Association Between Poorer Cognitive Function and Reduced Objectively Monitored Medication Adherence in Patients With Heart Failure

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Background—Subclinical cognitive impairment is prevalent in heart failure (HF); however, its role in important clinical outcomes, such as HF treatment adherence, is unclear. Given the complex polypharmacy in HF treatment, cognitive deficits may be important in predicting medication management. Thus, the objective of the current study was to examine the impact of cognitive function on medication adherence among community-dwelling patients with HF using objective assessments.

Methods and Results—A prospective observational cohort design of 309 community-dwelling patients with HF (59.7% male, 68.7±9.7 years) and no history of dementia or neurological disease. Cognition was assessed using a neuropsychological battery at baseline. Medication adherence was objectively measured for 21 days using an electronic pillbox. Regression analyses tested whether attention, executive function, or memory predicted 21-day medication adherence. In unadjusted analyses, lower scores on all 3 cognitive domains predicted poorer medication adherence (β=0.52–85; P=0.001–0.009). After adjusting for demographic, clinical, and psychosocial variables, memory continued to predict medication adherence (β=0.51; P=0.008), whereas executive function (β=0.24; P=0.075) and attention were no longer a predictor (β=0.34; P=0.131).

Conclusions—Poorer cognitive function, especially in regard to memory, predicted reduced medication adherence among patients with HF and no history of dementia. This effect remained after adjustment for factors known to predict adherence, such as depressed mood, social support, and disease severity level. Future studies should examine the link from cognitive impairment and medication nonadherence to clinical outcomes (eg, hospitalization and mortality).

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01461629.

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Nearly 6 million adults in the United States have heart failure (HF)[1] and its associated risks of poorer biopsychosocial outcomes,[2–4] including multidomain cognitive impairment.[5–7] Although cognitive deficits are most common and severe in inpatient samples (≤80%), cognitive impairment is also widespread even among community-dwelling HF populations (15%–25%).[5–7]

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Though cognitive deficits are pervasive, cognitive screening is not yet a practice guideline for HF management.[8] One reason is that these deficits are rarely examined as predictors of objectively measured patient behaviors or hard clinical outcomes; thus, their clinical impact is not yet known. The lack of evidence on clinical effects is problematic because initial data suggest that cognitive function may impact patients' abilities to adhere to the complex HF treatment regimen.[9,10] Medication adherence may be especially difficult for those with cognitive impairment given the increasingly complex nature of pharmacotherapy for HF.[11,12] To our knowledge, only 2 studies have examined cognitive function in relation to objectively measured medication adherence in patients with HF.[9,10] Both suggest that cognitive deficits contribute to poorer adherence but were limited by lack of sample diversity (ie, veterans)[9] or failure to examine multiple cognitive domains.[10]

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Difficulties with medication adherence might be expected even among cognitively intact patients[13] because the typical patient with HF is prescribed 11 different medications, including but not limited to angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, aldosterone antagonist, and vasodilators.[11,12] Comorbid diseases add complexity to this already extensive regimen, with some patients taking >20 medications.[12] This polypharmacy results in challenging dosing patterns in which patients take >10 doses/day.[11] As an example, a patient may be taking oral lisinopril (20 mg) and spironolactone (50 mg) once/day, carvedilol (25 mg) twice/day, and hydralazine (75 mg) 3× per day for HF symptoms alone—not to mention medications for hyperglycemia and depression. Unfortunately, poorer adherence to HF medication has serious consequences because partially adherent and nonadherent HF patients demonstrate more adverse coronary events, hospitalizations, and all-cause mortality compared with their adherent counterparts.[14–16]

Thus, the role of cognitive function in medication adherence should be further explored using objectively measured medication adherence, as well as multiple cognitive domains. Examining the cognitive function–adherence relationship among community dwelling HF patients is particularly important because these individuals will likely not benefit from the adherence-promoting mechanisms that are in place for the most cognitively impaired patients (eg, 24-hour care in nursing facilities). Accordingly, the primary objective of the current study was to examine the impact of cognitive function on medication adherence among community dwelling patients with HF using objective assessments. To test our hypothesis that poorer cognitive function would predict poorer adherence to medications, we used a neuropsychological battery and objectively monitored medication adherence using an electronic pillbox. If cognitive deficits predict patient adherence behaviors, they should be assessed and used to identify patients at risk for nonadherence and poorer clinical outcomes. Such information may also be used to guide interventions to improve adherence efforts among this population.

Methods

Participants

The Heart ABC study (Heart Adherence Behavior and Cognition; Trial Identifier: NCT01461629 http://clinicaltrials.gov) is a National Institutes of Health–funded prospective cohort study of patients with HF. Heart ABC enrolled 372 patients recruited from a variety of cardiology practices in 2 major hospital systems in northeast Ohio. Eligibility requirements were chosen to maximize the number of HF patients presenting with cognitive impairment but minimize the possibility that the impairment was a result of non-HF-related disease processes (eg, head injury, psychoticism, Alzheimer's, substance use disorder, etc). The criteria were as follows: (1) aged 50 to 85 years at enrollment, (2) systolic HF diagnosis for at least 3 months and verifiable in the medical record (within 3 years of study enrollment), (2) New York Heart Association (NYHA)[17] class II or III ≥3 months duration (patients with NYHA class IV at baseline were excluded; however, some participants advanced to NYHA class IV during the study), (3) no cardiac surgery within last 3 months, (4) no history of neurological disorder or injury (eg, Alzheimer's disease, stroke), (5) no history of moderate or severe head injury, (6) no past or current history of psychotic disorders, bipolar disorder, learning disorder, developmental disability, renal failure requiring dialysis, or untreated sleep apnea, (7) no substance use disorder currently or within the past 5 years, and (8) no current use of home tele-health monitoring program for HF. The primary rationale of the majority of the exclusion criteria is that they represent potential adverse impact to cognitive function that may not be related to HF (eg, recent invasive surgery, head injury, untreated sleep apnea, etc). Telemonitoring was used as an exclusion criterion because of its possible invention effects in our purported observational study, as well as the potential liability and safety concerns associated with connecting the electronic medication pillbox to a patient's landline that was also connected to his/her telehealth device, such as an implanted device or scale. Of note, the analyses in the current study are based on the 309 patients with complete medication adherence data.

Measures

Medication Adherence

Medication adherence was measured objectively using MedSignals Pillbox (VitalSignals, LLC, Lexington, KY). MedSignals Pillbox was selected because of ease of use for the participants, the ability to monitor multiple medications simultaneously, and the capacity to transmit daily adherence data via bluetooth and home phone to a secure electronic server. Research assistants were trained on the installation, problem solving, and instructing participants on the use of the pillbox and provided technical support to patients during the trial. The pillbox tracked adherence data for ≤4 of the more common HF medications (chosen according to a predetermined priority list that included β-blockers; Figure 1) for 21 days. Adherence, which was used as the primary outcome variable in analyses, was defined as the percent of days that the patient was compliant with their personally prescribed medication regimen divided by the number of total days monitored (possible range of scores: 0%–100%). The calculations included one time or multiple doses per day. Medication adherence was calculated separately for each of the 4 medication bins according to the instructions for the medication in that bin. Given that the correlations between adherence scores for each bin were high ($r \geq 0.85$), we averaged the scores for each bin to yield 1 adherence score for analyses. All reminder alerts and alarms were deactivated during the study. We excluded days the participant knowingly did not use the box (eg, out of town or hospitalized). For descriptive purposes, nonadherence was defined using the standard of <80% of days compliant with medication regimen to determine the number of nonadherent patients.[18]

Cognitive Function

Multiple domains of cognitive functioning were measured using neuropsychological tests that have strong validity and reliability and have been previously used among patients with HF.[18] The 4 cognitive domains were as follows:

1. Global cognitive function: General cognitive ability across a variety of domains. Global cognitive function was examined with the Modified Mini-Mental Status Examination.[19] The Modified Mini-Mental Status Examination has better validity, reliability, and sensitivity than the Mini Mental State Exam.[19,20] Higher scores indicate better global cognitive

	Choice A	Choice B	Choice C
Bin 1	Beta Blocker	Aldosterone Antagonist (aldactone/ eplereone)	Statin
Bin 2	ACE	ARB	Digoxin
Bin 3	Diuretic	Plavix	Statin
Bin 4	Aspirin	Diuretic	Statin

Figure 1. Pillbox medication choices. ACE indicates angiotensin-converting enzyme; and ARB, angiotensin receptor blocker.

function (possible range: 0–100), with scores ≤90 indicative of some degree of cognitive impairment.[21] Importantly, we include the Modified Mini-Mental Status Examination screener for descriptive and comparative purposes. The Modified Mini-Mental Status Examination was not used in the primary analyses, given that we assessed each cognitive domain separately using gold standard neuropsychological tests (below).

2. Attention: The capacity to attend to and process information. Attention was measured by the Stroop Word and Color subtests,[22] Trail Making Test A,[23] and Letter–Number Sequencing.[24]
3. Executive function: The capacity to problem-solve, plan, inhibit, and reason. Executive function was assessed using the Stroop Color Word subtest,[22] Trail Making Test B,[23] and the Frontal Assessment Battery.[25]
4. Memory: The capacity to retain and recall verbal information. Memory was measured using the Rey Auditory Verbal Learning Test Learning Over Time, True Hits, Short Delay, and Long Delay scores.[26]

Using published age- and education-adjusted normative data,[24,27–29] raw scores on each neuropsychological test were converted to scaled scores (mean =10, SD=3). Scaled scores were converted to T scores to facilitate interpretation (mean =50, SD=10), and the T scores of the relevant tests were averaged to create a composite score for each domain. T scores ≤35 are associated with scores ≥1.5 SD below the test mean for the normative sample and are indicative of cognitive impairment. For the primary analyses, we examined the test scores as continuous variables. For descriptive purposes, a dichotomous cognitive impairment variable was created (T scores ≤ 35 are cognitively impaired and scores > 35 are not impaired).

Demographic, Medical, and Psychosocial Variables

The following demographic and clinical variables were also assessed: age (years), sex (0, female and 1, male), race–ethnicity (0, white and 1, nonwhite), education level (1, no schooling; 2, 8th grade or less; 3, 9–11th grade; 4, high school; 5, technical or trade school; 6, some college; 7, bachelor's degree; and 8, master's degree), socioeconomic status (SES), self-reported current HF severity, medical comorbidity, medication regimen complexity, depressed mood, anxiety, social support, and health literacy. The SES score was calculated as a *z* score using indicators of income and education for each zip code,[30] with zero as the sample mean and higher scores indicating higher SES. HF severity was determined by asking patients about their current symptoms and functional limitations (eg, "Do you markedly reduce physical activity due to tiredness, heart fluttering, shortness of breath, anginal pain?"). Based on their responses, we categorized patients' HF severity as class I, II, III, or IV based on their current self-reported symptoms and limitations. Medical comorbidity was assessed using the Charlson Comorbidity Index,[31] which yields a summary score of comorbid medical conditions (eg, diabetes mellitus, peripheral vascular disease, myocardial infarction, etc). Medication complexity was assessed using the Medication Regimen Complexity Index[32]; higher scores reflect greater complexity. Depressive symptoms were assessed using the Patient Health Questionnaire-9.[33] Anxiety was assessed using the 7-item Patient Reported Outcomes Measurement Information System Anxiety Subscale.[34] Social support was assessed using the Multidimensional Scale of Perceived Social Support.[34] Health literacy was assessed using the Medical Term Recognition Test,[35] with higher scores indicative of greater health literacy.

Procedure

All patients were recruited from a variety of cardiology practices in northeast Ohio and gave their written, informed consent to participate. All procedures were approved by the Institutional Review Boards of Kent State University, Summa Health Systems, Inc, and University Hospitals of Cleveland. After recruitment and written consent, a research assistant obtained baseline demographic and medical data from the official medical records and conducted the series of self-report questionnaires and neuropsychological testing (Visit 1). At Visit 2, research assistants installed the electronic pillbox in patients' homes, which collected adherence data for 21 days.

Data Analyses

The characteristics of participants were summarized using mean±standard deviation for continuous variables (eg, age and percent daily medication adherence) and frequencies and percentages for categorical variables (eg, sex and nonadherent status). Correlations were calculated to determine the relationship between all medication bins used and ranged from 0.85 to 0.87. For studying association between medication adherence (highly skewed variable) and cognitive function after controlling for several covariates, we used median regression. Measurements of several variables, including attention, executive function, and memory, were missing for a wide variety of reasons (eg, attrition, colorblindness, refusal, and fatigue). Specific missingness for each variable was 8.3% for attention (n=31), 9.1% for executive function (n=34), and 4.7% for memory (n=17). We assume that the missing data follow the missing at random probability mechanism (ie, missing values do not carry any extra information about why they are missing than what is already available in the observed data). The median regressions,[36] a robust regression procedure, were performed on the 20 imputed data sets separately, and the results are combined. We generated the imputed data sets by simulating from a (approximate) Bayesian posterior predictive distribution of the missing data. We applied predictor selection methodology in studying the association between various covariates (demographic characteristics and medical psychosocial factors) and medication adherence (ie, percent of days that the patient was compliant with their medication regimen). Finally, the association between cognitive function and medication adherence was examined while adjusting for covariates that are associated with the outcome using a multivariable median regression model. Covariates in the final analyses met the following 2 criteria: (1) the variable had clinical significance to the primary variables (ie, cognitive function or medication adherence) and (2) when entered as the single predictor, the variable was associated with medication adherence using a statistically significant *P* value of <0.15.[37] Covariates meeting these criteria were used in the multivariable regression models, with one of the cognitive function measures (attention, executive function, or memory) as the primary predictor. To correct for testing of multiple, correlated cognitive outcomes (mean r=0.49), a partial Bonferroni correction was applied using the simple interactive statistical analysis (SISA) program with the following input parameters: α=0.05, N of tests =3, correlation =0.49, and degrees of freedom =308.[38] Using these parameters, a *P* value <0.028 is required for significance. All the analyses were performed using software Stata 13.0 (StataCorp, LP, College Station, TX).

Results

Sample Characteristics

The sample was predominantly older (68.7±9.7 years), white (72.0%), male (59.7%), and had class II or III self-reported HF severity (84.9%) and a high school education level or higher (87.3%; Table 1). Most patients were cognitively intact (T scores ≥35); mean composite scores for each cognitive domain and individual test are presented (Table 1). At the group level, patients exhibited an average medication adherence of 73.0% (SD=25.4), and the majority (53.4%) of the sample was adherent (with ≥80% adherence; Figure 2). However, 46.6% of patients were considered nonadherent (<80% adherence), with nearly 12% of patients adhering to ≤50% of their daily medications (Figure 2; Table 1).

Table 1. Characteristics of Participants (max *N*=309)

	Total Sample, Mean±SD or N (%)	Adherent, Max n=165	Nonadherent, Max n=144
Demographic, medical, and psychosocial factors (possible range)			
Age	68.5±9.6	69.6±8.9	67.2±10.2*
Female	122 (39.5)	62 (37.6)	60 (41.7)
Race–ethnicity			
White	227 (73.5)	131 (79.4)	96 (66.7)*
Black	79 (25.7)	33 (20.0)	46 (31.9)*
American Indian	2 (0.6)	0 (0.0)	2 (1.4)
Asian/Pacific Islander	1 (0.3)	1 (0.6)	0 (0.0)
Education level			
8th grade or less	5 (1.6)	2 (1.2)	3 (2.1)
9–11th grade	29 (9.4)	12 (7.3)	17 (11.8)
High school	88 (28.5)	50 (30.3)	38 (26.4)
Technical or trade school	31 (10.0)	17 (10.3)	14 (9.7)
Some college	85 (27.5)	43 (26.1)	42 (29.2)
Bachelor's degree	42 (13.6)	26 (15.8)	16 (11.1)
Master's degree	29 (9.4)	15 (9.1)	14 (9.7)
SES z score	0.09±4.2	0.8±4.1	-0.7±4.3*
Charlson Comorbidity Index† (0 to no max)	3.3±1.7	3.3±1.6	3.3±1.8
Medication Regimen Complexity Index (1.5 to no max)	22.6±12.5	21.8±12.1	23.6±13.0
Self-reported HF severity at baseline (NYHA)			
Class I	29 (9.4)	18 (10.9)	11 (7.6)
Class II	77 (24.9)	46 (27.9)	31 (21.5)
Class III	188 (60.8)	98 (59.4)	90 (62.5)
Class IV	15 (4.9)	3 (1.8)	12 (8.3)*
Depressive symptoms (PHQ-9) (0–27)	4.5±4.9	3.8±4.5	5.3±5.2*
Anxiety symptoms (PROMIS-Anxiety) (5–35)	13.0±5.3	12.4±5.1	13.6±5.5
Social support (MSPSS) (12–84)	69.1±14.5	71.2±12.0	66.7±16.6*
Medical Term Recognition Test (METER) (0–40)	35.5±6.1	36.1±5.1	34.7±7.0*
Global Cognition Impaired (3MS < 90) (0–100)	89 (29.0)	48 (29.1)	41 (28.9)
Cognitive function T scores (20–80)			
Attention composite	44.9±7.4	46.0±7.1	43.7±7.5*
Trails A	42.8±10.2	43.3±9.9	42.1±10.4
Letter–Number Sequencing	47.3±10.4	49.1±10.2	45.2±10.2*
Stroop Color	45.8±9.5	46.7±8.8	44.7±10.2
Stroop Word	43.4±9.5	44.8±9.0	41.7±9.7*
Executive function composite	46.3±7.9	47.3±7.8	45.1±7.9*
Trails B	41.9±11.9	44.2±11.3	39.2±12.1*
Frontal assessment battery	51.0±8.2	51.5±8.3	50.4±8.0
Stroop color–word	45.5±10.1	45.8±10.2	45.1±9.9
Memory composite	47.7±8.0	48.9±8.0	46.3±7.7*
Hits	48.9±9.0	49.6±9.2	48.0±8.7
Short delay	45.4±11.0	47.5±10.8	43.0±10.9*

(*Continued*)

Table 1. Continued

	Total Sample, Mean±SD or N (%)	Adherent, Max n=165	Nonadherent, Max n=144
Long delay	47.1±9.6	48.6±9.8	45.4±8.9*
Learning over time	49.2±11.1	49.9±11.1	48.5±11.0
Medication adherence variables			
Average 21-day adherence (0%–100%)	73.0±25.4	92.1±6.4	51.0±20.7*
Patients not adherent (<80% adherence)	144 (46.6)	…	…

Means and standard deviations are presented for continuous variables. Sample size and percentages are presented for categorical variables. HF indicates heart failure; 3 MS, Modified Mini-Mental Status Examination; MSPSS, Multidimensional Scale of Perceived Social Support; NYHA, New York Heart Association; PHQ-9, Patient Health Questionnaire-9; PROMIS-Anxiety, Patient-Reported Outcomes Measurement Information System Anxiety Scale; and SES, socioeconomic status.

*t Test or χ^2 difference test between adherent and nonadherent groups significant at $P<0.05$.

†Most common comorbidities reported on the Charlson and corresponding % of participants: myocardial infarction (51.3%), diabetes mellitus (44.1%), and chronic obstructive pulmonary disease (COPD; 27.4%).

Cognitive Function Predicting Medication Adherence

Composite higher attention, executive function, and memory scores were all significantly associated with greater medication adherence in the unadjusted regression analysis (Table 2). After adjusting for age, minority status, SES, HF severity, depression, and social support, there was no longer an association between attention and medication adherence (β=0.34; P=0.131; Table 3). After adjusting for these covariates, the relationship between reduced executive function and poorer medication adherence was not significant (β=0.24; P=0.075; Table 3). The relationship between reduced memory and poorer medication adherence remained significant in the adjusted analysis (β=0.51; P=0.008; Table 3).

Demographic, Medical, and Psychosocial Predictors of Medication Adherence

Several of the demographic, medical, and psychosocial variables were significantly associated with medication adherence (Table 2). Among demographic variables, white race (β=−13.75; P=0.001) and higher SES (β=1.26; P=0.001) were significantly associated with greater medication adherence, whereas older age was not significant (β=0.37; P=0.064). There was no association between sex or education and medication adherence. Among medical variables, individuals in NYHA class III (β=−10.00; P=0.048) and NYHA class IV (β=−41.25; P=0.000) had significantly poorer medication adherence. There was no association between medication adherence and NYHA class II status, comorbidity index, or medication regimen complexity. Among psychosocial factors, greater depressed mood was associated with poorer adherence to medication (β=−1.54; $P<0.001$) whereas greater social support score was associated with greater adherence to medication (β=0.33; P=0.024). There was no association between anxiety or health literacy and medication adherence.

Discussion

The current study examined the relationship between cognitive function and objectively monitored medication adherence in a community sample of adults with HF. Although the majority of our sample (53%) met or exceeded the recommended adherence level of 80%, nearly half (47%) of patients failed to meet this level. Indeed, 1 of every 5 patients had adherence levels of ≤50%. Extrapolating this figure to the national rates (5.1 million) suggests that nearly 1 million

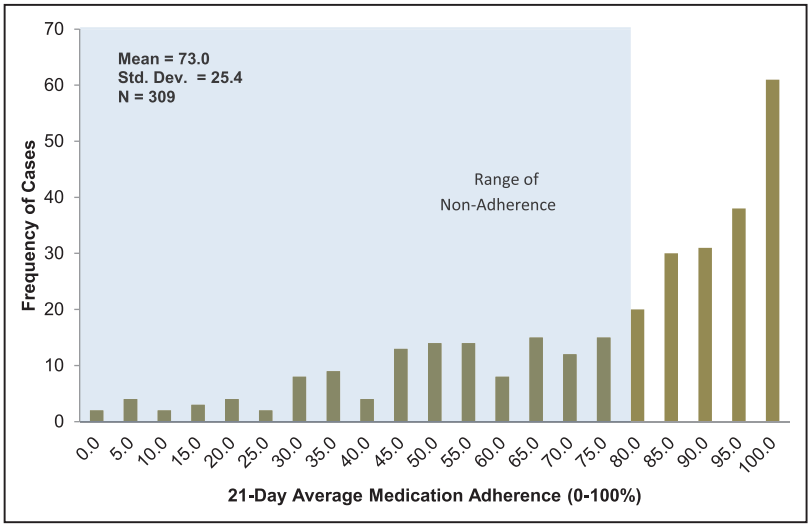

Figure 2. Twenty-one-day average medication adherence among patients with heart failure. Shaded region depicts range of nonadherence (<80% adherence). Percentage of patients who were in range nonadherence =46.6% (N=144).

Table 2. Unadjusted Median Regressions of Demographic, Medical, Psychosocial, and Cognitive Factors Predicting 21-Day Medication Adherence (% of Days Adherent)

Factors	*B* (95% CI)	SE	*P* Value
Demographic/medical			
Age	0.37 (–0.02, 0.75)	0.20	0.064
Race–ethnicity	–13.75 (–21.97, –5.5)	7.18	0.001*
SES	1.26 (0.49, 2.03)	0.39	0.001*
NYHA Class II	–5.75 (–16.61, 5.11)	5.52	0.298
NYHA Class III	–10.00 (–19.89, –0.11)	5.03	0.048*
NYHA Class IV	–41.25 (–56.98, –25.52)	4.66	0.000*
Psychosocial			
Depression (PHQ-9)	–1.54 (–2.22, –0.85)	0.35	0.000*
Social support (MSPSS)	0.33 (0.04, 0.61)	0.14	0.024*
Cognitive domains			
Attention	0.61 (0.15, 1.06)	0.23	0.009*
Executive function	0.52 (0.20, 0.85)	0.17	0.002*
Memory	0.85 (0.36, 1.34)	0.25	0.001*

MSPSS indicates Multidimensional Scale of Perceived Social Support; NYHA, New York Heart Association; PHQ-9, Patient Health Questionnaire-9; SE, standard error; and SES, socioeconomic status.

*Significant at $P<0.05$.

of patients with HF are taking only half of their medications or less. Importantly, poorer performance on all 3 cognitive domains predicted poorer objectively monitored medication adherence when examined in unadjusted models. The effect of poorer memory on adherence remained after the adjustment of medical and psychosocial factors known to predict adherence (eg, depression, social support, and disease severity level). For every 8-point decrease in patients' standardized memory scores at baseline, adherence rates dropped by 13% points. For a patient taking 10 doses per day, this drop in adherence would translate to missing 9 doses/week or nearly 40 doses/month. In contrast, attention and executive function were no longer significant.

Whether alone or in fully adjusted models, poorer memory function predicted worse adherence to objectively monitored medication adherence. Memory may be a more potent predictor than attention and executive function because it is among last cognitive domains to be impacted by the disease process,[39] and thus, deficits in the memory domain might reflect greater severity of physical and cognitive impairment. Memory function may also be more relevant to medication taking behavior than attention or executive functions, given its role in a person's ability to retain information and directions related to their medication prescriptions and dosing regimens.

Our results are consistent with those of the few studies that have examined the relationship between cognitive function and objectively monitored medication adherence in HF.[9,10] The results also parallel those indicating that lower cognitive function is associated with poorer treatment adherence in the domains of self-reported adherence[18] and self-care behaviors.[40] Importantly, similar to our results, Hajduk et al[41] also reported that memory was the only domain of cognitive function associated with poor self-care in HF. Taken together, the clinical implications of the findings from our study and others are that cognitive domains, especially memory function, should be examined in patients with HF to identify those who may be at risk for poorer treatment adherence, especially related to medication-taking behaviors.

The current findings are subject to several limitations. First, the monitoring period of 21 days was relatively short and may have resulted in the high levels of adherence observed because of measurement reactivity, although the range of 21-day adherence was wide (1.25%–100%) and the standard deviation was large (22%), which suggests adequate variability in adherence rates. Second, we did not ask patients to keep a diary detailing reasons for missing certain doses given potential measurement reactivity of the diary, but this information could be helpful in recording intentional missing of doses (eg, at provider's recommendation). Next, the generalizability of these findings to samples with other characteristics (eg, preserved ejection fraction, younger, higher SES, and diastolic HF) may be limited. Our screening procedures excluded NYHA class IV HF for safety reasons, but each patient's self-reported HF symptoms were reassessed during the study, and some were judged to have class IV HF. Thus, a more severely ill population may have had more cognitive impairment. In addition, our findings may not generalize to the hospitalized HF population, a group typically exhibiting higher rates of cognitive impairment. Thus, future studies should certainly include more diverse samples to confirm whether our results will replicate among patients with different medical or demographic characteristics. Another significant limitation is the quality of our NYHA assessment, which

Table 3. Adjusted Median Regressions of Cognitive Function Predicting 21-Day Medication Adherence (% of Days Adherent)

	Cognitive Domains*								
	Attention			Executive Attention			Memory		
Variables	β (95% CI)	SE	*P* Value	β (95% CI)	SE	*P* Value	β (95% CI)	SE	*P* Value
Demographic/medical									
Age	0.27 (–0.06, 0.59)	0.17	0.110	0.35 (0.09, 0.60)	0.13	0.009†	0.17 (–0.16, 0.50)	0.17	0.319
Race–ethnicity	–5.05 (–13.20, 3.10)	4.14	0.224	–4.57 (–10.96, 1.82)	3.24	0.160	–6.80 (–15.33, 1.74)	4.33	0.118
SES	0.41 (–0.40, 1.23)	0.41	0.320	0.46 (–0.17, 1.10)	0.32	0.152	0.57 (–0.27, 1.41)	0.43	0.182
Self-reported NYHA									
Class II	–6.50 (–17.69, 4.69)	5.69	0.254	–5.36 (–14.14, 3.41)	4.46	0.230	–9.21 (–20.81, 2.39)	5.89	0.119
Class III	–6.18 (–16.67, 4.32)	6.33	0.248	–5.52 (–13.70, 2.66)	4.15	0.185	–7.95 (–18.78, 2.89)	5.50	0.150
Class IV	–23.65 (–40.48, –6.82)	8.55	0.006†	–23.64 (–36.70, –10.57)	6.63	0.001†	–18.92 (–36.1, –1.75)	8.72	0.031†
Psychosocial									
Depression (PHQ-9)	–0.55 (–1.25, 0.15)	0.36	0.124	–0.48 (–1.03, 0.08)	0.28	0.090	–0.62 (–1.34, 0.08)	0.36	0.081
Social support (MSPSS)	0.19 (–0.03, 0.41)	0.11	0.098	0.16 (–0.02, 0.34)	0.09	0.087	0.21 (–0.02, 0.44)	0.12	0.071
Cognitive domains									
Attention	0.34 (–0.12, 0.57)	0.22	0.131	…	…	…	…	…	…
Executive Function	…	…	…	0.24 (0.02, 0.51)	0.14	0.075	…	…	…
Memory	…	…	…	…	…	…-	0.51 (0.14, 0.89)	0.19	0.008†

MSPSS indicates Multidimensional Scale of Perceived Social Support; NYHA, New York Heart Association; PHQ-9, Patient Health Questionnaire; and SES, socioeconomic status.

*Each cognitive domain was examined in a separate model.

†Significant at $P<0.05$.

could have been enhanced by using a validated interview,[42] reassessing the medical record, or contacting providers directly. Relatedly, the dearth of objective measurement of HF severity or vascular disease (eg, stenosis and white matter hyperintensities) is problematic and should encourage future studies to determine the degree to which physiological heart or brain damage is related to cognition and medication adherence. The examination of cerebrovascular damage and perfusion is especially warranted, given that nonadherent patients were twice as likely to report a history of cerebrovascular accident or transient ischemic attack compared with adherent patients (13% versus 6%) and may have hypoperfusion.[43] Finally, these data cannot determine whether better medication adherence preserves cognitive function in HF.[44] Certainly, better medication adherence would be expected to predict better outcomes,[14] but this possibility needs to be tested in prospective trials in which medication adherence and cognitive function are measured at multiple time points over an extended period.

Conclusions

To briefly summarize, we found that cognitive impairment, and memory in particular, is associated with objectively monitored medication adherence in patients with HF. Given the substantial number of patients who were nonadherent and the known association between medication nonadherence and poorer HF outcomes, these findings highlight the importance of considering cognitive function in the management of patients with HF. Such considerations might include standard screening of cognitive impairment and added intervention for those with identified deficits. Future studies are needed, which examine the link from cognitive impairment and poor medication adherence to actual hard clinical outcomes, such as hospitalization and mortality.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Heart failure patients with memory impairment may be at risk for poorer adherence to medications. For every 8-point decrease in patients' standardized memory scores at baseline, adherence rates dropped by 13% points. For a patient taking 10 doses per day, this drop in adherence could translate to missing nearly 40 doses/month. Practitioner responses to these findings may include (1) using brief cognitive screening methods (eg, Montreal Cognitive Assessment) to identify cognitively at-risk patients, (2) referring patients for comprehensive neuropsychological testing if indicated by abnormal cognitive screener results, and (3) implementing tailored interventions to compensate for poorer medication adherence, such as eliciting caregiver support or scheduling more frequent follow-up visits to prevent symptom exacerbation because of nonadherence.

Association Between Poorer Cognitive Function and Reduced Objectively Monitored Medication Adherence in Patients With Heart Failure

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