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What puts heart failure patients at risk for poor medication adherence?

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Background: Medication nonadherence is a major cause of hospitalization in patients with heart failure (HF), which contributes enormously to health care costs. We previously found, using the World Health Organization adherence dimensions, that condition and patient level factors predicted nonadherence in HF. In this study, we assessed a wider variety of condition and patient factors and interactions to improve our ability to identify those at risk for hospitalization.

Materials and methods: Medication adherence was measured electronically over the course of 6 months, using the Medication Event Monitoring System (MEMS). A total of 242 HF patients completed the study, and usable MEMS data were available for 218 (90.1%). Participants were primarily white (68.3%), male (64.2%), and retired (44.5%). Education ranged from 8–29 years (mean, 14.0 years; standard deviation, 2.9 years). Ages ranged from 30–89 years (mean, 62.8 years; standard deviation, 11.6 years). Analyses used adaptive methods based on heuristic searches controlled by cross-validation scores. First, individual patient adherence patterns over time were used to categorize patients in poor versus better adherence types. Then, risk factors for poor adherence were identified. Finally, an effective model for predicting poor adherence was identified based on identified risk factors and possible pairwise interactions between them.

Results: A total of 63 (28.9%) patients had poor adherence. Three interaction risk factors for poor adherence were identified: a higher number of comorbid conditions with a higher total number of daily medicines, older age with poorer global sleep quality, and fewer months since diagnosis of HF with poorer global sleep quality. Patients had between zero and three risk factors. The odds for poor adherence increased by 2.6 times with a unit increase in the number of risk factors (odds ratio, 2.62; 95% confidence interval, 1.78–3.86; $P<0.001$).

Conclusion: Newly diagnosed, older HF patients with comorbid conditions, polypharmacy, and poor sleep are at risk for poor medication adherence. Interventions addressing these specific barriers are needed.

Keywords: heart failure, medication adherence, multiple chronic conditions, risk factors, self-care, sleep quality

Introduction

Heart failure (HF) affects more than five million adults (12% of older adults) in the United States.[1] For patients, the symptoms of fatigue, shortness of breath, depression, poor memory, and impaired sleep make HF burdensome.[2] Symptoms drive hospitalization: one in four HF patients is readmitted to a hospital within 30 days of hospital discharge, and almost half are readmitted within 6 months.[3] These hospitalizations are the primary contributor to the staggering medical cost of HF: $30.7 billion annually.[4] This cost is projected to increase more than twofold by 2030, making HF the most expensive condition billed to Medicare.[5]

A variety of reasons for HF hospitalization have been described, but as noted by Desai and Stevenson[6] a robust and actionable model of risk factors for hospitalization is needed. In a prior study, we developed an effective model of risk factors for

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hospitalization and demonstrated that medication nonadherence was the best predictor of hospitalization in a sample of HF patients, after considering numerous demographic, support, clinical, symptom, cognitive, and self-care factors.[7] This result is not surprising, in that most authors have found medication nonadherence rates between 40% and 60% in patients with HF.[8] At this point, the urgent need is to identify modifiable factors associated with medication nonadherence.

In the prior study, we used recently developed adaptive modeling methods to analyze objectively measured medication adherence as collected prospectively, using the Medication Event Monitoring System (MEMS®; AARDEX Group Ltd, Sion, Switzerland), which records the date and time of each opening of the MEMS device, and presumably the taking of a dose of the associated medication. We identified individual patient medication adherence patterns over time and clustered these patterns into adherence types.[7] These adherence types were used to identify the two categories of poor versus (vs) better adherence, an approach that is distinctly more sensitive than categorizations of adherence based on percentage prescribed doses taken (eg, $<80\%$ vs $\geq 80\%$). This nuanced approach contributed significantly to the predictive capability of the model for hospitalization, which had excellent discrimination characteristics.[7] In this article, we build on previously identified individual patient adherence patterns and types and describe risk factors for poor adherence.

This is a second article exploring predictors of medication adherence in HF patients. In the first article, we used the World Health Organization[9] dimensions of adherence (socioeconomic, condition, therapy, patient, and health care system) to focus our analyses.[10] These dimensions reflect the types of variables found to predict treatment adherence in various populations.[11,12] In our first study of HF patients, we determined that patient and condition characteristics contributed most to a steep decline in medication adherence. Patients with lapses in attention (odds ratio [OR], 2.65; $P=0.023$), excessive daytime sleepiness (OR, 2.51; $P=0.037$), and two or more medication dosing intervals per day (OR, 2.59; $P=0.016$) were more likely to have a steep decline in adherence over time than to have persistent adherence.[10] However, as only a select group of possible predictors was tested in that study and no interactions were explored, in this current study, we build on our earlier work by assessing a wider variety of available conditions and patient-level risk factors for poor adherence. The purpose of this work is to identify risk factors associated with medication adherence problems in HF patients, with the ultimate goal of identifying and implementing interventions that address important barriers to adherence, and so reduce the chance of hospitalization. This purpose will be addressed in three steps: identify individual risk factors for poor adherence, identify a multiple risk factors model for poor adherence, and identify a multiple risk factors and interactions model for poor adherence.

Materials and methods

This was a secondary analysis of adherence data from a prospective cohort study of a consecutive sample of 280 adults with a confirmed diagnosis of HF enrolled from three outpatient sites in the northeastern United States; 242 (86.4%) of these patients completed the 6-month study.[13] Institutional review board approval was obtained at the University of Pennsylvania, the participating sites where we enrolled participants, and the University of North Carolina at Chapel Hill, and all participants gave informed consent. The primary objective of the parent study was to clarify the extent to which excessive daytime sleepiness influences HF self-care and clinical outcomes and the mechanism of the effect. Study methods have been described previously.[13] Participants were preferentially sampled for variability in daytime sleepiness and cognition. Patients with severe depression, dementia (Telephone Interview for Cognitive Status [TICS] scores ≤ 24[14]), renal failure requiring dialysis, terminal illness, or history of serious drug or alcohol abuse within the past year were excluded. Because the parent study focused on sleepiness, patients with night-shift responsibilities were excluded. Study participants were followed-up for 6 months, with home visits at baseline, 3, and 6 months, where data were collected by research assistants. A list of all medications taken, including over-the-counter and as-needed medications, was made on the basis of visual assessment by the research assistant during the home visit. As almost half of all HF patients are readmitted to a hospital within 6 months, a 6-month interval was deemed adequate for follow-up.[3,6,15] Nurses abstracted clinical information, including comorbid conditions, from medical records. All data were collected between 2007 and 2009.

Measures

Medication adherence was assessed using MEMS, a valid method of measuring medication-taking behavior.[16,17] Methods used to collect these MEMS data have been described in detail elsewhere,[10] but MEMS data were collected for a single selected medication scheduled to be taken one to three times daily. Our preference was that the MEMS be used with a medication taken in multiple daily doses, but sometimes negotiation was necessary when the medication to be used in the device was chosen. Only one medication was monitored, a practice

that has been shown to be adequate because a single drug can be used to illustrate medication-taking patterns.[18,19] Most patients (56.7%) put their beta-blocker in the device, but 15.2% put an angiotensin-converting-enzyme inhibitor in it. Putting a diuretic in the device was strongly discouraged, and only seven patients (3.2%) put their diuretic in the MEMS. MEMS data were downloaded for each patient at 3 and 6 months and were cleaned based on patient diaries, with clarification provided by telephone as needed. Specifically, patients were asked to note in their research diary whether something unusual happened that gave misleading data. An example would be that, after refilling a prescription, the device was opened an extra time that day to fill it with medicine. These types of incidents were captured in the diary and adjusted in the raw data. Participants were fully informed about the MEMS device, but telling patients that their medication dosing will be monitored is not sufficient to change behavior significantly.[20]

The World Health Organization[9] dimensions of adherence (socioeconomic, condition, therapy, patient, and health care system) were used to focus the choice of additional indicators of the most promising dimensions and patient-related and condition-related factors. Patient-related variables were grouped into the categories of demographic (Table 1) and social support (Table 2). Condition-related factors were classified as clinical (Table 3), self-care (Table 4), symptom (Table 5), and cognition (Table 6) variables. Only baseline values for these variables were used in analyses. A variety of standard scales were considered; these scales and their psychometric properties are summarized in Table 7. Cognition was measured by a battery of neuropsychological tests, including the Digit Symbol Substitution Test, the Letter Number Sequencing subtest, the Probed Memory Recall Task, and the Trail Making Test: A and B.[21] The non-scale-based variables of Tables 1–6 are self-explanatory.

Some variables were derived from investigator-generated lists such as the Compensatory Activities Score. Participants were presented with a list of behaviors used by patients (eg, lists) and support persons (eg, reminders) to compensate for memory problems. The number endorsed was used to compute the Compensatory Activities Score. Fatigue was measured as the sum of two items from the Kansas City Cardiomyopathy Questionnaire.[22] These items ask how many times fatigue has limited the ability to do activities and how bothersome fatigue has been. Each item is scored 1 to 7. Fatigue scores ranging from 2 to 14 were reversed so that higher scores indicate more fatigue. The alpha coefficient of the fatigue measure was 0.90.

Data analysis

In our prior study using adaptive methods[23] to model the effect of medication adherence on hospitalization for the

Table 1 Summary statistics for available demographic variables

Variable and observed range	n (%)*	Mean (SD; n)*
Employment status		
Retired	97 (44.5)	
Unemployed or disabled	62 (28.4)	
Employed (full or part time)	59 (27.1)	
Sex		
Male	140 (64.2)	
Female	78 (35.8)	
Income		
Do not have enough	35 (16.1)	
Have enough or more	183 (83.9)	
Insurance		
Government or none	122 (56.0)	
Commercial or health maintenance organization	96 (44.0)	
Race		
Nonwhite	69 (31.7)	
White	149 (68.3)	
Age		
30–89		62.8 (11.6; 218)
ANART score		
0–49		31.0 (11.2; 218)
Years of education		
8–29		14.0 (2.9; 218)

Note: *Out of 218 patients with some Medication Event Monitoring System data.
Abbreviations: SD, standard deviation; ANART, American National Adult Reading Test.

Table 2 Summary statistics for available social support variables

Variable and observed range	n (%)*	Mean (SD; n)*
Living alone		
Yes	48 (22.0)	
No	170 (78.0)	
Marital status		
Single, divorced, separated, or widowed	88 (40.4)	
Married or partnered	130 (59.6)	
Quality of support		
Satisfactory to good	75 (34.4)	
Very good	143 (65.6)	
MSPSS score		
14–84		72.9 (11.3; 210)

Note: *Out of 218 patients with Medication Event Monitoring System data.
Abbreviations: SD, standard deviation; MSPSS, Multidimensional Scale of Perceived Social Support.

same adherence data, we identified seven adherence types.[7] First, individual adherence patterns were generated for each patient, consisting of possibly nonlinear mean adherence and adherence variability curves over time. These adherence patterns were adjusted for prescribed medication rates so that the ideal adherence pattern had mean adherence 1 at each time, with no variability. Then, these patterns were clustered into seven adherence types consisting of patients with similar adherence patterns. The best combination of these seven adherence types for predicting hospitalization was the dichotomous adherence type of poor adherence (ie, with very low adherence some time during study participation) versus better adherence (ie, primarily moderate or better levels of adherence throughout study participation). This dichotomous poor adherence type is modeled in reported analyses.

Table 3 Summary statistics for available clinical variables

Variable and observed range	n (%)*	Mean (SD; n)*
Exercise		
None	36 (16.5)	
Some	182 (83.5)	
Body mass index, kg/m^2		
15–67		30.8 (7.9; 218)
Blood urea nitrogen		
6–97		24.8 (13.8; 216)
Charlson total		
1–11		2.7 (1.8; 218)
Comorbidities		
0–9		3.0 (2.1; 218)
Creatinine		
0.5–3.4		1.3 (0.5; 215)
Diastolic blood pressure		
45–103		68.9 (110.8; 216)
Ejection fraction		
5–80		35.8 (17.4; 217)
Hemoglobin		
8.1–18.4		13.1 (1.8; 209)
Months since heart failure diagnosis		
0–508		76.2 (75.5; 203)
Pulse		
42–100		69.8 (11.5; 218)
Serum sodium		
131–146		139.1 (2.9; 213)
Systolic blood pressure		
80–176		116.0 (17.5; 217)

Note: *Out of 218 patients with some Medication Event Monitoring System data.
Abbreviation: SD, standard deviation.

In this study, adaptive methods[23] were used to identify risk factors, individually and in combination, for poor adherence, as previously identified from MEMS adherence data.[7] Adaptive methods have been used previously for modeling adherence for HIV-positive patients,[24,25] hypertensive patients,[26] and HF patients.[7] These methods use k-fold likelihood cross-validation (LCV) scores for model selection. The data are randomly partitioned into k distinct subsets, called folds. Likelihoods are computed for each fold, using parameter estimates for the data in the other folds. These deleted fold likelihoods are then combined into a LCV score, with larger scores indicating better models for the data. LCV scores provide for an objective evaluation of models, independent of the size of estimated parameter values (such as ORs for logistic regression models) and of *P*-values. Reported analyses used 10-fold LCV scores computed from likelihoods for logistic regression models.

The model with the largest LCV score is not always the best choice. A less-complex model may be preferable if the reduction in the LCV score is insubstantial (nonsignificant or indistinct). LCV ratio tests, analogous to likelihood ratio tests, can be used to make such assessments. Although these are χ^2-based tests, they are expressed in terms of a cutoff for a substantial (significant or distinct) percentage decrease in the LCV score. A model generating a percentage decrease in the LCV score greater than this cutoff is substantially improved on by the model with the larger LCV score.

Table 4 Summary statistics for available self-care variables

Variable and observed range	n (%)*	Mean (SD; n)*
Prescribed rate for medication controlled by MEMS		
2–3	133 (61.0)	
1	85 (39.0)	
DHFKS score		
7–15		11.7 (1.6; 211)
SCHFI self-care confidence		
42–100		75.7 (14.4; 218)
SCHFI self-care maintenance		
32–92		66.8 (11.6; 215)
SCHFI self-care management		
29–100		66.1 (18.6; 94)**
Total medications		
1–25		9.9 (3.9; 218)

Notes: *Out of patients with available MEMS data; **patients with missing SCHFI self-care management values were those with no symptoms to manage.
Abbreviations: SD, standard deviation; MEMS, Medication Event Monitoring System; DHFKS, Dutch Heart Failure Knowledge Score; SCHFI, Self-Care of Heart Failure Index.

In contrast, a model generating a percentage decrease in the LCV score less than or equal to the cutoff is a competitive alternative to the model with the larger LCV score. If the model with the lower score is also less complex, then it is a parsimonious, competitive alternative and, thus, preferable. For example, if the constant model for predicting adherence generates an insubstantial percentage decrease in the LCV score in comparison with the model based on a specific risk factor, then the constant model is preferable, and so the risk factor is not a substantive predictor of adherence. The cutoff changes with the sample size.

Patients with poor adherence were characterized by identifying risk factors for poor adherence from among the variables of Tables 1–6. Categorical variables were used as reported. For each continuous and ordinal variable, observed values were categorized into lower versus higher values, using each observed value as a cutoff. The cutoff with the best (largest) LCV score was used to determine the associated

Table 5 Summary statistics for available symptom variables

Variable and observed range	n (%)*	Mean (SD; n)*
General health perception		
Poor	24 (11.0)	
Fair to excellent	194 (89.0)	
Health compared with a year ago		
Poor	17 (7.8)	
Fair to excellent	201 (92.2)	
Trouble breathing or ankle swelling within past month		
Yes	94 (43.1)	
No	124 (56.9)	
NYHA class		
IV	41 (18.8)	
I–III	177 (81.2)	
Fatigue		
2–13		6.4 (3.0; 218)
SSS score		
1–6		2.2 (1.2; 218)
ESS score		
0–23		6.7 (4.5; 218)
PSQI global sleep score		
0–19		7.1 (4.0; 218)
PHQ total		
0–18		4.4 (3.6; 218)

Note: *Out of 218 patients with some Medication Event Monitoring System data.
Abbreviations: SD, standard deviation; NYHA, New York Heart Association; SSS, Stanford Sleepiness Scale; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; PHQ, Patient Health Questionnaire.

Table 6 Summary statistics for available cognition variables

Variable and observed range	Mean (SD; n)*
CAS	
0–23	9.4 (4.4; 218)
DSST score	
11–96	54.4 (16.7; 217)
LNS score	
1–20	8.9 (3.4; 214)
PMR score	
0–4	2.1 (1.2; 217)
PVT lapses	
0–79	7.8 (12.4; 214)
TICS score	
26–40	33.8 (2.9; 218)
TMTA score	
14–120	41.5 (17.3; 218)
TMTB score	
8–300	105.3 (53.3; 217)
Dimensions cognitively impaired	
0–5	1.6 (1.0; 218)

Note: *Out of 218 patients with some Medication Event Monitoring System data.
Abbreviations: SD, standard deviation; CAS, Compensatory Activities Score; DSST, Digit Symbol Substitution Test; LNS, Letter Number Sequencing; PMR, Probed Memory Recall; PVT, Psychomotor Vigilance Task; TICS, Telephone Interview for Cognitive Status; TMTA, Trail Making Test: A; TMTB, Trail Making Test: B.

potential risk factor. The risk factor category corresponded to the range of values generating an OR greater than 1 for poor adherence. When a predictor had missing values, those observations were conservatively assigned to the non-risk factor category. In this way, all patients having an identified risk factor had non-missing values for the associated predictor. Cutoffs with less than 10% of the observations in either the lower or higher categories were excluded to avoid sparse cases.

Categorizing continuous/ordinal variables into dichotomous risk factors has the advantage of allowing for missing values without loss of data and of having a practical clinical interpretation. However, the disadvantage is possible loss of information. Whether substantial information has been lost or not can be assessed by comparing LCV scores for a dichotomous risk factor model with the model based on the associated continuous/ordinal variable. This is only possible if that variable has no missing values, as LCV scores are only comparable when based on the same set of data.

Bivariate models were generated for all potential risk factors. Then a multiple risk factors model was generated, using the adaptive modeling process of Knafl et al[23] considering only the risk factors with significant ($P<0.05$) bivariate effects. This adaptive modeling process has been described elsewhere.[7,26] In this case, the process first adds risk factors systematically to the model and then contracts the expanded model to remove extraneous risk factors, if any, using a LCV ratio test to decide when to stop the contraction.

Next, an adaptive model was generated with this same process, but considering the same set of risk factors as well as possible pairwise interactions between any two of them to obtain an assessment of the effect of interactions between risk factors. Pairwise interactions holding for less than 10% of the observations were excluded to avoid sparse cases. Finally, this latter model was used to compute a risk index for poor adherence for patients as the count of that model's risk factors and risk factor interactions.

Results

Sample

Usable MEMS data were available for 218 (90.1%) of the 242 parent study subjects who completed that study. Summary statistics for the patients with usable MEMS data are presented in Tables 1–6 for available variables within the six categories described earlier. For example, patients were primarily white (68.3%), male (64.2%), and retired (44.5%). Education ranged from 8–29 years, with a mean of 14.0 years (standard deviation, 2.9 years), whereas ages ranged from 30–89 years, with a mean of 62.8 years (standard deviation, 11.6 years). A total of 63 (28.9%) of the patients with usable MEMS data had poor medication adherence.

Risk factors for poor adherence

Table 8 presents results for characterizing poor adherence, considering the variables of Tables 1–6, one at a time. Individual risk factor analyses identified 12 significant ($P<0.05$) individual risk factors for poor adherence, including one demographic, zero social support, three clinical, one self-care, four symptom, and three cognition risk factors. The cutoff for a substantial percentage decrease in LCV scores for these analyses is 0.88%. The percentage decrease for the constant model exceeds this cutoff for only two (16.7%) of the twelve variables (LCV scores not reported), indicating that LCV ratio tests are more conservative than tests for zero coefficients, and thus are similar in effect to multiple comparisons procedures.

There are five continuous/ordinal variables with no missing values generating individual risk factors in Table 8. For two of these variables (number of comorbidities and TICS score), the LCV scores were better for the individual linear models, but with insubstantial percentage decreases for the associated individual risk factor model (0.55357 vs 0.55543 and 0.54778 vs 0.54826, with percentage decreases of 0.33% and 0.09%, respectively). For two other of these variables

Table 7 Summary of each standard scale used

Scale name	Description	Psychometric properties
American National Adult Reading Test (ANART)[53,54]	Measure of premorbid, crystalized intellect. A list of 50 phonetically irregular words (eg, aisle) is read aloud. The number of words pronounced correctly is used as the score.	Reliabilityby Cronbach's alpha was 0.93. Validity was demonstrated by comparing with the Wechsler Adult Intelligence Scale-Revised (WAIS-R) vocabulary test; coefficient was 0.75.
Multidimensional Scale of Perceived Social Support (MSPSS)[55,56]	A 12-item measure assessing social support from family, friends, and a significant other. Responses range from 1 (very strongly disagree) to 7 (very strongly agree), with higher scores indicating more perceived support.	Reliability coefficients range from 0.85–0.91. Factorial validity has been confirmed repeatedly.
Charlson Comorbidity Index[57]	Seventeen broad categories of conditions scored with 1–6 points. Scores range from 0–34 and can be classified as low, moderate, and high comorbidity.	Established validity for predicting mortality, complications, health care resource use, length of hospital stay, discharge disposition, and cost.
Dutch Heart Failure Knowledge Score[58]	Fifteen items measuring general knowledge of HF and knowledge of HF treatments, HF symptoms, and symptom recognition.	Items based on established patient education guidelines of the Netherlands Heart Foundation, which mirror those of the American Heart Association.
Self-Care of Heart Failure Index (SCHFI V6.2)[59]	Twenty-two items, measured using a four-point self-report response format, which form three scales: self-care maintenance, management, and confidence.	Internal consistency tested by factor score determinacy, coefficients all >0.70. Moderate to high correlations over time in test–retest reliability testing. Construct validity has been demonstrated. The SCHFI is sensitive to subtle behavioral changes in a variety of HF samples.
Epworth Sleepiness Scale (ESS)[60]	A measure of global or typical sleepiness. Respondents rate the likelihood of falling asleep in eight soporific situations using a four-point Likert scale ranging from never dozing (0) to high chance of dozing (3).	Test–retest reliability (r=0.82) and internal consistency (α=0.88) have been established. Single factor structure. ESS correlates significantly with the frequency of apneas and has a sensitivity of 93.5% and a specificity of 100% for distinguishing pathological from normal sleepiness.
Stanford Sleepiness Scale[61]	The Stanford Sleepiness Scale provides a rating of sleepiness at a particular moment in time. Current degree of sleepiness is rated 1 (vital, alert, or wide-awake) to 7 (feeling that sleep onset is soon).	Sensitive to both sleep deprivation and time of day. Reliability tested as the correlation between alternative forms was adequate (0.88).
Patient Health Questionnaire (PHQ-9)[27]	The PHQ-9 is a measure of depression. Scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression, respectively.	Reliable and valid in numerous populations including HF.
Pittsburgh Sleep Quality Index (PSQI)[62]	A self-report measure of the perception of habitual sleep quality measuring seven domains for the prior month: 1) sleep quality; 2) latency; 3) duration; 4) habitual sleep efficiency; 5) use of sleep medications; 6) disturbance; and 7) daytime dysfunction. A global score (0–21 points) is obtained by summing scale domain scores. Higher scores indicate poorer global sleep quality.	Internal consistency reliability is in the range of 0.77–0.83. In test–retest reliability testing, scores were not significantly different. PSQI scores have been validated by comparison with polysomnography and shown to discriminate among known groups.
Psychomotor Vigilance Test (PVT)[63]	Measure of simple attention. Subjects press a button in response to a series of red digits "000" in an automated light-emitting diode counter window of a small, portable device. Signals are presented at random intervals over a 10-minute period. Metrics involving response speed and lapses are the best primary outcomes for the 10-min PVT.	Highly sensitive measure of sleep deprivation.

Abbreviation: HF, heart failure.

(age and total medications), the LCV scores were worse for the individual linear models, but with insubstantial percentage decreases compared with the associated individual risk factor model (0.54820 vs 0.55160 and 0.54622 vs 0.54894, with percentage decreases 0.62% and 0.50%, respectively). For the fifth variable (Patient Health Questionnaire[27] total score), the LCV score was worse for the individual linear model and with a substantial percentage decrease compared

with the associated individual risk factor model (0.54308 vs 0.54857, with percentage decrease 1.00%). These results indicate that, in this case, consideration of dichotomous risk factors does not result in loss of predictive capability over associated linear models. Further, sometimes dichotomous factors even provide distinct improvements in predictive capability.

The adaptive multiple risk factors model, generated considering the twelve significant risk factors of Table 8, had three risk factors: higher Trail Making Test: B, a measure of complex attention (P=0.002; OR, 3.36; 95% confidence interval [CI], 1.56–7.25); higher number of comorbid conditions (P=0.025; OR, 2.04; 95% CI, 1.09–7.25); and lower HF duration (P=0.007; OR, 2.61; 95% CI, 1.30–5.22). The LCV score was 0.56824. In contrast, the best individual risk factor model based on a higher Trail Making Test: B score had an LCV score of 0.55545, with a substantial percentage decrease of 2.25%, indicating that the multiple risk factors model substantially improved on each of the individual risk factor models.

The adaptive modeling process is based on LCV scores, so individual risk factors with large ORs need not be included in the adaptively generated multiple risk factor model, unless those risk factors also generate large LCV scores. For example, the risk factor based on a larger Pittsburgh Sleep Quality Index global sleep score generated the largest OR of 4.78 in Table 8. However, it had the fourth largest LCV score among individual risk factors (scores not reported in Table 8) and was not included in the adaptively generated multiple risk model. In contrast, the risk factor based on a larger Trail Making Test: B score had the second largest OR of 3.51 in Table 8. However, it also had the largest LCV score among individual risk factor models and was included in the adaptively generated multiple risk factor model.

The adaptive model also considering pairwise risk factor interactions is described in Table 9. This model included three risk factor interactions (and no noninteraction risk factors): a higher number of comorbid conditions with a higher total number of medications, older age with poorer global sleep quality, and fewer months since diagnosis of heart failure (ie, less experience with the illness) with poorer global sleep quality. The c-index (also called the c-statistic; the same as the area under the receiver-operating characteristics curve) was 0.72, which is considered acceptable discrimination.[28] The LCV score for this model was 0.57665. The noninteraction multiple risk factors model generated a substantial percentage decrease in the LCV score of 1.46%, indicating that consideration of interactions provided a substantial improvement over only using noninteraction risk factors for predicting poor adherence.

To assess the possibility of collinearity between these three interactions, we computed logistic regression models

Table 8 Significant individual risk factor models of poor versus better adherence

Variable	Factor	n (%)*	*P*-value	OR	95% CI
Demographics					
Age, years	≥61 vs <61	132 (60.6)	0.018	2.17	1.15–4.12
Social support					
–					
Clinical					
Comorbidities	≥4 vs <4	87 (39.9)	0.008	2.26	1.24–4.10
Months since heart failure	≤21 vs >21 or missing	50 (22.9)	0.008	2.43	1.26–4.71
Diastolic blood pressure	≥82 vs <82 or missing	22 (10.1)	0.026	2.77	1.13–6.77
Self-care					
Total medications	≥9 vs <9	132 (60.6)	0.038	1.95	1.04–3.68
Symptoms					
General health perception	Poor vs fair to excellent	24 (11.0)	0.019	2.80	1.19–6.64
Trouble breathing or ankle swelling within past month	Yes vs no	94 (43.1)	0.040	1.86	1.03–3.35
PHQ total	≥10 vs <10	22 (10.1)	0.026	2.80	1.13–6.77
PSQI global sleep score	≥3 vs <3 or missing	195 (89.4)	0.039	4.78	1.09–21.0
Cognition					
DSST score	≤42 vs >42 or missing	55 (25.2)	0.016	2.21	1.16–4.21
TICS score	≤30 vs >30	36 (16.5)	0.027	2.30	1.10–4.80
TMTB score	≥148 vs <148 or missing	36 (16.5)	0.001	3.51	1.68–7.33

Note: *Out of 218 patients with some Medication Event Monitoring System data.

Abbreviations: OR, odds ratio; CI, confidence interval; PHQ, Patient Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; DSST, Digit Symbol Substitution Test; TICS, Telephone Interview for Cognitive Status; TMTB, Trail Making Test: B; vs, versus.

Table 9 Multiple Risk Factor Interactions Model for poor versus better adherence

Description	Interaction term 1		Interaction term 2		At risk group, n (%)*	*P*-value	OR	95% CI
	Variable	Risk factor	Variable	Risk factor				
Higher number of comorbidities with higher total medications	Comorbidities	≥4 vs <4	Total medications	≥9 vs <9	67 (30.7)	0.2	2.89	1.18–7.06
Older age with poorer global sleep quality	Age	≥61 vs <61	PSQI global sleep score	≥3 vs <3 or missing	117 (53.7)	0.004	3.20	1.45–7.07
Fewer months since diagnosis of heart failure with poorer global sleep quality	Months since heart failure	≤21 vs >21 or missing	PSQI global sleep score	≥3 vs <3 or missing	44 (20.2)	0.006	2.82	1.35–5.85

Note: *Out of 218 patients with some Medication Event Monitoring System data.
Abbreviations: OR, odds ratio; CI, confidence interval; PSQI, Pittsburgh Sleep Quality Index; vs, versus.

predicting each of these three dichotomous interactions as a function of the other two. The largest Nagelkerke R^2 value for these models was 4.5%, indicating that collinearity was not a problem for the risk factor interactions model.

Patients had zero to three of the three interaction risk factors, with 69 (31.7%) patients having none of the interaction risk factors, 78 (35.8%) patients having one, 63 (28.9%) patients having two, and eight (3.7%) patients having three factors. For patients with poor adherence, percentages increased from 10.1% to 26.9%, 47.6%, and 62.5% of the 69, 78, 63, and eight patients with zero to three interaction risk factors, respectively. The risk index model based on the number of risk factor interactions as the only predictor of poor adherence had an LCV score 0.57954. The risk factor interaction model was a parsimonious, competitive alternative with an insubstantial percentage decrease in the LCV score of 0.50%. The c-index for the risk index model was acceptable, at 0.71, and the estimated OR for a unit increase in the risk index variable was 2.62 (95% CI, 1.78–3.86; $P<0.001$).

Discussion

In this study, we characterized poor medication adherence, as determined from our prior assessment of electronically monitored patient adherence.[7] Our major finding was that three pairs of interaction risk factors successfully predicted having poor versus better medication adherence levels: a higher number of comorbid conditions with a higher total number of medications, older age with poorer global sleep quality, and fewer months since diagnosis of heart failure with poorer global sleep quality. The addition of even one interaction risk factor increased the odds of poor adherence by about 2.6 times. Some of these risk factors are modifiable and provide direction for intervention.

These results differ in important ways from our prior analysis of predictors of MEMS-based adherence data.[10] First, in that analysis, using growth mixture modeling, we identified two distinct patterns, and 22% of HF patients were in the "steep decline" or poorest medication-adherence group. In the current analysis, when the seven distinct types, accounting for both means adherence and adherence variability over time, as identified earlier,[7] were collapsed into two types, 28.9% were in the poor medication adherence type. Second, having focused the analysis of contributors to a steep decline in adherence on a select group of variables suggested by the World Health Organization model, we identified only three contributors: lapses in attention, excessive daytime sleepiness, and two or more medication doses per day. Moreover, interactions were not considered. In this analysis, we tested more potential contributors in the promising dimensions of patient- and condition-related factors and assessed potential interactions. This approach revealed three specific pairs of interacting risk factors likely to increase the odds of medication nonadherence. Interestingly, the number of daily medication doses for the drug used in the MEMS device did not predict adherence, although this factor has been found repeatedly in other studies.[29,30] Perhaps this was a result of considering adherence variability along with mean adherence, rather than just mean adherence, in forming adherence types.

We found that a higher number of comorbid conditions plus more medications taken daily or polypharmacy, conventionally defined as the chronic use of five or more medications,[31] predicted poor medication adherence. These results are consistent with those of others who have found that more comorbid conditions and more pills taken each day predicted poor medication adherence.[32] We found previously that HF patients with multiple comorbid conditions find that differentiating the symptoms of multiple conditions is one of the most challenging self-care skills.[33] Having multiple conditions also decreases self-efficacy or confidence in one's ability to perform specific self-care tasks such as medication

taking.[34] When intervention studies were examined in a systematic review, medication adherence increased most consistently with behavioral interventions that reduced medication dosing demands,[35] illustrating that polypharmacy adds a level of complexity to life with multiple chronic conditions that predisposes patients to poor medication adherence. In fact, the essence of medication reconciliation, a popular approach for patients with multiple chronic conditions, involves analyzing and resolving medication discrepancies and typically decreases the number of pills taken daily.[36]

Another pair of risk factors for medication nonadherence was the interaction of older age and poorer sleep quality. We are not the first investigators to identify older age as a factor in nonadherence.[5,15,37] Poor sleep quality is also known to impair the ability to pay attention and make good decisions.[38,39] However, the interaction of older age and poor sleep quality may be best explained by the compelling mechanistic explanation described by Neupert et al[37] who examined how daily fluctuations in cognition and busyness are related to daily fluctuations in forgetting to take medications and whether these within-person relationships differed for younger and older adults. On days when the older adults in their study were relatively less busy, they were at lower risk for forgetting to take their medicines, but only if they were also performing well on the everyday cognition assessments. This observation is consistent with our findings that poor sleep quality contributes to forgetting to take medications.[10,13] Together these results reinforce the salience of daily routines and lifestyle factors such as sleep routines, as they influence memory in older adults.

Finally, patients with a shorter duration of HF or less experience with the diagnosis and poor sleep quality were at higher risk for nonadherence. Others have demonstrated previously that patients who are newly diagnosed with HF struggle with self-care.[40,41] Dickson et al described a typology in which novices lacked experience and skill in caring for their HF diagnosis.[42] Knowing that attention and decision-making are impaired by poor sleep and that better decisions are made by people with illness experience, the interaction between shorter duration of HF and poor sleep quality in predicting nonadherence is not surprising.

Together, these results suggest that older age, multiple comorbid conditions, polypharmacy, lack of experience, and poor sleep quality put HF patients at risk for poor medication adherence. Fortunately, interventions addressing some of these predictors are available. Systematic evaluation and modification of the medication regimen (including over-the-counter medicines) in all HF patients could address many of the problems caused by polypharmacy. Multidrug combinations or "polypills" have been advocated as a solution to drug–drug interactions and poor treatment adherence.[43] Lack of experience is best addressed with education and support. We found previously that about 2 months after being diagnosed with HF, patients improve in their abilities to adhere to the treatment program, detect symptoms, and make good decisions about those symptoms.[41] Steering newly diagnosed patients toward a sustainable routine during that 2-month period may decrease problems with medication adherence.

Surprisingly, interventions for poor sleep quality are the most challenging. For people with sleep apnea, continuous positive airway pressure is effective, but adherence to treatment is problematic.[44] For people with insomnia, the most common treatments used are over-the-counter antihistamines, alcohol, and prescription medications such as benzodiazepine receptor agonists.[45] These prescription hypnotics have been shown to have good short-term efficacy[46] and good durability over time frames of up to 12 months,[47,48] but clinical outcomes do not persist after treatment discontinuation, and issues such as rebound insomnia, dependence, abuse potential and respiratory depression[49,50] make providers and patients hesitant to use them. Cognitive behavioral therapy for insomnia is effective,[51] but it is initially time-intensive and costly, and not all patients are willing or able to engage in this form of psychotherapy. Research identifying other treatment options for the general population with poor sleep quality may have an added benefit of improving medication adherence.

Limitations of this study include possible selection bias, as the data were taken from a prospective cohort study in which patients were selected for variability in daytime sleepiness and cognitive function. In addition, as a group, these patients were younger and better educated than some community samples of HF patients. Future research is needed to test these results in more general populations. Because the analyses were exploratory, further research is needed to confirm these results. Further research is needed to investigate longitudinally both the effects of prior risk factors on adherence and of that adherence on subsequent risk factors. Adherence was measured with MEMS for a single HF medication. There is no guarantee that a dose of the medication was taken every time the MEMS device was opened. Moreover, adherence for medications not controlled by the MEMS has not been accounted for. These limitations are offset by several strengths. The statistical approach took into account patterns over time for both mean adherence and adherence variability, allowing a more nuanced understanding of medication adherence than prior studies. Other

strengths include the prospective design and the objective measurement of medication adherence.

In conclusion, medication adherence is a continuing problem for which solutions are urgently needed. In this study, we identified three pairs of variables associated with nonadherence. Together, these three pairs suggest that clinicians caring for HF patients who are of older age, those with multiple comorbid conditions and taking numerous medications, and those who are newly diagnosed should anticipate problems with medication adherence and discuss ways to assist patients to avoid adherence problems. Asking patients about their sleep quality should be a routine element of all clinical encounters.[52] Future research is needed to identify interventions that adequately address these predictors of nonadherence.

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Disclosure

The authors report no conflicts of interest in this work.

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