Symptoms of Anxiety and Cardiac Hospitalizations at 12 Months in Patients with Heart Failure

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OBJECTIVE: Heart failure (HF) is a leading cause of hospitalization. Clinical and socio-demographic factors have been associated with cardiac admissions, but little is known about the role of anxiety. We examined whether symptoms of anxiety were associated with cardiac hospitalizations at 12 months in HF patients.

METHODS: HF outpatients (N=237) completed the Hospital Anxiety and Depression Scale (HADS) at baseline (i.e., inclusion into the study). A cutoff ≥8 was used to indicate probable clinical levels of anxiety and depression. At 12 months, a medical chart abstraction was performed to obtain information on cardiac hospitalizations.

RESULTS: The prevalence of symptoms of anxiety was 24.9% (59/237), and 27.0% (64/237) of patients were admitted for cardiac reasons at least once during the 12-month follow-up period. Symptoms of anxiety were neither significantly associated with cardiac hospitalizations in univariable logistic analysis [OR=1.13, 95% CI (0.59–2.17), p=0.72] nor in multivariable analysis [OR=0.94, 95% CI (0.38–2.31), p=0.89]. New York Heart Association (NYHA) functional class III [OR=3.00, 95% CI (1.08–8.12), p=0.04] and a history of HF-related hospitalizations [OR=1.18, 95% CI (1.01–1.38), p=0.03] were independently associated with 12-month cardiac admissions.

CONCLUSIONS: The current study found no significant association between symptoms of anxiety and cardiac hospitalizations at 12 months in HF patients. In contrast, clinical indicators (i.e., NYHA class III and a history of HF-related hospitalizations) were significantly associated with admissions due to a cardiac cause. Future studies are warranted to investigate the importance of symptoms of anxiety in HF using a larger sample size and a longer follow-up duration.

KEY WORDS: cardiac hospitalizations; heart failure; anxiety; depression.

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INTRODUCTION

Heart failure (HF) is considered the end stage of most heart diseases,[1,2] and is a chronic and progressive condition.[3] Currently, HF is a leading cause of hospitalization, especially in patients 65 years or older.[4] In order to decrease morbidity, mortality, and health-care costs, and to improve quality of life, a growing body of literature has focused on the identification of patients at high risk for hospitalizations for HF. Clinical, demographic, socioeconomic, and psychological factors have been established as important associates of hospitalizations among HF patients.[5,6]

Most studies on the role of psychological factors in HF have focused on depression,[7] with several studies indicating that symptoms of depression are related to increased cardiovascular mortality and morbidity,[8–10] including cardiac hospitalizations.[11–13] Although symptoms of anxiety are commonly observed in HF,[14] only a paucity of studies have examined the association between symptoms of anxiety and clinical outcomes,[7,15] with these results being conflicting.[3] In some studies, symptoms of anxiety were not associated with cardiac events,[12,16] mortality,[10,14,17] or cardiac hospitalizations,[13,14,16] while other studies in HF patients showed that anxiety was associated with higher rates of cardiac events[18,19] and cardiac admissions.[12,20,21]

Given this gap in knowledge on the role of anxiety and the preliminary associations between anxiety and HF outcomes still being inconclusive, we examined whether symptoms of anxiety were associated with 12-month cardiac hospitalizations in HF patients.

METHODS

Participants and Procedure

The total sample comprised 381 consecutive HF outpatients recruited between June 2006 and December 2008 from the outpatient clinics of two teaching hospitals (St. Elisabeth Hospital, Tilburg, and Amphia Hospital, Breda, The Netherlands). All patients were treated according to the most recent European Guidelines on HF.[22]

Inclusion criteria were (1) diagnosis of HF, (2) left ventricular ejection fraction (LVEF) ≤40%, (3) New York Heart Association (NYHA) functional class I-III, and (4) stable on oral medication 1 month prior to inclusion. Patients were excluded from participation in case of age ≥80 years, myocardial infarction 1 month prior to inclusion, hospital admissions 1 month prior to inclusion, insufficient understanding of the Dutch language, other life-

threatening diseases (e.g., cancer), cognitive impairments, and presence of a chronic severe psychiatric condition (e.g., psychosis).

At baseline (i.e., inclusion into the study), HF patients were asked to complete a self-report questionnaire to assess symptoms of anxiety and depression, and purpose-designed questionnaires were administered to collect data on patients' socio-demographics. Clinical characteristics were obtained at baseline from patients' medical records, and at 12 months a medical chart abstraction was performed to obtain information about cardiac hospitalizations between baseline and 12 months follow-up.

The study protocol was approved by the medical ethics committees of the participating hospitals, and the study was conducted according to the Helsinki declaration.[23] Patient participation was voluntary, with patients being able to withdraw from the study at any moment, without this decision having implications for future medical treatment. Every patient provided written informed consent.

Measures

Demographics, Clinical Characteristics, and Treatment Variables. Socio-demographic variables included gender, age, marital status (having a partner vs not having a partner), educational level (secondary education and higher vs primary education), and employment status (working vs not working). Clinical variables were obtained from patients' medical records and included LVEF, NYHA class (NYHA class I/II vs NYHA class III), body mass index (BMI), etiology (ischemic etiology vs non-ischemic etiology), cardiac history [i.e., previous myocardial infarction (MI), coronary artery bypass graft surgery (CABG), or percutaneous coronary intervention (PCI)], cerebrovascular history [cerebrovascular accident (CVA) or transient ischemic attack (TIA)], co-morbidities (i.e., diabetes, renal disease, liver disease, chronic obstructive pulmonary disease (COPD), peripheral arterial disease (PAD), or gastrointestinal comorbidities), risk factors (i.e., hypertension or hypercholesterolemia), time since HF diagnosis in years, previous HF hospitalizations, and self-reported smoking (smoking vs not smoking). In addition, treatment variables were collected and included participation in cardiac rehabilitation, device therapy [i.e., pacemaker, biventricular pacemaker, or implantable cardioverter defibrillator (ICD)], and prescribed medications [i.e., ACE-inhibitors, angiotensin II receptor antagonist (ARB), diuretics, digoxin, beta-blockers, nitrates, calcium-antagonists, oral anticoagulants, aspirin, statins, antidepressants, hypnotics, or anxiolytics].

Symptoms of Anxiety and Depression. Patients filled out the Dutch version of the Hospital Anxiety and Depression Scale (HADS) to assess symptoms of anxiety and depression.[24,25] Both subscales consist of seven items that are answered on a four-point Likert scale ranging from 0 to 3.[24] A cutoff score of ≥8 on each subscale represents clinically relevant levels of anxiety and depression.[26] The HADS has been demonstrated to be a valid screening tool for detecting symptoms of anxiety and depression in HF.[27] The internal consistency has been demonstrated previously with Cronbach's alpha of 0.83 for the anxiety subscale and 0.82 for the depression subscale, respectively.[26] In the current study, the correlation between both subscales was 0.56, and Cronbach's alphas were 0.84 for HADS-A and 0.81 for HADS-D, respectively.

Endpoint. The endpoint was defined as cardiac hospitalizations at 12 months, as documented in the patients' medical records. Hospitalization was defined as any planned or unplanned overnight stay in the cardiology clinic of the two participating hospitals. These cardiac hospitalizations comprised HF-related admissions (e.g., HF aggravation) as well as cardiac admissions not directly related to HF [e.g., myocardial infarction (MI)]. Furthermore, cardiac day treatments that required an overnight stay in the cardiology clinic (e.g., coronary angiography or cardioversion) were recorded as cardiac hospitalizations as well. Events were not adjudicated. However, the cause of hospitalization had to be documented by the medical specialists in the patients' medical records.

Statistical Analyses. Group differences were examined using the chi-square test for dichotomous variables and Student's t-test for independent samples for continuous variables. Logistic regression analysis was conducted to determine whether symptoms of anxiety were associated with 12-month cardiac hospitalizations. Covariates were entered into the model using the Enter method, thereby reducing the risk of overfitting.[28] In multivariable analysis, we adjusted for symptoms of depression (cutoff≥8), gender, cardiac history, and NYHA class (I/II versus III), LVEF, and history of HF-related hospitalizations. All covariates were selected a priori based on the literature.[12,16,28–30] Odds ratios (OR) with their corresponding

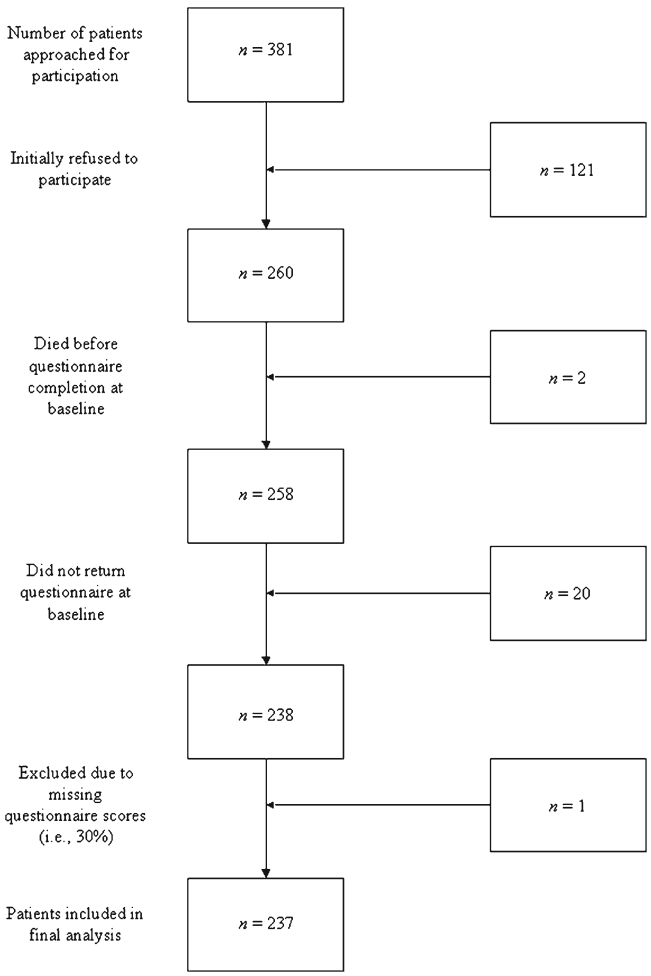

Figure 1. Flow chart of patient selection.

95% confidence intervals (CI) were reported. All results were based on two-tailed tests, and a p-value<0.05 was used to indicate statistical significance. All statistical analyses were performed using SPSS for Windows 17.0 (SPSS Inc., Chicago, IL).

RESULTS

Patient Characteristics

Of 381 patients, 121 initially refused participation (68.2% response rate). Due to death prior to completion of the baseline questionnaire, the questionnaire not being returned, or exclusion due to missings on the questionnaire, final analyses were based on data from 237 patients. A flow chart of the patient selection is provided in Figure 1. No systematic differences between participants and non-participants were found except for non-participants more often being classified in NYHA III compared with participants [31.6% vs 9.3%; $X^2(1)=6.81$, $p=0.01$).

The prevalence of symptoms of anxiety was 24.9% (59/237). Moreover, 27.0% (64/237) of patients were admitted for cardiac reasons at least once during the 12-month follow-up period. Patient characteristics stratified by symptoms of anxiety are presented in Table 1. Some significant differences emerged between anxious and non-anxious HF patients, with anxious patients more often being female, prescribed nitrates and hypnotics, having a cardiac history, having a job, and experiencing symptoms of depression, compared with non-anxious patients (all ps<0.05).

Symptoms of Anxiety and Cardiac Hospitalizations at 12 Months

Figure 2 displays cardiac hospitalizations at 12 months stratified by symptoms of anxiety. In univariable logistic regression analysis, symptoms of anxiety were not significantly associated with increased cardiac hospitalizations at 12 months [OR= 1.13, 95% CI (0.59–2.17), $p=0.72$].

Table 1. Patient Characteristics Stratified by Symptoms of Anxiety*

	Total sample (N=237)	Symptoms of anxiety (i.e., HADS-A≥8) (n=59)	No symptoms of anxiety (i.e., HADS-A≤7) (n=178)	p
Demographics				
Women	51 (21.5)	20 (33.9)	31 (17.4)	0.01‖
Age, mean (SD)	66.9 (8.7)	68.8 (8.5)	66.3 (8.7)	0.05
Having a partner	183 (77.2)	44 (74.6)	139 (78.1)	0.71
Secondary education and higher	91 (39.1)	19 (32.2)	72 (41.4)	0.27
Having a job	33 (13.9)	3 (5.1)	30 (16.9)	0.04‖
Clinical variables				
BMI, mean (SD)	28.2 (5.2)	28.7 (5.0)	28.0 (5.3)	0.36
Self-reported smoking	55 (23.5)	16 (27.1)	39 (22.3)	0.56
NYHA functional class I/II	205 (90.7)	50 (84.7)	155 (92.8)	0.12
LVEF, mean (SD)	33.6 (6.7)	34.6 (5.6)	33.2 (7.1)	0.14
Time since diagnosis in years, mean (SD)	5.0 (4.6)	5.7 (5.5)	4.8 (4.3)	0.28
Ischemic etiology	155 (65.4)	42 (71.2)	113 (63.5)	0.36
Cardiac history†	165 (69.6)	48 (81.4)	117 (65.7)	0.04‖
Cerebrovascular history‡	30 (12.7)	8 (13.6)	22 (12.4)	1.00
Diabetes mellitus	70 (29.5)	21 (35.6)	49 (27.5)	0.31
Renal disease	17 (7.2)	6 (10.2)	11 (6.2)	0.46
COPD	48 (20.3)	15 (25.4)	33 (18.5)	0.34
PAD	29 (12.2)	9 (15.3)	20 (11.2)	0.56
Hypertension	120 (50.6)	26 (44.1)	94 (52.8)	0.31
Hypercholesterolemia	163 (68.8)	43 (72.9)	120 (67.4)	0.53
History of HF-related hospitalizations, mean (SD)	1.5 (2.0)	1.7 (1.9)	1.4 (2.1)	0.35
Symptoms of depression (i.e., HADS-D≥8)	65 (27.4)	42 (71.2)	23 (12.9)	<0.001‖
Treatment variables				
Cardiac rehabilitation	24 (10.4)	6 (10.3)	18 (10.4)	1.00
Device therapy§	32 (13.5)	10 (16.9)	22 (12.4)	0.50
ACE-inhibitor	140 (59.1)	34 (57.6)	106 (59.6)	0.91
ARB	76 (32.1)	18 (30.53)	58 (32.6)	0.89
Diuretics	152 (64.1)	41 (69.5)	111 (62.4)	0.41
Digoxin	39 (16.5)	11 (18.6)	28 (15.7)	0.75
Beta-blocker	162 (68.4)	40 (67.8)	122 (68.5)	1.00
Nitrates	92 (38.8)	30 (50.8)	62 (34.8)	0.04‖
Calcium-antagonist	35 (14.8)	12 (20.3)	23 (12.9)	0.24
Oral anti-coagulants	147 (62.9)	35 (59.3)	112 (62.9)	0.74
Aspirin	86 (36.3)	23 (39.0)	63 (35.4)	0.73
Statins	168 (70.9)	43 (72.9)	125 (70.20)	0.82
Hypnotics	17 (7.2)	11 (18.64)	6 (3.4)	<0.001‖
Anxiolytics	15 (6.3)	7 (11.9)	8 (4.5)	0.09

Results are presented as n (%) unless otherwise stated

†*Myocardial infarction (MI), percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)*

‡*Cerebrovascular accident (CVA) or transient ischemic attack (TIA)*

§*Either single, biventricular, or implantable cardioverter device (ICD)*

‖*p<.05*

Abbreviations: ARB = angiotensin II receptor blockers; BMI = body mass index (kg/m^2); COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class; PAD = peripheral arterial disease

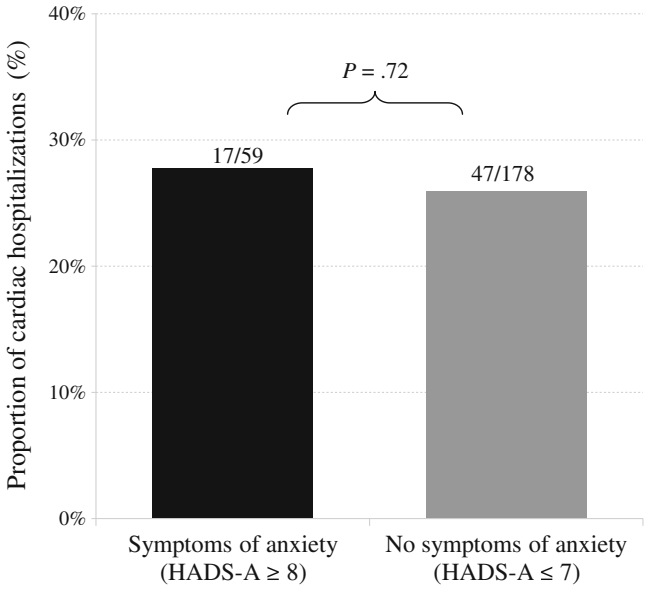

Figure 2. Proportion of cardiac hospitalizations at 12 months stratified by symptoms of anxiety.

In multivariable analysis, symptoms of anxiety were not independently associated with cardiac hospitalizations at 12 months (Table 2), while NYHA functional class III [OR=3.00, 95% CI (1.08–8.12), p=0.04] and a history of HF-related hospitalizations [OR=1.18, 95% (1.01–1.38), p=0.03] were related to increased cardiac hospitalizations. Secondary analysis, in which continuous anxiety scores were examined as possible associates of cardiac hospitalizations, yielded similar results.

DISCUSSION

Heart failure (HF) is a leading cause of hospitalization. Clinical and socio-demographic factors have been associated with cardiac admissions, but little is known about the role of anxiety. Results of the current study demonstrated that symptoms of anxiety were not independently associated with 12-month cardiac hospitalizations. However, patients with a higher NYHA class and a history of HF-related hospitalizations were at 3-fold and 1.5-fold increased odds for hospital admissions due to a cardiac cause, respectively.

In the current study, the prevalence of symptoms of anxiety of 24.9% was relatively low compared with previous studies reporting rates of 28–56% in HF.[13,18,19,21] However, previous studies mainly used the Spielberger State-Trait Anxiety Inventory (STAI) to assess symptoms of anxiety (e.g., [13,18]), which hampers comparability with the current study as we used the HADS. The proportion of patients that was admitted due to a cardiac cause at least once (26.9%) is in line with findings from previous studies, reporting rates between 22% and 28%.[12,16,20,21]

The results of the current study are in line with previous studies, demonstrating that symptoms of anxiety were not significantly associated with cardiac hospitalizations in cardiac patients.[13,14,16] Although other studies demonstrated that symptoms of anxiety were associated with hospitalizations[12,20,21] the current study did not corroborate these findings. However, these discrepancies may be explained by smaller or different sample sizes (i.e., 65 HF outpatients, 111 HF outpatients, and 139 HF outpatients, respectively) and the assessment of symptoms of anxiety using other instruments than the HADS.

In the current study, symptoms of depression were not significantly associated with cardiac hospitalizations at 12 months. This finding is in contrast with previous studies, demonstrating that symptoms of depression were significantly associated with clinical outcomes in HF, including admissions for cardiac reasons,[11–13] and cardiovascular morbidity and mortality.[8–10] These discrepancies may possibly be attributed to the instruments used to assess symptoms of depression or differences in the follow-up duration. In the current study, symptoms of depression were assessed with the HADS, whereas previous studies mainly used the Beck Depression Inventory (BDI) (e.g., [8,10,13]) or the Center for Epidemiologic Studies Depression scale (CES-D).[11]

Clinical factors were the most important associates of cardiac admissions in the current study. Higher NYHA functional class and a history of HF-related hospitalizations were independently associated with cardiac hospitalizations at 12 months. These results are consistent with the literature on disease progression in HF, which describes that in the end stages of cardiovascular disease, like HF, clinical indicators are associated with poor prognosis (e.g., [10,16]). Hence, psychological factors, like symptoms of anxiety, may be mainly important in evaluating the burden of HF on patients, whereas in the prediction of clinical deterioration (such as cardiac hospitalizations) psychological factors may play less of a role.[17]

Following this line of thought, it is possible that symptoms of anxiety may be associated with clinical outcomes in earlier stages of cardiovascular disease rather than in HF. Previous studies support this notion, showing that symptoms of anxiety are associated with higher rates of recurrent coronary events, cardiac hospitalizations, and cardiac mortality in patients admitted for elective CABG or valve surgery,[31] post-MI patients,[32] and ICD patients.[33] In addition, anxiety symptoms have been linked with poor patient-centered outcomes in HF, such as impaired health-related quality of life.[34,35] Although symptoms of anxiety may not be associated with clinical HF outcomes, patient-centered outcomes are important in their

Table 2. Independent Associates of Cardiac Hospitalizations in HF Patients at 12 Months*

	OR	95% CI	p
Symptoms of anxiety (i.e., HADS-A≥8)	0.94	0.38–2.31	0.89
Female gender	0.46	0.19–1.11	0.09
Symptoms of depression (i.e., HADS-D≥8)	1.22	0.52–2.84	0.65
Cardiac history†	1.23	0.60–2.49	0.57
NYHA functional class III‡	3.00	1.08–8.12	0.04‖
LVEF§	0.99	0.94–1.04	0.57
History of HF-related hospitalizations	1.18	1.01–1.38	0.03‖

*Multivariable analysis
†Myocardial infarction (MI), percutaneous coronary interventions (PCI), or coronary artery bypass graft surgery (CABG)
‡NYHA = New York Heart Association functional class
§LVEF = Left ventricular ejection fraction
‖p<.05

own right, as they may serve as performance measures in clinical practice to optimize clinical care[36] and have independent prognostic value beyond demographic and clinical risk markers.[37]

The findings of the current study should be interpreted with some caution. First, subclinical symptoms of anxiety and depression were assessed using self-report, and no information on an established clinical diagnosis of anxiety was collected. Second, since patients with more severe HF were not seen in the outpatient clinic, the majority of patients included were classified as NYHA I/II, which hampers generalizability to the general HF population and to patients with more severe HF in particular. Third, information on hospitalizations was only collected from the hospitals in which patients were enrolled in the study, and adjudication was not included in the study protocol. Hence, no information was available on cardiac hospitalizations from other centers, which could have led to a potential underestimation of the number of admissions. However, we also collected information on 12-month clinical events, including cardiac hospitalizations, by means of a self-report questionnaire. We compared information on these self-report admissions with the information retrieved from patients' medical records, and overall, hospitalizations were comparable. Fourth, the sample size of the current study was relatively small, although comparable to previous studies in HF patients (e.g., [13,20,21]). Nevertheless, power problems may have possibly occurred and limit the generalizability of the findings. Strengths of the study include its multicenter design, and the use of a validated and reliable questionnaire that is frequently used in patients with cardiovascular disease and HF.[38]

Given that HF is a leading cause of hospitalizations,[4] it is important to identify risk markers for hospitalizations in HF. To date, only a paucity of studies has examined the association between symptoms of anxiety and subsequent clinical outcomes in HF,[7,15] with follow-up ranges mainly varying between 6 and 12 months.[10,12,20] In order to optimize clinical care, future studies using a larger sample size and a longer follow-up duration are warranted to more precisely investigate the complex nature of anxiety as an associate of hospitalizations in HF patients. Especially the co-occurrence of symptoms of anxiety and depression should be considered in future research, since these frequently go together [39] and have been associated with impaired health outcomes.[17]

In conclusion, symptoms of anxiety were not independently associated with cardiac hospitalizations at 12 months in HF patients. In contrast, clinical indicators of disease severity (i.e., higher NYHA functional class and a history of HF-related hospitalizations) were significantly associated with increased cardiac admissions. Future studies are warranted to examine the influence of anxiety in the context of HF using a larger sample size and a longer follow-up duration than in the current study.

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Conflict of Interest: *None disclosed.*

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