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Medication Adherence Mediates the Relationship Between Heart Failure Symptoms and Cardiac Event-Free Survival in Patients with Heart Failure

Jia-Rong Wu, PhD, RN[a] and **Debra K. Moser, PhD, RN**[b,c]

[a]University of North Carolina at Chapel Hill, School of Nursing, Chapel Hill, NC

[b]University of Kentucky, College of Nursing, Lexington, KY

Abstract

BACKGROUND—Heart failure (HF) symptoms such as dyspnea are common and may precipitate hospitalization. Medication nonadherence is presumed to be associated with symptom exacerbations, yet how HF symptoms, medication adherence, and hospitalization/death are related remains unclear.

OBJECTIVE—To explore the relationships among HF symptoms, medication adherence, and cardiac event-free survival in patients with HF.

METHODS—At baseline, patients' demographic, clinical data, and HF symptoms were collected in 219 patients with HF. Medication adherence was monitored using the Medication Event Monitoring System. Patients were followed for up to 3½ years to collect hospitalization and survival data. Logistic regression and survival analyses were used for analyses.

RESULTS—Patients reporting dyspnea or ankle swelling were more likely to have poor medication adherence (p=.05). Poor medication adherence was associated with worse cardiac event-free survival (p=.006). In Cox regression, patients with HF symptoms had 2 times greater risk for a cardiac event than patients without HF symptoms (p=.042). HF symptoms were not a significant predictor of cardiac event-free survival after entering medication adherence in the model (p=.091), indicating mediation.

CONCLUSION—Medication adherence was associated with fewer HF symptoms and lower rates of hospitalization and death. It is important to develop interventions to improve medication adherence that may reduce HF symptoms and high hospitalization and mortality in patients with HF.

Keywords

symptoms; medication adherence; heart failure; outcomes; mediator

[c]Address for correspondence: Jia-Rong Wu, PhD, RN, University of North Carolina at Chapel Hill, School of Nursing, 435 Carrington Hall, Chapel Hill, NC 27599-7460, Phone 919-966-8057, Fax 919-843-9900, jiarongw@email.unc.edu.

DISCLOSURES

None.

INTRODUCTION

Heart failure (HF) is a chronic and costly condition with high morbidity and mortality.[1] Approximately 6 million Americans have heart failure (HF), and it is estimated that more than 8 million Americans may be living with this condition by 2030.[1, 2] Patients with chronic HF have symptoms of congestion, such as dyspnea and ankle swelling, and symptoms commonly worsen and lead to hospitalizations.[3–5]

Poor medication adherence is associated with worse health outcomes, including higher rates of hospitalizations and death in patients with HF.[6–10] In Riegel's original and recently revised Self-care of Heart Failure Model, relationships among self-care maintenance (including medication adherence), symptom monitoring, symptom recognition, self-care management and outcomes are described. Specifically, treatment adherence (e.g., medication adherence) is important to maintaining patient's physiologic stability.[11] Better adherence to self-care should lead to better health-related quality of life and reduce hospitalizations/death.[11–15] Poor medication adherence is presumed to be associated with greater HF symptom burden.[11, 13, 16] To our knowledge, the relationship between medication adherence and presence of HF symptoms has not been established in the current literature.[16]

It is not clear how HF symptoms, medication adherence, and hospitalization are related. Thus, the purposes of this study were to examine the relationship between medication adherence and HF symptoms and further explore the relationships among HF symptoms, medication adherence, and cardiac event-free survival in patients with HF. We tested whether the association between HF symptoms and the composite endpoint of event-free survival (i.e., time to cardiac-related hospitalizations or cardiac-related mortality) could be explained by medication adherence.

METHODS

Study Design

This was a secondary data analysis of two prospective studies in which medication adherence was measured objectively using the Medication Event Monitoring System (MEMS) and cardiac event-free survival was followed for up to 3 ½ years in patients with HF (both studies had similar mean follow-up days of 390+ days).[9, 17] Both studies were designed to examine the relationships among demographic, psychosocial, and clinical factors, medication adherence, and health outcomes.[8, 9, 17–23] The inclusion and exclusion criteria were identical in both studies. The data were collected between 2004–2007 for the first study and 2007–2009 for the second study. The attrition rate over time was low with less than 10% for each study. In the current study, we examined the relationships among HF symptoms, medication adherence, and cardiac event-free survival in patients with HF.

Samples and Setting—Detailed eligibility criteria and recruitment methods have been published previously.[9, 17] Briefly, patients were recruited from either outpatient cardiology clinics or inpatient cardiology units. Patients who had a confirmed diagnosis of chronic HF and were on stable doses of HF medications were included. Patients were excluded if they had obvious cognitive impairment or a co-existing terminal illness.

Measurement of Variables

Heart Failure symptoms: HF symptoms were assessed using a single item from the Self-Care of Heart Failure Index (SCHFI). All participants were asked "In the past three months, have you had trouble breathing and/or ankle swelling? (Yes/No)" The SCHFI is a reliable, valid, and the most widely used instrument to measure self-care behaviors in patients with HF.[24]

Medication adherence: Medication adherence was assessed using the MEMS (AARDEX®-USA, Union City, CA). The MEMS data were collected for 3 months for the first study and 1 month for the second study. We used MEMS data to compute medication adherence. The MEMS has been used extensively in many patient populations (including patients with HF) and is a valid, objective, and sensitive method of determining medication adherence.[25] The MEMS is the most commonly used electronic monitoring system and is considered the gold standard in measuring medication adherence.[25, 26] The MEMS data were collected from one HF medication for each patient. We chose the medication to monitor based on the following criteria. First, we chose a medication that was taken twice a day. If all medications were taken twice or only once per day, then we chose the beta-adrenergic blocking agent unless the patient was not prescribed one. In those cases, the angiotension-converting-enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) was used. If no beta-blocker or ACEI/ARB was prescribed, a diuretic (fixed dose, not as needed or adjustable one) was used in the MEMS device.

In this study, medication adherence was calculated as number of days the correct number of doses were taken (i.e., number of days the correct number of doses were taken during the monitoring period/total days during the monitoring period * 100%).[8, 27, 28] Patients who took the correct number of doses ≥ 88% of days were defined as medication adherent, while those who took < 88% were as defined as medication nonadherent. This cutpoint was chosen based on a study demonstrating that adherence at or above 88% predicted better event-free survival.[9]

Cardiac event-free survival: We calculated time from baseline to the first cardiac event (a cardiac hospitalization or cardiac death which came first) as the outcome variable. Outcome data were collected monthly by patient phone calls, hospital record review, and review of death certificates. To determine whether an event was cardiac-related, a trained research assistant reviewed data from patient interviews, medical records and/or death certificates to determine if the event was cardiac-related. Any uncertain events were adjudicated by the principal investigators (JRW and DKM). The RA and the PIs were blinded to participants' demographic and clinical data.

Other variables of interest: To completely describe the sample, compare differences in characteristics by groups, and obtain data on potential confounding variables, the following sociodemographic, clinical, and psychological data were collected.

Sociodemographics: Age, gender, marital status, race, and education level were collected from patient interview.

Clinical variables: Left ventricular ejection fraction (LVEF), etiology of HF, comorbidity (hypertension or diabetes), body mass index (BMI), and prescribed medications (ACEI/ARB and beta-blocker) were collected from the medical record and patient interview.

Procedure

Both studies were approved by the appropriate Institutional Review Boards. All patients provided informed, signed consent. Patients' sociodemographic and clinical characteristics were collected by interview and medical record review at baseline. After completion of the baseline assessment, patients were given instructions on use of the MEMS bottle. Patients started to use the MEMS bottle at baseline. Patients returned the MEMS bottle after one or three months of continuous use. Patients were contacted monthly by phone to collect data regarding hospitalizations and death.

Data Management and Analysis—A significance level of ≤ .05 was chosen to indicate statistical significance. Study variables were summarized descriptively, including means and standard deviations or frequency distributions and quartiles, as appropriate to the level of measurement. We examined differences between adherent and nonadherent groups and between presence or absence HF symptom groups using independent t-tests and chi-square tests. Data analyses were performed using SPSS (IBM, Armonk, NY), version 23.0.

Kaplan-Meier and log-rank tests were used to compare the time to first cardiac event between patients in adherent and nonadherent groups, and in presence or absence of HF symptom groups. Cox proportional hazards regression modeling was used to assess the cardiac event-free survival between those who did and did not report HF symptom with and without adjusting for the following potential confounding variables: age, body mass index (BMI), and ACEI use (as these variables were different between groups, please see Table 1). We also controlled for gender, left ventricular ejection fraction (LVEF), etiology of HF, and diabetes as these factors might impact cardiac event-free survival.[29–31] To account for differences between the two studies, we also controlled for study group (i.e., study 1 or study 2) in the final Cox regression models. We followed Baron and Kenny's steps to test for mediation by conducting a series of logistic and Cox regression models (Figure 1).[32]

RESULTS

Patient characteristics

Data from a total of 219 patients with HF were used in this study. The mean age of patients in the sample was 60 ± 12 years. About two thirds of patients were male. Fifteen percent of patients were African Americans. The average LVEF reflected enrollment of patients with and without systolic dysfunction: more than two fifths of the participants (42%) had HF with preserved systolic function (HFpEF, LVEF≥40%). The most common cause of HF was ischemic heart disease (50.2%). About one-fifth of the patients did not complete high school (21%). Most patients were unemployed (82%). There were 136 HF patients from study 1 and 83 HF patients from study 2. No demographic and clinical differences were found between subjects who participated from each study.

HF symptoms

About two thirds of the patients reported trouble breathing or ankle swelling (65.8%). Patients who reported HF symptoms were younger, had higher BMI, and were less likely to take ACE inhibitors compared with those who did not report HF symptoms. Age, BMI, and ACEI use were different between the two symptom groups. There were no differences between the two symptom groups in gender, race, education, marital status, LVEF, heart attack comorbidity, beta-blocker use, or study group (Table 1).

Medication adherence

Overall, 90 out of the 219 patients were categorized as nonadherent to prescribed HF medications (41%). A total of 46% of patients with HF symptoms were nonadherent to medication compared with 32% of patients without HF symptoms. In the unadjusted logistic regression model, patients with HF symptoms were 1.8 times more likely to be non-adherent compared with those without HF symptoms (odds ratio [OR] = 1.8, 95% CI: 1.00–3.23, p = . 05).

HF symptoms and cardiac event-free survival

There were 50 cardiac events (4 cardiac deaths and 46 cardiac hospitalizations) during the follow-up period, with 38 events in patients who reported having HF symptoms in the last 3 months and 12 events in those who reported no HF symptoms. No difference in the prevalence of cardiac mortality between HF symptom groups was found (2.1% vs. 1.3% p =1.00). There was a significant difference in the composite end-point of cardiac hospitalizations or cardiac mortality between HF symptom groups (26.4% vs. 16%, p=.036). Kaplan-Meier plots and log-rank tests demonstrated that cardiac event-free survival was significantly worse in patients who had HF symptoms (p =. 039) (Figure 2).

Mediation analysis

The first step of testing for mediation (Path A, Figure 1) explored whether HF symptoms were associated with medication adherence. There was an association between HF symptoms and medication adherence. Patients who reported HF symptoms were 80% more likely to be nonadherent to medication compared with those who did not report HF symptoms. In the second step (Path B), patients with medication nonadherence had a higher risk of experiencing a cardiac event. In the third mediation model (Path C), HF symptoms were associated with higher risk of experiencing a cardiac event. In the final model (Path D) that included both HF symptoms and medication adherence, HF symptoms were no longer a significant predictor of cardiac event-free survival with and without adjustment for all covariates (Table 2); this indicates complete mediation of the relationship between HF symptoms and cardiac event-free survival by medication adherence.

In the adjusted model with all covariates, none of the covariates were associated with cardiac event-free survival. In each adjusted regression model, all variance inflation factors were < 1.4, suggesting no parameter distortion due to multicollinearity.

DISCUSSION

In this study we explored the relationships among HF symptoms, medication adherence, and cardiac event-free survival in patients with HF and examined the mediating role of medication adherence in the relationship between HF symptoms and health outcomes. The most striking finding from this study was that medication adherence mediated the relationship between HF symptoms and cardiac event-free survival. Based on Riegel's Self-care of Heart Failure Model, self-care maintenance behaviors, such as medication adherence in this study are essential to maintain a patient's physiologic stability,[11, 13] therefore, reduce HF symptoms, delay the progression of HF, and improve health-related outcomes such as rehospitalizations.[12, 33–36]

In our prior studies, we have found that medication adherence mediated the relationships between African-American race and worse outcomes,[20] between depressive symptoms and worse outcomes,[21] and between single marital status and worse outcomes.[19] To our knowledge, this is the first study to provide evidence to support the important mediating role of medication adherence in the relationship between HF symptoms and worse outcomes. Thus, it is essential to develop effective interventions to improve medication adherence in patients with HF to improve a variety of health outcomes.

Our study confirms the hypothesis that better medication adherence, one of the major self-care maintenance behaviors, is associated with fewer HF symptoms. Lee proposed that effective self-care maintenance behaviors lead to better health outcomes through cardioprotective mechanisms, such as neurohormonal deactivation.[16] For example, if patients with HF adhere to prescribed neurohormonal blockers (e.g., beta-blockers or angiotensin-converting-enzyme inhibitors), medication adherence will help minimize the cardiocirculatory burden from increased neurohormone levels (e.g., norepinephrine and angiotensin II).[16]

In the current literature on drug studies, use of neurohormonal blockers is associated with better functional capacity and health-related quality of life (HRQOL), lower symptom burden, and lower hospitalization and death rates.[37–41] Yet, medication adherence was rarely evaluated, or had not been reported in these studies, so we are not sure whether positive health outcomes (better functional capacity and HRQOL, fewer HF symptoms and hospitalizations) can be attributed to adherence to neurohormonal blockers or to other causes such as better monitoring seen in clinical trials. Interestingly, in a trial to test the effect of a beta-blocker on mortality, investigators randomized 2,175 patients with myocardial infarction to receive propranolol or placebo, and found poor adherers were 2.6 times more likely than good adherers to die within a year of follow-up.[42] Poor adherers had an increased risk of death whether they were on propranolol or placebo. Our findings provide evidence that better medication adherence is indeed related to lower symptom burden.

As expected, patients with HF symptoms in the past 3 months had a greater risk of experiencing a cardiac event than those without HF symptoms. In prior studies, HF symptoms such as shortness of breath and ankle swelling were indicators of acute HF exacerbation and the most common causes patients were admitted to the hospital.[3–5, 43] In

line with prior studies, poor medication adherence was one of the most common preventable precipitating factors for acute HF exacerbation.[44, 45] Therefore, reducing HF symptoms can be an incentive to encourage patients with HF to improve/maintain medication adherence.

Our study has several limitations. First, the concept of HF symptoms is complex and multifaceted. It includes multiple elements (e.g., numbers, frequency, duration, and severity of HF symptoms, how much patients are distressed by their HF symptoms).[46, 47] We measured presence of HF symptoms only one time (baseline) using a single item, yes/no question from the Self-Care of Heart Failure Index that might not capture the full spectrum of HF symptoms. However, our findings, which demonstrate a significant relationship between HF symptoms and medication adherence and between HF symptoms and outcomes, suggest that the concept of HF symptoms were accurately reflected by the self-report measure in this study. Nevertheless, given that patients have difficulty with symptom recognition, and HF patients' symptoms might change in duration or severity over time;[13, 43, 46–48] future studies of this phenomenon should use a scale to capture multi-dimensional HF symptoms longitudinally so that the complex dynamics surrounding HF symptoms, medication adherence and outcomes can be better illuminated. The single item question measure of HF symptoms may be insensitive to reflect HF symptoms and may produce unstable results that need to be verified in a future longitudinal study. Thus our findings should be considered exploratory and the need for replication emphasized.

Second, patients in our study were relatively younger than patients with HF in general. The difference might have resulted from recruiting most patients in this study in the outpatient settings and not the in-hospital settings. Third, we only monitored one HF medication in the MEMS as it is costly and burdensome to the patients for using multiple MEMS for multiple medications. However, previous investigators have demonstrated that monitoring one medication is sufficient to capture overall medication adherence.[49, 50] Moreover, data were from 2 prospective studies collected in different time periods might introduce potential bias. Therefore, we controlled for original study group membership (Study 1 or 2) to account for potential differences between studies. Finally, although we included LVEF, etiology of HF, and diabetes as covariates in the statistical analysis, we acknowledge that patients with HF might have other concurrent conditions that may impact health outcomes that were not collected and controlled in our study.

CONCLUSION

We observed that patients with better medication adherence had fewer HF symptoms and that medication adherence mediated the relationship between HF symptoms and cardiac event-free survival. Therefore, it is imperative that clinicians educate/emphasize the importance of medication adherence to their HF patients to reduce HF symptoms and high hospitalization and mortality rates. Due to the importance of medication adherence and current low medication adherence rate, it is important to develop effective interventions to improve/sustain medication adherence to achieve better health outcomes in patients with HF.

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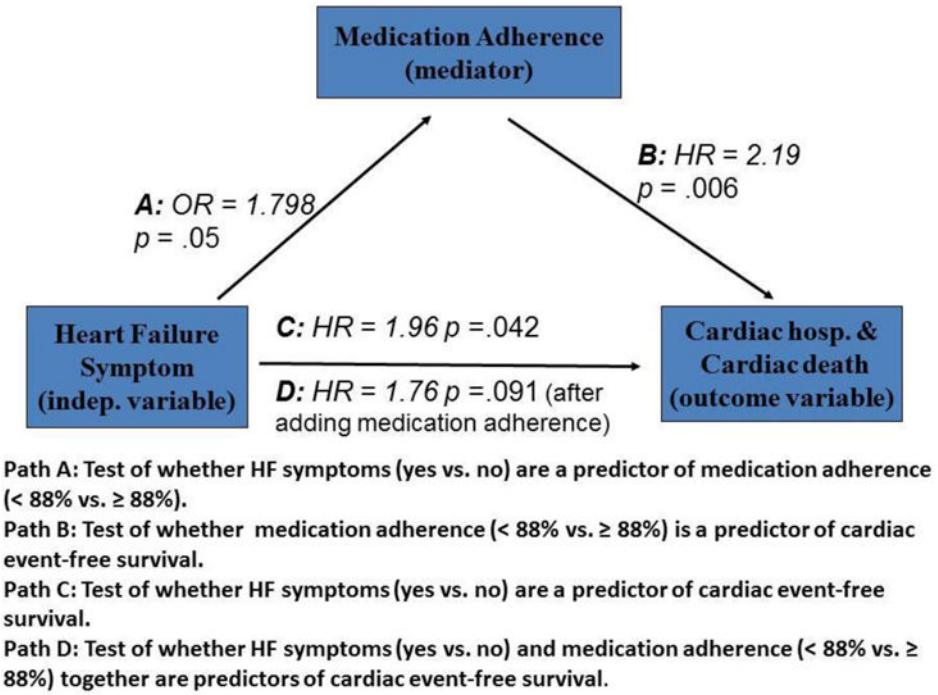

Figure 1.

Testing the hypothesis that medication adherence is a mediator of the relationship between heart failure symptoms and cardiac event-free survival

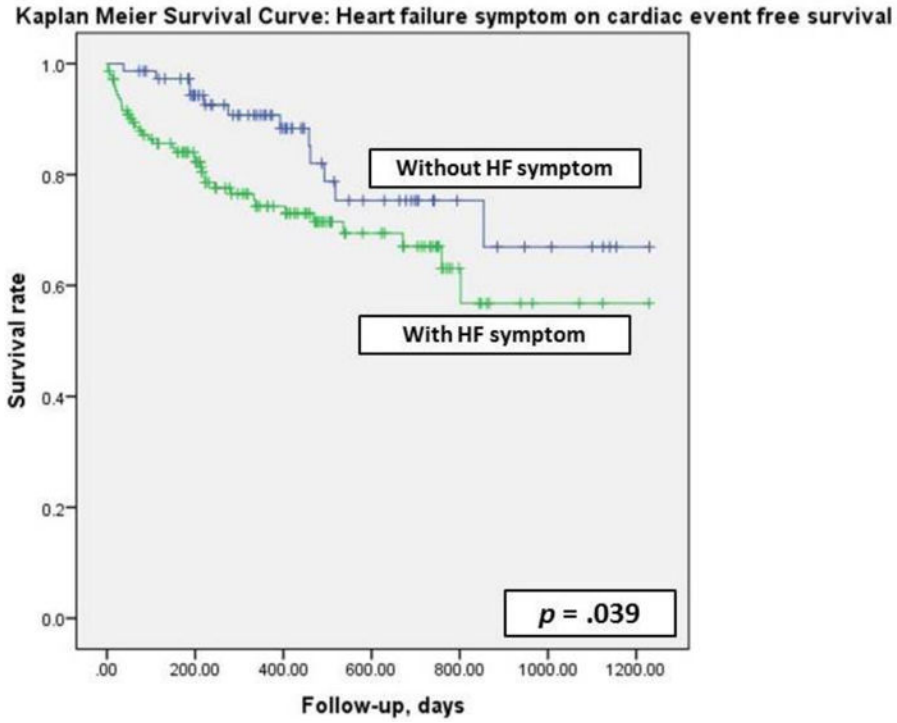

Figure 2.
Heart failure symptoms and cardiac event-free survival

Table 1

Sample Characteristics

Characteristics	**Without HF symptoms (*n* = 75) *Mean* ± *SD* or *n* (%)**	**With HF symptoms (*n* = 144) *Mean* ± *SD* or *n* (%)**	***p***
Age	63±11	59±12	.018
Female	21 (28)	56 (38.9)	.136
White	64 (85.3)	122 (84.7)	1.00
Education: < high school	16 (21)	29 (20)	.372
Marital status: married	51 (68)	82 (56.9)	.145
LVEF, %	37±14.9	35±13.9	.426
Body mass index	30.6±6.9	33.1±7.8	.021
Heart attack	41 (56.2)	75 (53.2)	.772
Diabetes	28 (38.4)	69 (47.9)	.196
Taking ACEI	63 (84)	91 (63.6)	.002
Taking beta-blocker	70 (93.3)	130 (90.3)	.614
Study group: Study 1 Study 2	 46 (61.3) 29 (38.7)	 90 (62.5) 54 (37.5)	.884
Intervention assignment: Intervention group	 20 (71.4)	 34 (64.2)	.623

ACEI =angiotensin-converting-enzyme inhibitor; LVEF =left ventricular ejection fraction

Table 2

Cox Regression: Heart Failure Symptom and Medication Adherence[§] on Cardiac Event-free Survival (N = 219)

Variable	Hazard Ratio	95% CI	Significance
Without covariate adjustment			
[*] *Step 1*			
With HF symptoms	**1.961**	**1.023–3.758**	**.042**
[**] *Step 2*			
With HF symptoms	1.759	.913–3.390	.091
Poor medication adherence	**2.035**	**1.157–3.578**	**.014**
With covariate adjustment			
[†] *Step 1*			
With HF symptoms	**2.053**	**1.022–4.124**	**.043**
[‡] *Step 2*			
With HF symptoms	1.947	.964–3.935	.063
Age	1.00	.974–1.027	.988
Female	1.354	.721–2.543	.347
Etiology of HF, non-ischemic	.610	.310–1.200	.152
Left ventricular ejection fraction (%)	.985	.961–1.009	.211
Body mass index	.966	.925–1.009	.120
ACEI user	.992	.491–2.003	.982
Diabetes	1.193	.645–2.208	.574
Study 1	1.148	.620–2.218	.660
Poor medication adherence	**2.009**	**1.122–3.597**	**.019**

CI =confidence interval; ACEI =angiotensin-converting-enzyme inhibitor; NYHA =New York Heart Association

[*] $\chi 2$ =4.274, p = .039;

[**] $\chi 2$ = 10.775, p =.005;

[†] $\chi 2$ = 13.105, p =.158;

[‡] $\chi 2$ = 18.618, p = .006