker patterns in response to exercise, and 3) test the efficacy of MI to improve HF self-care. This final chapter provides a summary and discussion of each study aim and concludes with recommendations for future research and implications for clinical practice.

Summary and Discussion of Principal Findings

Predictors and patterns of high sodium excretion using multiple analytic methods

The first aim was to identify predictors of high sodium consumption over time in patients with HF (Ch. II). The principal findings are summarized in **Table 7.1**. In brief, three factors were associated with excess sodium consumption, two of which, obesity and diabetes mellitus, are modifiable by changing dietary food patterns. The study reported in Ch. III is an extension of Ch II. Instead of setting *a priori* sodium levels based on Heart Failure Society of America (HFSA) guidelines,[10] naturally-occurring patterns of sodium intake were driven by the study data. Two patterns of sodium consumption were identified using growth mixture modeling (GMM), one that was much higher than recommended (>4.4 g/day) and the other that was broadly adherent (2.4 g/day) with current Institute of Medicine (IOM) recommendations.[11] In this study, the predictors of high sodium consumption were: 1) obesity, 2) diabetes mellitus and 3) younger age (< 65 years). These two studies provide a framework for targeting specific HF populations with nutritional counseling and guidance.

Table 7.1 Principal Findings: Specific Aim 1

Specific Aim 1: Identifying predictors and patterns of high sodium intake using multiple analytic methods	
Studies	**Principal Findings**
Identifying predictors of higher than recommended sodium intake in HF patients using a mixed effect logistic analysis of longitudinal data	The adjusted odds of higher sodium excretion were higher for patients who were obese, had diabetes and for patients who were cognitively intact.
Identifying subgroups of sodium adherence in adults with HF	Two distinct patterns of sodium intake were identified in patients with HF using GMM. Being overweight and obese, less than 65 years of age or having diabetes mellitus were associated with a 4-fold incremental

increase in the likelihood of being in the higher than
recommended pattern of urine sodium.

In addition to taking medications as prescribed, dietary sodium restriction is the
most common self-care behavior recommended for patients with HF.[12-14] As such, these
studies are an important contribution to the literature because they demonstrate that
patients with HF are consuming higher sodium intake than recommended and that
specific patient characteristics are associated with sodium consumption that is almost
double the recommended intake. Excess sodium consumption may be exacerbating
symptoms of HF and putting patients at higher risk for hospitalization and death.[15]

The topic of sodium restriction has come under intense debate following
conflicting reports about sodium restriction being either beneficial or harmful.[16] Some
observational studies report an association between a lower sodium diet and improved HF
outcomes.[15,17,18] Other studies report different results based on NYHA severity.[18,19]
Lennie and colleagues were the first to report differential event risk by HF severity based
on sodium intake.[19] Patients with NYHA class III/IV were more likely to be
rehospitalized if they consumed ≥ 3g/day of dietary sodium, and patients with NYHA I/II
were more likely to be hospitalized if sodium intake was < 3 g/day.[19] Similarly, Song and
colleagues reported differential event-free survival for patients with mild compared to
severe HF in response to three categories of sodium intake.[20] They found that sodium
restriction < 2 g/day was associated with higher event risk for patients with NYHA Class
I/II and lower event risk for patients with NYHA Class III/IV.[20] In another observational
cohort study by Pfister and colleagues, they reported a U-shaped association between
urine sodium excretion and risk of HF from the EPIC-Norfolk study.[21]

In contrast, the results of some RCTs indicate that dietary sodium restriction may actually cause harm.[22-24] Paterna and colleagues enrolled 232 patients with HF (New York Heart Association (NYHA) class II-IV, 55-83 years of age, ejection fraction < 35% and serum creatinine < 2 mg/dl).[23] Thirty-days after discharge, participants were randomized to a diet of either 1.8 or 2.8g of sodium per day. In addition, the study protocol included 250-500mg of furosemide twice daily and a 1-L fluid restriction. After 180 days the 2.8g sodium diet was associated with reduced admissions and lower mortality and the 1.8g sodium diet was associated with worse renal function.[23] These study results were repeated in a larger sample.[24] Another study also suggested that severe sodium restriction is harmful in patients with reduced ejection fraction.[22] Two limitations of these findings were that all studies came from the same group in a localized region in Italy and the results have not been replicated elsewhere. Due to the controversy between the observational and randomized studies, the Institute of Medicine (IOM) examined the evidence and now recommends a diet of no more than 2300 mg of sodium per day for all adult Americans, including those with comorbidities who were previously singled out as needing lower sodium thresholds (ie: diabetes mellitus and HF).[11]

While controversy has waged about the lower threshold of sodium consumption, the reality is that most patients with HF consume far more than the maximum recommended amount. The mean urine sodium excretion for the entire sample reported in Chapters II & III ranged from 2770 mg/d (1750-3950 mg/d) at baseline to 2780 mg/d (1900-3790 mg/d) at six months.[25] These values are consistent with other studies that report a mean consumption of 2671 mg/d[26] and 3190 mg/d of sodium.[27] The IOM's cut-off of no more than 2300 mg/d is lower than any of the means reported in these studies of

patients with HF. Given the context that the average adult American consumes

approximately 3,400 mg of sodium per day[28] and that most patients with HF consume

more than the maximum recommended guidelines, the messaging to patients with HF

should be consistent--it is still a priority to consume a low-sodium diet.

Successfully advocating for sodium restriction will take a multi-faceted approach,

including policy advocacy to reduce sodium in processed foods, consumer education and

behavior change. Arcand and colleagues provide a good example of how to navigate the

common lack of awareness about food sodium content in patients with HF by developing

a Web-based sodium intake screening tool called the Salt Calculator, in which individuals

can quantify their sodium intake.[29] In the future, genomic studies may also be able to

guide personalized sodium intake based on anthropomorphic measures.[30]

The strengths of the studies reported in Chapters II and III are that they both used

repeated measures of sodium excretion on the same individuals over a six-month period.

The study reported in Ch II also used robust and transparent imputation methods to

address potential bias from incomplete data. A limitation of the study reported in Ch II

was the selection of a binary cut-point for adherence to dietary recommendations based

on NYHA functional class scores published by the HFSA.[10] In retrospect, this was an

overly restrictive cut-point that allowed for simple associations, but did not allow more

granular detail and analysis of sodium consumption patterns. One of the strengths of the

study reported in Ch III was that due to the use of GMM, the patterns of sodium intake

(or self-care maintenance) could vary naturalistically.

The primary limitation of the studies reported in Chapters II and III is the measurement of sodium intake using a 24-hour urine sodium collection. There have been doubts about the validity of 24-hour urine sodium collection for patients with HF on evidence-based pharmacotherapy, specifically diuretic medications, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and aldosterone antagonists.[31,32] In addition, 24-hour urine sodium collection is limited in that it only captures sodium intake over 24 hours rather than over a longer time frame. There are also limitations of self-reported sodium intake, including reports that it is not reliable among patients with HF.[33] In general, following a low sodium diet is often interpreted by patients as not using salt for cooking, rather than reducing the consumption of high-sodium canned, frozen or take-away food.[33] Food diaries can also be subject to recall bias and the impact of social desirability.[34] Overall, despite the limitations of a 24-hour urine sodium collection, it is still considered the gold standard for an objective measure of sodium intake even for patients with HF on diuretics.[35]

While it is clear that very high sodium intake is not recommended for healthy adults or patients with HF, it is still not clear: (1) what the lowest and safest range of sodium intake is, (2) whether recommendations can be general or if they should be tailored to individuals or targeted to specific sub-groups, and (3) what the most reliable and valid approach is to measuring dietary sodium.[30] Changes in policy should focus on reducing excess sodium across the food environment so that consumers have more choice in how much sodium is in their food,[36] as well as raising consumer knowledge to identify and avoid high sodium foods.

Self-care maintenance: exercise and biomarkers

The second aim was to identify common and distinct patterns of change in serum

biomarkers of inflammation and myocardial stress and quantify the influence of exercise

therapy on patterns of change in a community-based sample of patients with HF. To

address this aim, an analysis was conducted with data from the Heart Failure: A

Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) RCT. The

principal findings are detailed in **Table 7.2**.

Table 7.2 Principal Findings: Specific Aim 2

Specific Aim 2: The primary aim was to identify common and distinct patterns of change in serum biomarkers of high-sensitivity C-reactive protein (hsCRP) and N-terminal pro b-type natriuretic (NT-proBNP) and quantify the influence of exercise therapy on the patterns of change.
Principal Findings
1. Three statistically independent and clinically meaningful biomarker patterns of NTproBNP and hsCRP were identified and titled: "lowest and improving," "elevated and stable," and "elevated and worsening."
2. Participants randomized to the exercise intervention were 75% less likely to have the *elevated/worsening* pattern of NT-proBNP and hsCRP

The sample of patients with HF in this sample were relatively young (58 years),

the majority were male (73%) with NYHA class II (71%). In this relatively high

functioning sample of patients with HF enrolled in an RCT, three distinct biomarker

patterns of inflammation and myocardial stress were identified. The most common

pattern, *"lowest/improving"* (61% of the sample), was the most favorable pattern because

it was characterized by the lowest levels of NT-proBNP and hsCRP at baseline and both

biomarkers declined over 12-months. The second pattern was labeled *"elevated/stable"*

(34% of the sample) and it was characterized by higher hsCRP and similar NT-proBNP

to the *lowest/improving* pattern. The third pattern *"elevated/worsening"* was the smallest,

but most deleterious, (5% of the sample) characterized by the highest levels of NT-proBNP and increasing hsCRP over 12-months.

Exercise was a protective factor for worse intermediary physiologic outcomes in patients with HF. Participants who were enrolled in the exercise intervention were much less likely (77%) to be in the *elevated/worsening* or *elevated/stable* pattern (47%). Overall, exercise therapy has been advocated for patients with HF to improve functional capacity[37] and clinical outcomes.[38] Moderate exercise is associated with a decreased risk of clinical events.[39] The results of this study support the benefits of exercise therapy as being protective and contributing to slowing the progression of HF. Some of the mechanisms for the protective effect of exercise may be improving myocardial contractility, perfusion, endothelial dysfunction,[40,41] angiogenesis,[42] and coronary and peripheral skeletal vessel dilation.[43]

The reported protective effect of exercise is particularly relevant in the context of the recent decision by the Centers for Medicare & Medicaid Services to reimburse cardiac rehabilitation for patients with stable, chronic HF.[44] Now that cardiac rehabilitation is reimbursable, there is a push for it to include broader self-care counseling to improve education and skills around medication compliance and monitoring/managing body weight.[45] Because the benefits of exercise are limited by patient adherence, tailored approaches to engage patients are critical for any improvement or benefit from exercise. In addition, system-wide support should be put in place to get patients referred to cardiac rehabilitation.[45]

Motivational Interviewing Tailored Intervention for Heart Failure (MITI-HF)

The third aim of this body of work was to integrate the previous two aims into a

pilot RCT. Taking what was learned from Chapters II-IV we designed MITI-HF to test

the comparative efficacy of a tailored MI intervention in improving HF self-care

behaviors, physical HF symptoms, and QOL. The principal finding of MITI-HF was that

the MI intervention improved the primary outcome of self-care maintenance over and

above usual care even after controlling for demographic, clinical and health service

factors **(Table 7.3)**.

Table 7.3 Principal Findings: Specific Aim 3

Specific Aim 3: Implement and evaluate MITI-HF for its impacts on HF self-care over 90 days. Examine the impact of MITI-HF on secondary outcomes of physical HF symptoms and health related quality of life over 90 days.
Principal Findings
1. MI was a successful approach for improving self-care maintenance. Participants in the MI group had statistical and clinical improvements in self-care maintenance compared to the usual care group.
2. There were no differences between the two study groups for self-care management, self-care confidence, QOL or physical HF symptoms and response.

The results of MITI-HF demonstrated that a tailored MI intervention improved

self-care maintenance in a sample of adults with HF. The study sample was

predominantly Black; participants had multiple comorbid conditions and most were

functionally compromised. At baseline the overall mean self-care maintenance score for

this sample was adequate. At 90 days, there was significant improvement in self-care

maintenance (p<0.01) in both groups; however, the absolute change was greater in the

intervention compared to the control group. After adjusting for gender, general health,

sleep apnea, financial status, coronary artery disease, support quality and having a home-

care nurse, there was a statistically and clinically significant 8.9 point[46] increase in self-care maintenance in the MI group compared to the usual care group. These results suggest that motivating people with HF to take more control over their health with self-care can help them achieve optimal health outcomes.[13]

A variety of educational approaches have been designed to improve self-care in patients with HF and results have been mixed.[47-53] Albert and colleagues reported improved self-care management behaviors and higher self-care scores (over 3-months) in response to a video, which could be watched at home repeatedly over 3-months.[50] In contrast, another intervention using remote patient education through a TV-channel found no differences in self-care behaviors over 288 days.[51] Caldwell and colleagues tested a simplified education intervention in a small sample of rural patients and found that daily weighting was the only self-care behavior that improved over 3-months.[52] Similarly, Baker and colleagues tested a telephone education/counseling versus single-education intervention and found that the "teach to goal" educational and behavioral support program provided benefit for self-care behaviors (irrespective of literacy levels).[47] Another study by Clark and colleagues also used an education support model and found that it improved several health status and self-care outcomes, including functional status, self-efficacy and self-care.[49] Overall, there has been substantial heterogeneity in study results of educational interventions on self-care outcomes.

Using skill-building rather than an educational approach, Dickson and colleagues found that a community-based tactical and situational HF self-care skill development delivered by lay health educators in community senior centers improved patients HF self-

care and knowledge but not health-related QOL.[54] The findings from the Dickson and colleague study are similar to MITI-HF, which reported improved self-care outcomes but not QOL at 90 days.

MI has been used to improve self-care behaviors, including physical activity, in older adults with HF.[55] Tse and colleagues have used MI to improve physical and psychological function and compliance with exercise.[56] MI has also shown promise for improving self-care in other chronic diseases, including chronic obstructive pulmonary disease (COPD),[57] fibromyalgia[58] and chronic pain.[56,59] MITI-HF built off a smaller pilot study results by Riegel and colleagues that found 71% of participants reported improved self-care in response to a MI intervention.[60] Now MITI-HF is one of the larger studies to date to specifically use MI to improve self-care in patients with HF. Philosophically, MI is a promising approach to improve self-care because it is consistent with the underlying value of self-are that patients should be pro-actively involved in the maintenance and management of their own health and prevention of disease.

Given the challenge of enrolling Blacks in RCTs,[61] a major strength of MITI-HF is that it is generalizable to a population that has a high prevalence of HF[62] and is under-represented in HF research.[63,64] In a mixed-methods study of 30 patients with HF, Dickson and colleagues described themes that self-care is highly influenced by cultural beliefs, such as HF being inevitable, attributed to stress and spirituality. Some self-care maintenance behaviors were well supported by cultural beliefs (medication adherence) whereas cultural preferences for specific foods were often not consistent with a low-

sodium diet.[65] Overall, there is a dearth of studies that test self-care interventions specifically among Blacks.

One of the biggest challenges of MITI-HF was patient follow-up and assessment of self-care outcomes. At the baseline phone call (post-hospitalization), 52 participants were excluded from MITI-HF. Almost half were excluded because they were unable to be contacted post-hospitalization, despite having contact information for the participant and close relatives. Inability to contact participants was apparently due to lack of continuity of housing, changing geographic locations and shifting support structures that many of these patients face. In part due to this challenge of follow-up, there was a lack of statistical power to detect changes in the secondary outcomes.

During the baseline phone call, 14% of patients were excluded prior to baseline data collection due to cognitive impairment. This was an unanticipated study limitation because severe cognitive impairment had been screened for using the 6-item screener[66] in the hospital. Participants had passed the six-item screener and yet at baseline did not remember enrolling in the study. We characterized this as evidence of mild cognitive impairment and participants were screened out of the study prior to any data collection. In retrospect, the Montreal Cognitive Assessment (MoCA) would have been a better cognitive screening tool. It is more sensitive and specific to mild cognitive impairment and mild Alzheimer's disease than the Mini-Mental State Exam (MMSE).[67] According to the results of MITI-HF and other studies of patients with HF,[68,69] good screening for cognitive impairment is important for the early identification of patients who may benefit from a tailored disease management program.

Cognitive impairment is highly prevalent among older patients hospitalized for HF; estimates range from 25-50% of patients.[70] This is consistent with estimates that 15% of patients with HF have dementia and 24% have mild cognitive impairment.[71] A recent systematic review reports that patients with mild cognitive impairment have problems performing self-care.[68,72] Further research is needed on how cognitive impairment specifically affects the ability to sustain attention, concentration, memory capacity, motor speed and capacity to engage in executive functioning (problem solving and abstract reasoning). Future research is also needed on strategies for engaging patients with HF and cognitive impairment in better self-care because cognitive impairment has serious implications for self-care,[73] including being a mediator for the effect of poor physical fitness on decreased functional independence in HF.[74]

Another study limitation of MITI-HF was that objective measures of self-care outcomes were not included. Including a 6-minute walk test for physical activity and a food diary or 24-hour urine sodium excretion for adherence to a lower sodium diet would have strengthened the study. The primary outcome, self-care maintenance, was limited as a self-report process outcome. The next step for this research, is having a fully powered study to detect statistically significant differences between groups for clinical and health status outcomes. In this study, although patient-reported outcomes such as physical HF symptoms and QOL were measured, the study was not adequately powered to detect less than very large changes in these measures over time.

Other study limitations include only two data collection points, limited follow-up timeframe (90 days) and differential attrition for self-care outcomes between the study

groups. More data collection points and a longer follow-up period would have allowed for non-linear assumptions of longitudinal data over time. At the same time, longer follow-up and more data points may have increased drop-out and missing data, which was already the largest limitation of the study.

In a follow-up study to MITI-HF in Rome, Italy by Vellone and colleagues, an additional study group is being added to include only HF patient informal caregivers. According to a recent systematic review, informal caregivers play an important role for patients with HF, assisting patients with both concrete and interpersonal activities.[75] Results from a cross-sectional study indicate that having family member accompaniment to routine medical visits is associated with higher self-care maintenance and management.[76] The impact of a patient-family partnership was tested in the Education and Support Interventions to Improve Self-Care [ENSPIRE] study. The intervention group of dyads received an intervention focused on dietary sodium intake and medical adherence by a master's-prepared research nurse trained in the study protocol.[27] Dietary sodium intake improved in the intervention groups compared to usual care, but medication adherence did not improve.[27] Another study by Vellone and colleagues sought to describe the manner in which QOL and self-care vary within a couple dealing with chronic HF.[77] Higher self-care maintenance (measured with the SCHFI 6.2) was associated with higher caregiver QOL.[77] These results are consistent with MITI-HF, in which better support quality was one of the strongest predictors of improvement in self-care maintenance (Beta Coefficient: 11.5, 95% CI: 1.3, 21.6, p= 0.028). While the involvement of caregivers, especially spousal caregivers, is ideal; some patients do not have that level of caregiving support. In a study with veterans receiving care at a Veteran

Affairs Medical Center, veterans reported that having an advocate—a member of the healthcare team, friends or family, helped them optimize their self-care management.[78] Given the challenge of cognitive impairment and the impact on caregivers, it is an important contribution to the literature that the MITI-HF follow-up study will include caregivers in the intervention and caregiver outcome data.

Summary

Overall, the results of this body of work are a significant contribution to the literature on HF self-care maintenance. There is now evidence that: 1) many patients with HF consume a high sodium diet; 2) modifiable predictors of consuming a high sodium diet include being obese or overweight and having diabetes; 3) non-modifiable predictors include younger age (< 65 years); 4) exercise was protective for being in the worst biomarker pattern of inflammation and myocardial stress; 5) a tailored MI intervention was feasible for patients with HF and improved patients' self-care maintenance. This body of work answered a number of research questions using biomarker data and multiple methodologies. This work also combined existing secondary data analyses with the collection of primary data to further develop the evidence base for self-care maintenance.

The results from the studies reported in this body of work indicate that many patients with HF experience a wide range of potential vulnerabilities (ie: financial, place of residence, health, age, functional status, developmental, ability to communicate effectively, race, ethnicity and gender) in addition to a lack of social and cognitive resources needed to successfully manage their health. Many patients also live with

multiple chronic illnesses. In the context of competing priorities, patients may need support to identify how to prioritize and make choices that optimize their health and wellness.

The GMM analytic approach was a strength of the studies reported in both Chapters III & IV. The use of GMM in Ch IV allowed for the identification of previously unobserved biomarker patterns of change in an existing dataset of patients with HF. GMM holds future potential as an analytic tool for helping to explain heterogeneity in response to many self-care behaviors that are common among patients with HF. To date, the GMM methodology has been used by other researchers to identify patterns of self-care management and changes in QOL,[79] profiles of self-care management versus consulting behaviors,[80] patterns of cognitive change in HF,[81] and patterns of medication adherence.[82]

One of the challenges of using GMM is that relative to other statistical methodologies, it is relatively new (though it has been used for the past twenty years)[83-85] and it takes time for methodological innovation to reach mainstream acceptance. The feedback from a primarily clinical audience has been skepticism and concern about why multiple biomarkers would be analyzed simultaneously or why these methods were implemented instead of linear modeling. Just as there is a long lag between getting research findings into clinical practice,[86] the same is true for methodological innovation.

Despite that limitation, there are multiple opportunities to use GMM in the future to identify specific archetypes or models of vulnerability in patients with HF. The first step will be a detailed systematic review and meta-analyses of existing literature to

statistically synthesize the effects of socio-demographic, environmental, clinical, symptom and behavioral factors on poor HF outcomes, and generate robust theoretico-empirical archetypes of vulnerability.[87] Archetypes of vulnerability can be characterized in a multicenter bio-behavioral research database containing socio-demographic, environmental, clinical, symptom, behavioral, QOL and clinical outcomes and tested in a large national dataset.

Recommendations for Future Research

The focus of this research is consistent with the mission of the National Institute of Nursing Research (NINR), which is to support research on the science of health, focused on the promotion of health and improving quality of life by managing symptoms and enhancing innovation in science and practice. NINR is focused on supporting research that: 1) develops informatics-based solutions to promote health; 2) develops and creatively applies new and existing knowledge to the implementation of health information technology, including electronic health records; 3) expands knowledge and application of health care technologies to facilitate decision support, self-management, and access to health care.[88]

Further development of informatics-based solutions to promote self-care in vulnerable populations, especially those with cognitive impairment, multiple chronic co-morbidities and other vulnerabilities is critical. This issue was highlighted in MITI-HF, where patient follow-up was a major challenge, primarily for people with cognitive impairment. Being able to collect data with a simple mobile health application (app) [89,90] may have helped to decrease study attrition. Sending text-reminders or simple email

prompts instead of calling someone on the telephone may have reduced that barrier to engagement.

There is also scope for improving remote monitoring systems and being able to more efficiently follow-up with vulnerable patients and improve patient-oriented outcomes. The effectiveness of telemonitoring to improve clinical outcomes (readmission for any reason or death from any cause within 180 days) for patients with HF was refuted in a large trial reported by Chaudhry and colleagues;[91] however, remote monitoring has successfully been used to engage patients with HF in more intense self-care.[92] Evangelista and colleagues found that after 3-months, patients who had transmitted their weight and blood pressure through the remote monitoring system had improved activation, self-care, and QOL.[92]

Likewise, in an effort to build better preventative services for Canadian patients with HF, Nolan and colleagues are testing a Canadian e-platform to provide counseling to facilitate adherence to self-care among patients with HF (ClinicalTrials.gov NCT01864369).[93] In vulnerable populations with multiple competing chronic illnesses, the use of technology for follow-up monitoring and prompts is one avenue to promote and advance research.

In future studies, I hope to utilize mobile apps for collecting data and smart phones with biological sensors to capture real-time data from vulnerable patients with HF who are also living with multiple chronic illnesses including cognitive impairment. Despite broad access to smart phone technology, there is still a digital divide by age and income.[94] Overall, 58% of adult Americans have a smart phone and the prevalence is

highest among African-Americans (59%) and Hispanics (61%). People over 65 years have less access to a smart phone (19%) compared to 83% of people ages 18-29 years. There are also discrepancies by income, 47% for people earning < $30,000/yr and 81% for people earning >$75,000/yr.[95] Future clinical research should harness the widespread use of smart phone technology for patient follow-up and address the limitations of health and technological literacy.

To stay at the cutting edge, I believe that it is imperative to develop interventions that are responsive to patients needs in real-time. Future collaboration with computer science and bio-engineers to develop sensors that can monitor hemodynamic congestion, fatigue and dyspnea is critical. In addition, using electronic patient records for follow-up on patient bio-markers and pairing follow-up data collection with clinical follow-up appointments will make it more convenient for patients and less time-intensive for research assistants. Collaboration with health economists for cost-effectiveness analyses of interventions is also critical. For instance, the cost-effectiveness of a specific mobile application designed to promote cardiac self-care among patients with heart disease in Leon and Castille, Spain has been conducted and estimated to reduce costs and treatment of cardiac diseases by one-third.[96]

Future research is needed on the decision making process and how to use tools to measure successful decision-making and outcomes to either reinforce or provide feedback for better decision-making. In the next era of genetics based personalized medication regimes, there is also scope for personalized bio-behavioral interventions because responses to interventions are often as disparate as responses to medications.

Recommendations for Clinical Practice

Many clinicians believe that patients with HF who take care of themselves will have better clinical and patient-oriented outcomes. While educating and promoting self-care is assumed to be part of discharge teaching and disease management programs,[97] it is usually rushed and abbreviated compared to what patients need. Health providers seldom have the time to adequately evaluate a patient's self-care skills and barriers to improvement. Results from this body of work support fostering self-care practices using the principals of MI, particularly in the home where self-care practices can be contextualized to the patient's natural environment.

In addition, this body of work supports the use of targeting more vulnerable groups of patients with nutritional support and counseling. For instance, younger patients, those who are obese and have diabetes mellitus are high risk for consuming sodium levels that are almost double the recommended values. Clinicians can use these data to support more targeted interventions for patients with these clinical characteristics in order to ensure that the patients understand the risks of high sodium consumption and how to quantify how much sodium they are consuming.

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