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HEART & LUNG

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Linkages between anxiety and outcomes in heart failure

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ABSTRACT

Objective: We investigated the relationship between anxiety and event-free survival (ie, composite endpoint of death, emergency department visits, or hospitalizations) for patients with heart failure (HF), and examined whether behavioral and physiologic mechanisms mediate any association between anxiety and outcomes.

Methods: In this longitudinal study, patients with HF completed the anxiety subscale of the Brief Symptom Inventory, and heart-rate variability and plasma norepinephrine levels were measured. Dietary adherence and medication adherence were measured according to 24-hour urine sodium level and the Medication Event Monitoring System, respectively. Patients were followed at least 1 year for event-free survival.

Results: In total, 147 patients were enrolled. Patients with high anxiety had a shorter (hazard ratio, 2.2; 95% confidence interval, 1.1-4.3; $P = .03$) period of event-free survival than patients with lower anxiety. Anxiety independently predicted adherence to medication ($P = .008$), which in turn predicted event-free survival (hazard ratio, 2.0; 95% confidence interval, 1.2-3.3; $P = .008$). The effect of anxiety ($P = .17$) on event-free survival was less significant when the regression model included both anxiety and adherence to medication than

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when the model only included anxiety ($P = .03$), indicating that adherence to medication mediated the relationship between anxiety and event-free survival.

Conclusion: This is the first study to show that nonadherence to medication links anxiety and event-free survival for patients with HF. Interventions that reduce anxiety and improve adherence may benefit outcomes.

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More than 5,700,000 Americans have heart failure (HF), a chronic condition that contributes to more than 292,000 deaths annually.[1] The effects of demographic, clinical, and treatment characteristics on outcomes are well-studied. Improved outcomes were associated with the use of angiotensin-converting enzyme (ACE) inhibitors,[2] β-adrenergic blockers,[3] angiotensin receptor blockers,[4] aldosterone inhibitors,[5] mechanical circulatory support devices,[6] ventricular reconstruction surgery,[7] cardiac resynchronization therapy,[8] nutritional therapy,[9] and disease management.[10] Nonetheless, hospitalizations for HF continue to rise.[11]

Patients with cardiac disease, including HF, often experience high levels of anxiety.[12-17] Anxiety was linked to adverse outcomes for patients with an acute myocardial infarction (AMI),[18,19] but the link between anxiety and outcomes is not well-established in HF.[20] Although the mechanisms whereby anxiety may be associated with cardiac outcomes are unclear,[13] evidence suggests that behavioral and physiologic pathways (Figure 1) may link anxiety and adverse outcomes.[13]

One physiologic model accounts for the relationships between psychological factors and heart disease outcomes.[21] According to the model, psychological factors, such as anxiety, stimulate sympathetic nervous system (SNS) activity and catecholamine release that, in time, produce harmful consequences. Elevated levels of plasma norepinephrine, which provide the standard biochemical method of assessing the severity of SNS activation, predict mortality for patients with HF.[22] For patients with AMI, but not healthy persons, elevated plasma norepinephrine levels were positively correlated with anxiety.[23] Others demonstrated that although patients with HF had higher baseline sympathetic activity and heart rates than healthy persons, patients with HF manifested even higher sympathetic activity and heart rates during mental stress, which is considered an equivalent to anxiety.[24] Controlling for physiologic variables, anxious patients with AMI had less baroreflex cardiac control than nonanxious patients, placing them at increased risk for dysrhythmias.[25] Further, patients with HF exhibit reduced heart rate variability (HRV),[26] attributable, in part, to high sympathetic activity.[27] Depressed HRV independently predicts morbidity and mortality for patients with HF.[28]

Others hypothesized that behavioral mechanisms, such as nonadherence to treatment, link anxiety and cardiac disease. Compared with nonanxious persons, those with high anxiety may consume an unhealthy diet, smoke, use drugs or alcohol, fail to adhere to therapy, or be physically inactive.[19,29,30] Anxious patients with AMI experience problems coping with challenges, which may adversely affect adherence to treatment and rehabilitation efforts.[31] Nonetheless, no investigators, to the best of our knowledge, have directly examined the hypothesized links of anxiety, SNS arousal, and poor treatment adherence with clinical outcomes for patients with HF.

This study investigated the relationship between anxiety and event-free survival for patients with HF, and examined whether behavioral or physiologic mechanisms mediate any associations between anxiety and outcomes. We hypothesized that (1) patients with HF and high anxiety would manifest worse event-free survival than patients with HF and low anxiety, and (2) SNS arousal and nonadherence to prescribed treatments would mediate the association between anxiety and event-free survival.

Materials and Methods

Design

This substudy was planned a priori as part of a prospective study to assess the relationship between depression and outcomes for patients with HF. The Institutional Review Board, University of Kentucky, approved the study, and all subjects gave written, informed consent.

Sample and Setting

Adult outpatients from a university-based medical center and its clinics and a private hospital located in the Midwestern United States were recruited for the study. Providers referred patients to the researchers, and the researchers posted signs and fliers about the study in outpatient clinics. Patients were eligible to enroll if they had a confirmed diagnosis of chronic HF, as confirmed by a physician using established criteria widely used by researchers.[32,33] In addition, all eligible patients had undergone an evaluation of their HF, were receiving stable doses of drug therapy, had not been

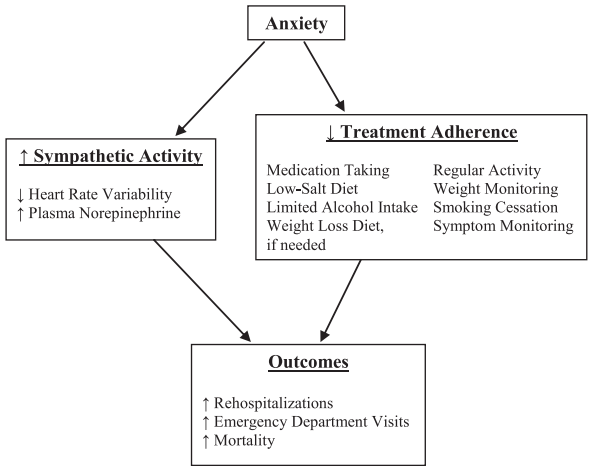

Figure 1 – Proposed physiologic and behavioral pathways linking anxiety and adverse outcomes.

referred for urgent heart transplantation, and read and spoke English. Patients were excluded if they had: (1) HF attributable to valvular heart disease, myocarditis or other inflammatory processes, or pregnancy; (2) a history of cerebral vascular accident within the preceding 3 months, or chronic major sequelae such as an inability to communicate or persistent hemiplegia or paraplegia; (3) an AMI infarction within the past 3 months; (4) a coexisting terminal illness; (5) a major psychiatric disorder, such as schizophrenia, that had been diagnosed by a clinician and that interfered with a patient's ability to answer questions, engage in a longitudinal study, or care for oneself; and (6) impaired cognition. Patients with symptoms of depression or anxiety were not excluded.

Measures

Anxiety

Anxiety was assessed using the anxiety subscale of the Brief Symptom Inventory (BSI).[34] The 6-item anxiety subscale includes brief descriptions of psychological symptoms that are associated with anxiety. Using a scale from 0 ("not at all") to 4 ("extremely"), participants rate their level of distress concerning these symptoms. The 6 items are averaged. The averaged score quantifies the patient's level of anxiety, and can range from 0 to 4. Higher scores denote higher anxiety. The normative value for healthy adults is .35 ± .45. However, normative data are unavailable for patients with HF or other cardiac disorders.[34] The subscale contains no physiologic indices of anxiety, such as heart rate or diaphoresis, that could spuriously overestimate measurements of anxiety in patients with physical disease. Evidence supporting the validity of each subscale of the BSI was reported.[34] Investigators reported that Cronbach's α ranged from .85 to .90 in patients with cardiac disease.[18,35,36] In this study, Cronbach's α coefficient for the BSI was .85.

SNS Arousal

Heart-rate variability is a noninvasive measure of autonomic nervous system tone. Patients with HF typically exhibit decreased HRV, related to high levels of sympathetic activity and decreased parasympathetic activity.[27,37] Heart-rate variability was measured in the time and frequency domains,[38] and assessed using data from 3-channel, 2-hour Holter (DigiCorder 483, Del Mar Avionics, Irvine, CA) electrocardiogram recordings. A 2-hour recording is long enough to accurately measure and assess HRV.[39] Recordings were scanned in semiautomatic mode (with operator verification of all beat types) on a Del Mar 373 Holter Analysis System Scanner (Del Mar Avionics). The data from these recordings included time of beat, type of beat, serial RR intervals (also termed normal-to-normal [NN] intervals) in milliseconds, and standard deviations of normal sinus RR intervals in 5-minute epochs for the 2-hour recording period. To demonstrate interrater and intrarater reliability, 2 members of the study team reviewed the recordings and scanned them twice. The members achieved identical findings for 90% of the recordings. When results differed, the members rescanned the recordings to review and resolve areas of disagreement.

Time-domain analyses are statistical calculations of RR intervals. Time-domain measures included standard deviations of all NN intervals for a selected time period (SDNN), and square roots of the mean squared differences of successive NN intervals.[38]

For frequency-domain (or spectral) analysis, fast Fourier transformation was used to apportion the HRV signal into its frequency components, and to quantify the power of these components.[38] Two frequency bands were of clinical interest: (1) the low-frequency (LF) band (.04 to .15 Hz), and (2) the high-frequency band (.15 to .4 Hz).[38] In humans, LF and HF peak frequencies are commonly centered around about 0.1 Hz and 0.25 Hz, respectively. The area under the curve of each frequency band represents the power within that band. Total power represents the variability of the entire signal, and is obtained by summing the powers of each frequency band. Low-frequency and HF power also were "normalized" (ie, expressed as a percentage of total power).[38] The reliability and validity of this method for reflecting autonomic nervous system tone in cardiac patients were demonstrated.[38] To perform frequency-domain analysis, the recording period was divided into consecutive 5-minute epochs.[38] An instantaneous heart rate function was sampled at 256-millisecond intervals, and smoothed using a 584-millisecond boxcar filter.[40] When an artifact or any non-normal complex occurred, the preceding and succeeding RR intervals were excluded from the analysis, and the instantaneous heart rate function was

estimated according to linear interpolation.[38] The entire 5-minute segment was excluded from analysis if more than 95% of the RR intervals were not NN intervals. The mean NN interval was subtracted from the sampled heart rate data, and a Hanning window was applied.[40] A fast Fourier transform was then computed, resulting in an absolute 5-minute power spectrum.

Plasma norepinephrine, a second measure of SNS arousal used in this study, provides a standard biochemical method of assessing the severity of SNS activation, and was shown to predict mortality in HF.[22] To ensure valid measurements, each blood sample was obtained under several conditions, to control for factors that extraneously affect norepinephrine release: (1) blood was drawn through a catheter that was placed at least 30 minutes before sampling, to avoid the pain and anxiety associated with venipuncture; (2) patients remained in the same semi-fowlers position for 30 minutes before the blood draw; (3) patients were asked to refrain from caffeine, alcohol, and nicotine for at least 8 hours before data collection; (4) the room was comfortably warm and quiet, with minimal interruptions; and (5) the collection of data was conducted at the same time of day (1300 to 1500 hours).[41] Blood was collected into centrifuge blood tubes containing ethylenediaminetetraacetic acid (an anticoagulant), immediately placed on ice, and centrifuged at 4°C. Specimens were stored in single-use aliquots at −80°C until the time of analysis. Plasma concentrations were determined using the Bi-Cat ELISA kit (American Laboratory Products Company, Windham, NH). Mean intra-assay and interassay coefficients of variation for the laboratory were <8%, indicating reproducible and valid measurements.

Adherence

Objective evidence of dietary adherence was measured using 24-hour urine sodium levels. Patients received urinals, urine collection hats, and urine jugs, as well as written and oral instructions regarding how to collect urine for 24 hours. Patients were instructed to record the time and amount of each void in their urination log. Either a member of the research team visited the patient's home to pick up the 24-hour urine collection, or the patient returned the collection to a member of the research team, usually in conjunction with another appointment. In either case, the team member reviewed the urine log for completeness with the patient.

A 2 to 3-g sodium diet is recommended for patients with mild HF.[42] Dietary sodium is absorbed and subsequently secreted. Urinary sodium represents approximately 86%[43] to 95%[44] of sodium intake, depending primarily on the amount of perspiration. Most patients with HF do not engage in strenuous physical activity that produces significant perspiration. Therefore, urinary sodium represents approximately 95% of sodium intake. Thus, urinary sodium at 2.85 g (123 mmol), which is 95% of 3 g, was used to define adherence to a sodium-restricted diet.

Objective evidence of medication adherence was measured using the Medication Event Monitoring System (MEMS, AARDEX, Union City, CA). The MEMS is a microelectronic device housed within the cap of a medication vial. The MEMS records the date and time when the patient removes the cap from the medication vial and presumably takes the correct dose of medication. In a diary, patients documented additional cap removals related to medication refills or other medication vial openings not associated with intake of the medication, thus ensuring accuracy. The MEMS collects real-time data that are later downloaded to a computer. Evidence supporting the validity of the MEMS to assess HF patients' adherence with prescribed medications was reported.[45-47] In fact, the use of an electronic monitoring device has become the preferred standard method to assess adherence.[48] Data were collected for 1 HF medication (ie, an ACE inhibitor, diuretic, β-adrenergic blocker, or digoxin) for each patient. The medication selected for MEMS monitoring was one that the patient took twice per day. If all medications were taken once daily, however, the MEMS was used for the β-adrenergic blocker. If no β-adrenergic blocker was prescribed, the MEMS was used for the ACE inhibitor or angiotensin receptor blocker. Patients used the MEMS for 3 months, and were unable to access data stored within the MEMS. We defined "medication adherence" as the percentage of days on which correct doses taken ([total number of days when dose was taken/total number of days prescribed] × 100). "Acceptable adherence" was defined as ≥88%, because Wu et al reported that this level of adherence was most sensitive and specific in predicting event-free survival.[49]

Procedure

The initial collection of data occurred at a research center. Sociodemographic data (ie, age, education level, gender, ethnicity, and marital status) and clinical characteristics (ie, left ventricular ejection fraction, comorbidities, smoking status, β-adrenergic blocker use, ACE inhibitor use, New York Heart Association [NYHA] functional class) were collected by patient interviews and medical record reviews. Patients completed the BSI Anxiety Subscale and questionnaires regarding demographic information. Next, patients were placed in a semi-fowlers position, a saline-filled butterfly access device was inserted, cardiac leads were placed on the patient's chest, and 2-hour Holter monitoring commenced. After 30 minutes, a plasma norepinephrine blood sample was drawn. Patients received written and verbal instructions on how to collect a 24-hour urine specimen and use the MEMS medication vial. Patients received a urine collection set, and arrangements were made to obtain a urine specimen.

Three-Month Data Collection
Three months after the initial collection of data, the patient returned the MEMS device by giving it to a study team member during a home visit, delivering it during a regularly scheduled clinic visit, or mailing it in a prepaid package. Company-provided equipment was used to download MEMS data to a personal computer.

Twelve-Month Data Collection
Twelve months after the initial collection of data, a study team member reviewed patients' medical records, the hospital administrative record database, death certificates, and patient diaries, and also interviewed patients and family members to collect data about rehospitalizations, emergency department (ED) visits, and mortality. Patients were followed until all had undergone their 12-month collection of data. Thus, some patients were followed for longer than 12 months. The reliability and validity of outcome measures were determined by having all investigators examine the same record and comparing their conclusions. In addition, the accuracy of classifying events was ensured by using multiple methods to determine whether and when an event occurred.

Data Analysis

Data were analyzed with SPSS software, version 16.0 (SPSS, Inc, Chicago, IL). For all analyses, $P \leq .05$ was considered statistically significant. To test the first hypothesis, patients were divided into quartile groups, based on their BSI anxiety score. Because these anxiety groups may have differed in some demographic and clinical characteristics that needed to be controlled statistically, baseline differences were examined using either analysis of variance or linear by linear association χ^2 tests (for dependent nominal variables), as appropriate. Cox proportional hazard modeling was used to assess whether anxiety predicted event-free survival, while controlling for the potential covariates of age, gender, left ventricular ejection fraction, NYHA classification, ACE inhibitor use, and β-adrenergic blocker use.

For the second hypothesis, a series of regression models was used to determine whether SNS arousal or adherence to prescribed treatments mediated any relationship between high anxiety and event-free survival. Mediation was considered to have occurred if a significant relationship was evident between anxiety and event-free survival that became nonsignificant when the mediator was included in the model. The test for mediation followed the steps outlined by Baron and Kenny.[50] In summary, the initial step tested whether anxiety predicted event-free survival, as already described to test the first hypothesis. The second step tested whether anxiety predicted each potential mediator (ie, dietary adherence and medication adherence), using multiple regression. The next step tested whether the mediators predicted event-free survival (using Cox regression), and finally whether anxiety and the potential mediator variables predicted event-free survival when entered together into the model. Mediation was present if, in the final regression, a mediator predicted the outcome, and the *P* value testing the relationship between anxiety and outcomes was less significant than the *P* value in the first step.

Table 1 – Sample demographic and clinical characteristics (n = 147)

Characteristic	
Age (years)	61 ± 11 (SD)
Education (years)	13 ± 3 (SD)
Women, n (%)	44 (30)
Ethnicity	
Caucasian, n (%)	130 (88)
Black, n (%)	16 (11)
Hispanic or Latino, n (%)	1 (1)
Marital status	
Married/cohabitating, n (%)	90 (61)
Widowed, n (%)	24 (16)
Divorced/separated, n (%)	19 (13)
Single, n (%)	14 (10)
Left ventricular ejection fraction (%)	35 ± 14 (SD)
Previous acute myocardial infarction, n (%)	85 (58)
Previous coronary arteries bypass grafting, n (%)	51 (35)
Previous hypertension, n (%)	113 (77)
History of diabetes, n (%)	70 (48)
Current smoker, n (%)	28 (19)
Prescribed β-adrenergic blocker, n (%)	131 (89)
Prescribed angiotensin-converting enzyme inhibitor, n (%)	106 (72)
New York Heart Association classification	
I, n (%)	9 (6)
II, n (%)	47 (32)
III, n (%)	65 (44)
IV, n (%)	22 (15)

SD, Standard deviation.

Results

Characteristics of the Sample

Characteristics of the sample are summarized in Table 1. The average age of the 147 participants was 61 ± 11 years, standard deviation (SD), and nearly one third were women (30%). Over half of the participants were married (61%), and the majority was Caucasian (88%).

Anxiety and Event-Free Survival

The mean anxiety score was .71 ± .74 (SD), and 79 (54.1%) patients reported higher anxiety than the

Table 2 – Mean anxiety score by quartile

Group	n	Mean BSI score
Lowest quartile (0% to 30%)	43	.00 ± .00
Second quartile (31% to 50%)	31	.30 ± .13
Third quartile (51% to 75%)	33	.84 ± .13
Highest quartile (76% to 100%)	39	1.73 ± .51

BSI, Brief Symptom Inventory.

Table 3 – First-event outcomes at follow-up point

Outcome	n (%)
Death because of heart failure	2 (1.4)
Other cause of death	1 (.7)
Hospitalization for heart failure	10 (6.8)
Hospitalization for cardiac disease	23 (15.6)
Other cause of hospitalization	29 (19.7)
Visit to emergency department because of heart failure	2 (1.4)
Visit to emergency department because of cardiac disease	4 (2.7)

reference norm of .35 for healthy adults. Based on the distribution of anxiety scores, subjects were stratified into 4 groups (Table 2), from lowest anxiety to highest anxiety, to facilitate Cox proportional hazard modeling. The 4 groups are not strict quartiles, because 30% of the patients reported no anxiety. No differences in sociodemographic or clinical variables were evident among the 4 anxiety groups.

The mean follow-up time to first event was 389 ± 324 days (SD). The first-event outcomes shown in Table 3 were used for event-free survival analyses. The data confirmed the first hypothesis. Cox proportional hazard modeling revealed that after adjusting for age, gender, NYHA class, left ventricular ejection fraction, ACE inhibitor use, and β-adrenergic blocker use, high anxiety independently predicted event-free survival (Figure 2 and Table 4). Patients in the highest anxiety group were more likely to visit the ED, to be hospitalized, or to die, compared with those in the 3 lower anxiety groups (hazard ratio, 2.2; 95% confidence interval [CI], 1.1 to 4.3; $P = .03$).

SNS Arousal as Mediator

The mean plasma norepinephrine level was .36 ± .23 nmol/L. The norepinephrine level was not related to anxiety, adherence, or any measures of HRV except SDNN (Table 5).

Heart-rate variability monitoring was performed in 65 subjects but was contraindicated in the remaining subjects, who exhibited atrial fibrillation or paced cardiac rhythms. As expected, the distribution of LF and HF power was positively skewed. Therefore, these values were log-transformed from the .04 to .15 Hz and from the .15 to .4 Hz frequency bands, respectively. The time-domain and frequency-domain measurements of HRV are shown in Table 6. No measures of HRV, except for SDNN, were correlated with anxiety, adherence, or norepinephrine level (Table 5).

Given the lack of association between both anxiety and plasma norepinephrine level, and anxiety and HRV (Table 5), the data did not support the hypothesis that SNS arousal mediates the association between anxiety and event-free survival.

Nonadherence as Mediator

Urinary sodium levels from the 24-hour urine specimen reached 196.27 ± 92.26 mmol/day, which computes to an average daily sodium intake of 4512.18 ± 2121.11 mg/day. Of the 141 patients (95.9%) with a useable 24-hour urine sample, 24% manifested a computed sodium intake of ≤3 g. No association between anxiety and dietary adherence was evident, as measured by 24-hour urine sodium level (Table 5). Thus, we did not use dietary adherence in any further mediation tests.

The MEMS data were available for 135 patients (91.8%). Subjects used the MEMS for 1 of their prescribed medications for an average of 94 ± 18 days. Based on date and time data from the MEMS, patients took the correct number of doses on 80.6% ± 22.8% days. Individually, 56% of patients took the correct number of doses on ≥88% of the days that they used the MEMS. Medication adherence was correlated with anxiety (Table 5).

Data regarding objectively measured medication adherence demonstrated that medication adherence mediated the relationship between anxiety and event-free survival, thus partially supporting the second hypothesis. To demonstrate a mediation effect of medication adherence, it is first necessary for anxiety to predict event-free survival. This finding was evident in the Cox regression already described, and was shown in Figure 2. Further demonstration of mediation requires evidence that anxiety predicts adherence to medication. The regression analysis in Table 7 demonstrates this relationship. It is then necessary to demonstrate a relationship between medication adherence and event-free survival. Figure 3 shows that after adjusting for age, gender, NYHA class, left ventricular ejection fraction, ACE inhibitors, and β-adrenergic blockers, adherence to medication independently predicted event-free survival ($P = .001$). Patients who took the correct number of doses on <88% of days were twice as likely (95% CI, 1.2 to 3.3; $P = .008$) to experience the combined endpoint. The final step in demonstrating mediation involves showing, in a regression that includes both anxiety and medication adherence, that the effect of anxiety on event-free survival has an associated P value that is higher (less significant) than the P value for the relationship between anxiety and event-free survival when anxiety is entered as a predictor without adherence. Tables 4 and 8 show that adherence to medication mediated the relationship between anxiety and poorer HF outcomes, because the effect of anxiety on

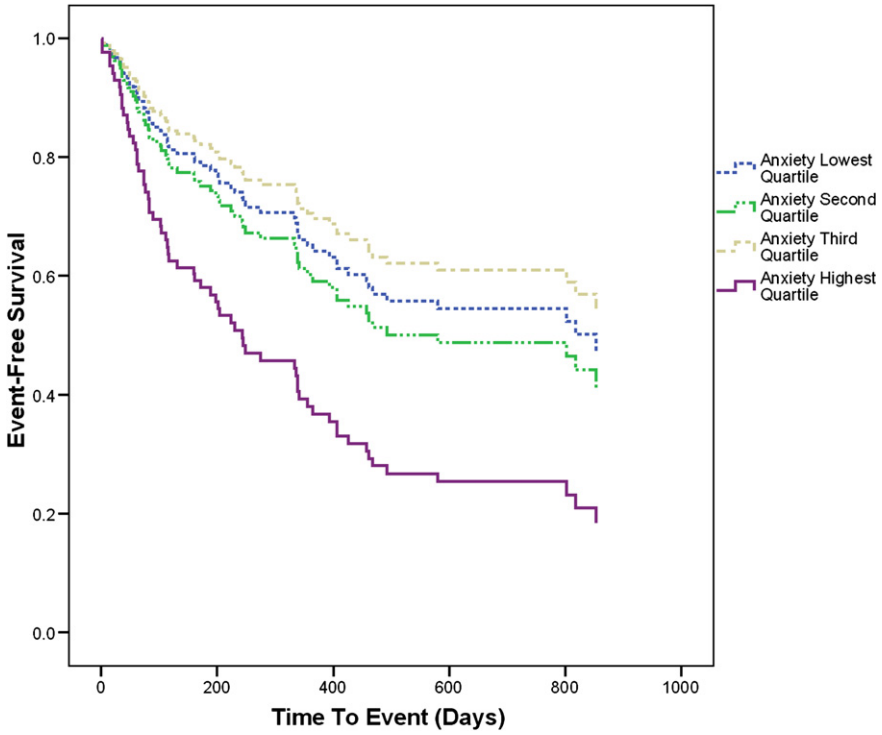

Figure 2 – Cox survival plot of anxiety by quartile and event-free survival.

event-free survival was less significant ($P = .17$) when the regression model included both anxiety and medication adherence than when the model only included anxiety ($P = .03$).

Discussion

To our knowledge, this is the first study to show that anxiety predicts event-free survival for patients with HF, and that medication adherence behavior mediates this relationship. The findings are unique because, unlike others,[51,52] we found that high anxiety independently predicted clinical outcomes. Although anxiety has contributed to poor outcomes for patients with other cardiovascular disorders,[18,19] this new evidence shows that high anxiety and nonadherence to prescribed medications help explain untoward outcomes for patients with HF that cannot be fully accounted for by sociodemographic or clinical variables. These data indicate that it is critical for clinicians to assess anxiety in all patients with HF.

These results align with past findings indicating that patients with HF have high levels of anxiety. In fact, patients with HF were shown to be more anxious than patients with other cardiac disorders.[53,54] Sources of anxiety for patients with HF may include progressive and debilitating physical symptoms with a poor long-term prognosis; complex medication, dietary, and activity treatment regimens; comorbidities; recurring hospitalizations; hopelessness and loss of control; the failure of usual coping mechanisms; isolation from family and friends; frustrations with a complicated healthcare system; financial worries; and fear of death.

The rates of nonadherence to prescribed medications for patients in this study, consistent with previous research,[55,56] revealed that individual patient adherence remains problematic. Measured objectively

Table 4 – Adjusted hazard ratios for the prediction of event-free survival from anxiety, controlling for age, gender, use of medications, left ventricular ejection fraction, and New York Heart Association classification (n = 147)

	Hazard Ratio	95% Confidence Interval	P Value
Age	1.015	.991 to 1.039	.22
Gender	.851	.490 to 1.480	.57
Prescribed angiotensin-converting enzyme inhibitor	.626	.351 to 1.118	.11
Prescribed β-adrenergic blocker	.472	.218 to 1.022	.06
Left ventricular ejection fraction	.987	.968 to 1.007	.22
New York Heart Association classification	1.2	.712 to 2.023	.49
Second anxiety quartile*	1.146	.523 to 2.511	.73
Third anxiety quartile*	.814	.383 to 1.729	.59
Fourth anxiety quartile*	2.167	1.091 to 4.304	.03

Omnibus test of model coefficients, $\chi^2 = 23.79$, $P = .005$.
*Compared with lowest quartile of anxiety.

Table 5 – Correlations between anxiety level, plasma norepinephrine level, dietary adherence, adherence to medications, and measures of heart rate variability

	Anxiety level*	Dietary adherence†	Adherence to medication‡	Plasma norepinephrine§
Anxiety level (n = 146)		.04; P = .67	.18; P =.04	−.10; P = .26
Dietary adherence (n = 141)	.04; P = .67		−.15; P = .11	−.05; P = .57
Adherence to medication (n = 135)	.18; P =.04	−.15; P = .11		−.01; P = .96
Plasma norepinephrine level (n = 143)	−.10; P = .26	−.05; P = .57	−.01; P = .96	
SDNN (n = 65)	−.13; P = .30	−.01; P = .97	−.17; P = .22	−.26; P = .03
RMSSD (n = 65)	−.21; P = .08	−.17; P = .18	.08; P = .56	−.08; P = .50
LF nu (n = 65)	.10; P = .41	.15; P = .26	−.22; P = .12	.07; P = .61
HF nu (n = 65)	−.10; P = .41	−.15; P = .26	.22; P = .12	−.07; P = .61
Log LF (n = 65)	.09; P = .49	.15; P = .25	−.14; P = .30	−.17; P = .18
Log HF (n = 65)	−.003; P = .98	.06; P = .64	−.01; P = .95	−.20; P = .12
Log LF/HF ratio (n = 65)	.15; P = .24	.15; P = .25	−.21; P = .13	.01; P = .95

LF, low frequency; *HF*, high frequency; *nu*, normalized units; *RMSSD*, square root of the mean squared differences of successive NN intervals; *SDNN*, standard deviation of all NN intervals.
* Measured at the continuous level.
† Reflected by 24-hour urine sodium excretion.
‡ Adherence as percentage of days when correct doses were taken.
§ Measured at the continuous level.

Table 6 – Mean time-domain and frequency-domain measurements of heart rate variability (n = 65)

Time domain	
SDNN (milliseconds)	56 ± 26
RMSSD (milliseconds)	32 ± 20
Frequency domain	
LF	248.9 ± 392.1
HF	241.4 ± 339.5
LF nu	49.8 ± 21.1
HF nu	50.2 ± 21.1
Log LF	4.6 ± 1.4
Log HF	4.9 ± 1.2
Log LF/HF ratio	1.0 ±.2

LF, low frequency; *HF*, high frequency; *nu*, normalized units; *RMSSD*, square root of the mean squared differences of successive NN intervals; *SDNN*, standard deviation of all NN intervals.

for 3 months, only 56% of patients took the correct number of medication doses on ≥88% of the days when they used the MEMS. Anxiety predicted adherence to medication. Nonadherence may be related to disagreements about the treatment regimen, the side effects of medications, complex dosing schedules, multiple medications, concerns about the effectiveness of medications, improved symptoms, attitudes about the importance of the medication, the cost of medications, and self-care deficit, all of which may be associated with anxiety.[57,58] Although the exact mechanism by which anxiety is related to adherence remains unknown, anxiety may impair patients' cognition, ability to learn, energy, motivation, and willingness and ability to adhere to treatment.[31] Further research is needed to elucidate how anxiety, a complex and distressing emotion with psychological, physiologic, behavioral, and cognitive manifestations, affects adherence to medications or other interventions that are commonly prescribed for patients with HF.

The objective measure of dietary adherence, the 24-hour urine sodium level, did not predict outcomes or mediate the relationship between anxiety and outcomes. This may be because we measured urine sodium level once. In contrast, we measured adherence to medication for 3 months.

Unlike others, we found no relationship between anxiety and measures of SNS arousal. Likewise, HRV arousal did not predict outcomes, likely because of the low number of patients eligible for HRV monitoring. In addition, most patients in this study were receiving β-adrenergic blockers and ACE inhibitors, which were shown to affect HRV and perhaps diminish autonomic nervous system and neurohormonal disturbances.[59,60] Although β-adrenergic blockers were shown to affect HRV,[60] we enrolled patients receiving these medications because β-adrenergic blockers are the standard of care for patients with HF.[42,61] Researchers were criticized for enrolling patients who are not representative of the typical patient with a given condition.[62] Thus, to avoid this pitfall, which would diminish our ability to generalize findings to the typical patient with HF, we enrolled patients who took β-adrenergic blockers. In addition, it would have been unethical to discontinue these therapies, and difficult to enroll sufficient numbers of patients who, for whatever reason, do not take these medications.

Practice guidelines for the management of HF mention the importance of adherence to medication, but ignore the assessment and management of anxiety, and do not include detailed recommendations

Table 7 – Multiple regression of demographic, clinical, and anxiety variables associated with adherence to medications (percentage of days when correct number of prescribed doses was taken) (n = 147)

Predictor variables	Step F	Step *P* value	R^2	Adjusted R^2	F for change in R^2	*P* value for change in R^2	Standardized β	β *P* value
Step 1	2.64	.052	.06	.04	2.64	.052		
Age							.07	.44
Gender							−.10	.27
NYHA class							−.20	.02
Step 2	3.61	.008	.10	.08	6.20	.01		
Age							.01	.91
Gender							−.09	.33
NYHA class							−.17	.06
BSI anxiety score							−.22	.01

BSI, Brief Symptom Inventory; *NYHA*, New York Heart Association.

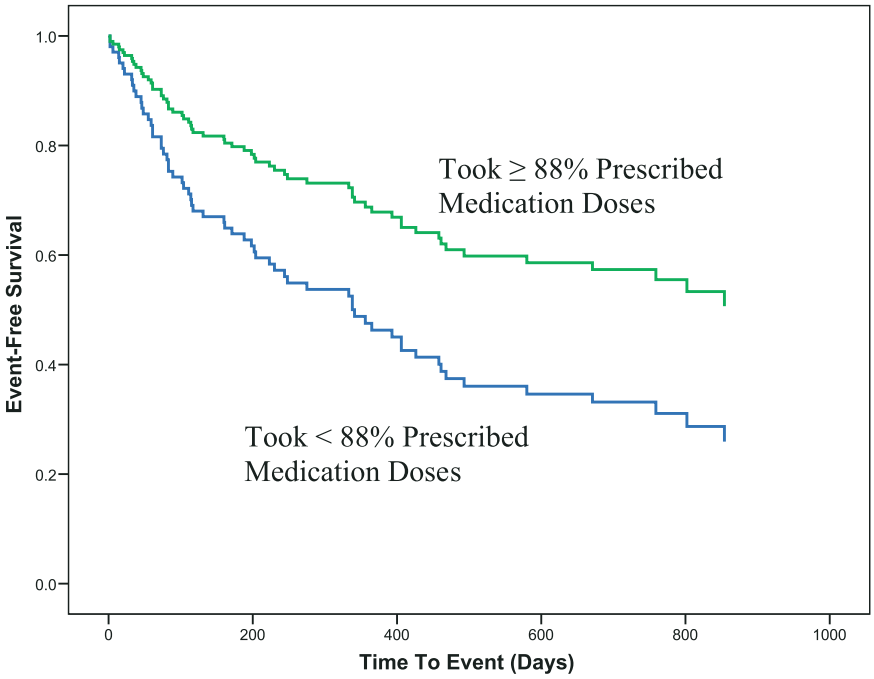

Figure 3 – Cox survival plot of adherence to medications and event-free survival.

on how to improve adherence to medication.[42] Hundreds of clinical trials were conducted to test interventions designed to improve adherence for patients with cardiovascular or other chronic disorders. In summary, adherence to medication and outcomes were shown to improve with physician-supervised, nurse-mediated, home-based management strategies; patient education and discharge planning; reminder cards, calls, or alarms; improved medication container designs; improved patient communication with clinicians; improved dosing schedules; extended clinic hours; the prescription of once-daily formulations or "polypills;" positive reinforcement; electronic monitoring systems; social support; and patient-centered medication instructions.[58,63-65] In a previous study, married patients were more likely to be adherent than patients without a spouse, indicating that interventions designed to improve adherence should include the patient's spouse.[66] However, the guidelines fall short when, at best, they encourage clinicians to consider the patient's psychological state when deciding how to educate and manage patients. No recommendations are available on assessing anxiety or initiating interventions to reduce anxiety. Similarly, recent reviews and clinical studies contain a plethora of strategies that clinicians can use to improve adherence, but omit mention of anxiety.[57,58,67] Importantly, our findings indicate that anxiety predicts adherence to medication, which in turn mediates the relationship between high anxiety and worse outcomes.

Limitations

Four limitations of this study exerted the greatest impact on our findings. First, more subjects than expected manifested atrial fibrillation or paced cardiac

Table 8 – Adjusted hazard ratios for the prediction of event-free survival from anxiety and adherence to medications, controlling for age, gender, medication use, left ventricular ejection fraction, and New York Heart Association classification

	Hazard ratio	95% confidence interval	*P* value
Age	1.007	.982 to 1.032	.60
Gender	.902	.487 to 1.670	.74
Prescribed angiotensin-converting enzyme inhibitor	.538	.293 to .988	.05
Prescribed β-adrenergic blocker	.442	.181 to 1.078	.07
Left ventricular ejection fraction	.988	.966 to 1.010	.29
New York Heart Association classification	1.141	.632 to 2.050	.66
Second anxiety quartile*	.884	.336 to 2.321	.80
Third anxiety quartile*	.952	.413 to 2.194	.91
Fourth anxiety quartile*	1.682	.795 to 3.560	.17
Medication adherence	1.345	1.060 to 1.708	.02

Omnibus test of model coefficients, $\chi^2 = 29.73$, $P = .001$.
*Compared with lowest quartile of anxiety.

rhythm, preventing HRV analyses of these subjects. Second, we used the documented admission diagnosis in each subject's medical record for first-event outcomes. We did not anticipate a large number of nonspecific diagnoses, such as edema and shortness of breath, that were consistent with a diagnosis of HF but not documented as such. As a result, we classified more subjects than expected as "other hospitalization." Third, the sample size was small, but nonetheless adequate to demonstrate a relationship between anxiety and event-free survival. We recommend that future investigators conduct a larger study to confirm or refute our findings, and to test the best strategies for improving adherence. Fourth, although the ethnicity of the sample reflects the patient population where the study was performed, the sample lacks racial diversity.

Conclusions

We found that anxiety predicted event-free survival for patients with HF, and that adherence to medication mediated this relationship. Although causality cannot be inferred from our data, our results suggest that it may be important for clinicians to assess medication adherence objectively for patients with HF, and to consider customizing interventions according to patient needs and preferences. An assessment of adherence to medication should be included in clinical practice guidelines for the management of patients with HF. Nearly all patients used the MEMS without difficulty, and were accepting of it. Objective assessment of adherence to medication in *all* patients may not be feasible or cost-effective. Nonetheless, our findings indicate that clinicians are obliged to pay special attention to medication adherence, especially among highly anxious patients and those who frequently require hospitalizations or visit the ED. If nonadherence is suspected, the MEMS offers an attractive method of assessment. Further, the approximate $100 cost of the MEMS is justified if nonadherence is corrected and hospitalizations or ED visits are avoided.

In conclusion, the mediation effect of nonadherence to prescribed medications on the relationship between anxiety and outcomes adds to the body of research. The astute assessment of anxiety and adherence to medication merits increased attention from clinicians who manage patients with HF, because adherence to medication helps explain how anxiety is associated with adverse outcomes. Although we did not conduct a randomized trial to test intervention strategies in patients with differing levels of anxiety, the findings of this study indicate a need for such research, particularly among patients with the highest levels of anxiety. Interventions designed to reduce anxiety and improve adherence to prescribed medications may improve outcomes.

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