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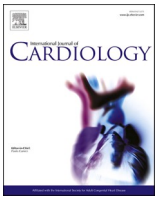

Temporal evolution of anxiety and depression in chronic heart failure and its association with clinical outcome

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ABSTRACT

Background: Although anxiety and depression have been associated with adverse outcomes in chronic heart failure (HF), data on temporal evolution of these symptoms are scarce. We aimed to investigate the association between repeatedly measured depression and anxiety symptoms and clinical outcome in chronic HF patients.
Methods: In this prospective observational study, outpatients with chronic HF were included and followed-up for a maximum of 2.5 years. The hospital anxiety and depression scale (HADS) questionnaire was conducted every six months. The primary endpoint was a composite of HF hospitalization, cardiovascular death, heart transplantation and left ventricular assist device (LVAD) implantation. Cox and joint models were used to investigate the association between the HADS score and the endpoint.
Results: A total of 362 patients filled out a median (25th–75th percentile) of 3 [2–4] questionnaires each. Mean ± SD age was 63 ± 13 years, 72% were men. Anxiety scores remained relatively stable leading up to the endpoint, while depression scores increased. Higher baseline depression scores were significantly associated with the endpoint (hazard ratio [HR] 1.68 and 95% confidence interval [CI] 1.19–2.36 per log(score+1), $p = 0.003$), while higher baseline anxiety scores did not reach statistical significance (HR [95% CI] 1.34 [0.99–1.83], $p = 0.061$). When repeatedly measured, both higher anxiety (HR [95% CI] 1.57[1.07–2.30], $p = 0.022$) and depression (HR [95% CI] 2.04 [1.39–3.06], $p < 0.001$) scores were significantly associated with the endpoint.
Conclusion: Serial measurements of depression and anxiety symptoms identify chronic HF patients with increased risk of adverse clinical outcomes. Screening for both disorders should be considered in clinical practice.

1. Introduction

Chronic heart failure (HF) poses a great burden to society, with 1–3% of the general adult population suffering from this condition [1]. Moreover, the 5-year mortality is high at 50–75% [1]. In order to optimize the care and treatment of HF patients, it is vital to understand which factors and comorbidities impact the prognosis and course of the disease.

In the HF population, depression and anxiety are quite common. Circa 22% of the patients with HF is diagnosed with depression [2], while anxiety is diagnosed in 13% [3]. Furthermore, the prevalence of patients experiencing symptoms of angst lies as high as 55% [3]. Previous studies have shown that depression has a negative impact on the prognosis of HF, and entails a higher risk of HF (re)admissions as well as mortality [4–7]. Several studies have demonstrated an association between depression and mortality in HF patients [4–10], including a study by Diez-Quevedo et al. [8], performed in HF outpatients from a specialized tertiary unit in Spain that were prospectively studied for a median follow-up of 5.4 years, and a study by Faller et al. [9] in patients who participated in the extended Interdisciplinary Network Heart Failure study and were followed for 18 months. In a study by Moraska et al. in HF outpatients and inpatients, with a mean follow-up of 1.6 years, depression independently predicted mortality as well [10]. Although anxiety has not been explored as extensively as depression, it is thought

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to also pose a higher risk of (re)admissions [7,11]. Following these findings, the European Society of Cardiology (ESC) has incorporated the advice for physicians to screen their patients when there is a clinical suspicion of depression into their 2021 guidelines [12]. However, these guidelines do not address screening for anxiety.

Above-described previous studies investigating depression and anxiety in HF patients carried several limitations. Often, depression and anxiety were investigated using separate questionnaires [13–15]. Also, most studies related one single 'baseline' measurements to disease-related outcomes that occurred over the subsequent years [13,16]. This approach does not take into account the dynamic nature of anxiety and depression, nor of HF. So far to our knowledge, repeated assessment of symptoms has only been investigated once in the outpatient setting, by Freedland et al. [14], who conducted questionnaires trimonthly in 400 HF patients and linked them to readmission rate. However this previous study did not investigate anxiety symptoms, nor associations with mortality.

Therefore, in this study we aimed to investigate the association between repeatedly measured depression and anxiety symptoms and adverse clinical outcome including cardiovascular mortality in chronic HF patients.

2. Methods

The Serial Biomarker Measurements and New Echocardiographic Techniques in Chronic Heart Failure Patients Result in Tailored Prediction of Prognosis (the Bio-SHiFT study), is a prospective cohort study in patients with HF, conducted in the Erasmus MC, Rotterdam, and Northwest Clinics, Alkmaar, in the Netherlands, from August 2011 to November 2020. This study has been described previously [17]. Adult outpatients with chronic HF were screened for eligibility, which included a HF diagnosis according to the ESC guidelines at least 3 months prior, a stable course (i.e. no hospitalization for HF within the past 3 months) as well as being able to sign informed consent. Patients were excluded for 1) HF secondary to high output conditions, 2) scheduled for surgery or intervention within 6 months of inclusion, 3) renal failure with need for dialysis, 4) known moderate or severe liver disease, 5) COPD Gold stage IV, 6) congenital heart disease or 7) life expectancy $\leq$1 year. For the current investigation, patients with HF with preserved ejection fraction (HFpEF) were also excluded from the cohort, because the number of patients with HFpEF was very low ($n = 15$). This can most likely be attributed to the fact that in the Netherlands at the time, most HFpEF patients were treated by the general practitioner or in secondary referral centers. The study was approved by the medical ethics committees, conducted in accordance with the Declaration of Helsinki, and registered in ClinicalTrials.gov (NCT01851538). All patients signed informed consent.

2.1. Baseline assessment and follow-up

At baseline, all patients were examined by research physicians or research nurses, who collected data on HF-related symptoms, medical history, medication use and performed a physical examination. The Hospital Anxiety and Depression Scale (HADS) questionnaire was also conducted [18]. The HADS consists of 14 questions, including 7 questions regarding depression and 7 questions regarding anxiety symptoms. Each question is scored from 0 to 3, with 0 being no symptoms and 3 being the most severe symptoms. This results in a total score for both depression and anxiety symptoms separately, which is then divided into one of three categories: 0–7: "normal", 8–10: "borderline abnormal" and 11–21: "abnormal" [18].

Pre-scheduled study follow-up visits took place every 3 months ($\pm$1 month) until 2.5 years of follow up. During the visits blood samples were collected and a research physician or research nurse conducted a brief medical evaluation. Every 6 months during the entire follow-up period, the HADS questionnaire was also conducted. Moreover, information regarding medication changes and occurrence of clinical adverse events was collected.

The primary endpoint was a composite of cardiovascular death, heart transplantation, left ventricular assist device (LVAD) implantation and hospitalization for HF, whichever occurred first. These endpoints were recorded in the electronic case report form by trained research physicians, and the corresponding hospital records were collected. Following that, a clinical event committee, blinded for the biomarker results, thoroughly examined hospital records and discharge letters to adjudicate the primary endpoint. Hospitalization for HF was defined as exacerbation of symptoms typical of HF, in combination with 2 of the following: BNP or NT-proBNP $>3 \times$ upper limit of normal (ULN), signs of worsening HF, such as pulmonary rales, raised jugular venous pressure or peripheral oedema, increased dose or intravenous administration of diuretics, or administration of positive inotropic agents.

2.2. Statistical analysis

To determine the distribution of the continuous variables, the Shapiro-Wilk test was used. Normally distributed variables are depicted as the mean $\pm$ standard deviation and non-normally distributed variables as the median with the 25th–75th percentile. Categorical variables are presented as numbers and percentages. Non-normally distributed variables were transformed (log+1) for the purpose of the analysis.

For the first analysis, the cutoff point between no symptoms ("normal") and some symptoms ("abnormal") was used ($\geq$8 points). Differences in baseline characteristics between the patients with baseline HADS score $\leq$ 7 and the patients with $\geq$8 points were tested using the independent samples *t*-test or Mann-Whitney test for continuous variables, depending on distribution, and the Chi^2-test or Fisher's exact test for categorical variables, as appropriate.

To examine the association between the baseline characteristics and the baseline HADS score on the continuous scale, linear regression was used, with the HADS score as the dependent variable and the baseline characteristics as the independent variables. The assumptions of the linear regression were tested using Q-Q plots of the residuals in R. Next, linear mixed effects (LME) models (with random intercepts and slopes) were used to examine the associations between the baseline characteristics and the repeatedly measured HADS score.

To examine the association between baseline HADS scores and the occurrence of the primary endpoint, Cox proportional hazards models were used. To examine the association between the repeatedly measured HADS scores and the occurrence of the primary endpoint, joint models were used. Joint models combine LME models for the temporal evolution of the HADS score, with time-to-event relative risk models for the time-to-event data. Results are presented as Hazard Ratios (HRs) with their 95% confidence intervals (CI). All models were adjusted for variables that showed statistically significant associations with a higher or lower HADS score at baseline, and additionally for variables that were deemed clinically relevant. Specifically, the models for anxiety were adjusted for age, sex, duration of HF, NTproBNP, use of antidepressants, NYHA class and BMI. The models for depression were adjusted for age, sex, duration of HF, NTproBNP, use of antidepressants, NYHA class and hypertension.

To account for missing data in the HADS questionnaires, the individual missing fields were imputed based on the available data from the fields that had been entered, after which the total score was calculated, using Multiple Imputation by Chained Equation (MICE). For 19 patients who did not fill out the baseline HADS questionnaire at all, the data could not be imputed. As a sensitivity analysis, all analyses were repeated excluding all HADS questionnaires that contained any missing fields.

All analyses were performed with R Statistical Software version 2023.03.1 using packages nlme [19] and JMbayes2 [20]. Two-tailed *P*-values $<$0.05 were considered statistically significant.

3. Results

In total, 398 patients were included in Bio-SHIFT. Fifteen patients had HFpEF and 21 did not fill out the baseline HADS questionnaire. Thus, a total of 362 patients were available for the current investigation. Each patient filled out a median (25th–75th percentile) of 3 [2–4] questionnaires.

The baseline characteristics are presented in Table 1. Seventy-eight patients had a HADS anxiety score ≥ 8 at baseline (21.4%), while 71 patients had a HADS depression score ≥ 8 at baseline (19.5%). Patients with anxiety scores ≥8 at baseline were younger (mean age 60.8 vs. 64.4, $p = 0.03$), had higher BMI (28.25 vs. 26.69, $p = 0.007$) and higher NYHA class ($p = 0.004$). Patients with depression scores ≥8 at baseline had a higher NYHA class ($p = 0.001$) and more often had hypertension (54.9% vs. 40.4%, $p = 0.04$). Both for anxiety and depression, the use of antidepressants was higher in the groups with the higher scores (11.5% vs. 2.1%, p = 0.001 and 9.9% vs. 2.8%, $p = 0.02$ respectively).

Associations of baseline characteristics with anxiety and depression scores on the continuous scale are further quantified in Fig. 1, and were in line with the above. Anxiety score was associated with lower age, higher NYHA class, and higher antidepressant use, lower systolic blood pressure and lower proportion of ischemic heart disease etiology. Depression score was associated with higher NYHA class, hypertension, and antidepressant use, as well as with chronic renal failure and currently smoking. Supplementary Table S1 shows the beta-coefficient with the corresponding 95% confidence intervals for the association between the baseline characteristics and the baseline HADS score.

As shown in Table 2, when adjusted for age, sex, duration of HF, baseline NTproBNP, antidepressants and all variables that showed statistically significant differences in Table 1, higher depression scores at baseline were associated with a higher risk of reaching the primary endpoint (HR per log(score+1) 1.68 [95% CI 1.19–2.36], $p = 0.003$). The association of higher anxiety scores at baseline with the primary endpoint did not reach statistical significance (HR 1.34 [95% CI 0.99–1.83], $p = 0.06$).

Fig. 2 shows the temporal evolution of the scores in patients who reached the endpoint and those who did not. The depression scores increased slightly leading up to the primary endpoint or censoring (increase of 0.005 (95% CI (−0.001–0.003) in log(score+1) per 3 months, $p = 0.09$). Anxiety scores, however, remained relatively stable (decrease

Table 1
Baseline patient characteristics in relation to baseline HADS scores.

	Overall	HADS anxiety score		p-value	HADS depression score		p-value
		score ≤ 7 points	score ≥ 8 points		score ≤ 7 points	score ≥ 8 points	
n	362	284	78		291	71	
Patient characteristics							
Sex, males (%)	263 (72.7)	203 (71.5)	60 (76.9)	0.4	208 (71.5)	55 (77.5)	0.4
Age, years (mean (SD))	63.60 (13.08)	64.36 (13.24)	60.81 (12.14)	**0.03**	63.52 (13.18)	63.89 (12.77)	0.8
BMI (mean (SD))	27.03 (4.51)	26.69 (4.32)	28.25 (4.98)	**0.007**	26.83 (4.45)	27.83 (4.68)	0.09
NYHA class (%)				**0.004**			**0.001**
NYHA class I	91 (25.3)	81 (28.5)	10 (12.8)		85 (29.4)	6 (8.5)	
NYHA class II	171 (47.5)	124 (43.7)	47 (60.3)		133 (46.0)	38 (53.5)	
NYHA class III	95 (26.4)	76 (26.8)	19 (24.4)		68 (23.5)	27 (38.0)	
NYHA class IV	3 (0.8)	1 (0.4)	2 (2.6)		3 (1.0)	0 (0.0)	
Duration of heart failure, years (median [IQR])	4.12 [1.58, 9.51]	3.91 [1.28, 8.91]	5.73 [1.83, 10.36]	0.09	4.11 [1.59, 8.94]	4.38 [1.55, 10.87]	0.7
NTproBNP, pmol/L (median [IQR])	145.50 [55.26, 284.67]	165 [57, 278]	126 [34, 290]	0.1	141 [57, 261]	177 [52, 464]	0.2
Systolic blood pressure, mmHg (mean (SD))	115.40 (21.29)	116 (21)	114 (22)	0.5	115 (21)	116 (24)	0.7
Diastolic blood pressure, mmHg (mean (SD))	70.05 (10.58)	70 (11)	69(10)	0.4	70 (11)	70 (10)	0.97
Implantable Cardioverter Defibrillator (%)	117 (32)	91 (32)	26 (33)	0.9	94 (32)	23 (32)	1
Cardiac resynchronization therapy (%)	110 (30)	89 (30)	24 (31)	1	84 (29)	26 (37)	0.3
Etiology of heart failure							
Ischemic heart disease (%)	159 (55.6)	127 (44.7)	32 (41.0)	0.2	129 (56.3)	30 (52.6)	0.7
Cardiomyopathy (%)	113 (48.7)	82 (28.9)	31 (39.7)	0.5	88 (48.1)	25 (51.0)	0.8
Hypertension (%)	33 (13.8)	29 (10.2)	4 (5.1)	0.2	26 (13.8)	7 (13.7)	1
Secondary to valvular disease (%)	11 (5.1)	10 (3.5)	1 (1.3)	0.4	8 (4.7)	3 (6.7)	0.9
Unknown (%)	25 (11.5)	20 (7.0)	5 (6.4)	0.8	21 (12.0)	4 (9.3)	0.8
Comorbidities							
Myocardial infarction (%)	140 (39.2)	110 (38.7)	30 (38.5)	1	113 (39.4)	27 (38.6)	1
PCI (%)	120 (33.1)	94 (33.1)	26 (33.3)	1	96 (33.0)	24 (33.8)	1
CABG (%)	51 (14.1)	39 (13.7)	12 (15.4)	0.9	44 (15.1)	7 (9.9)	0.3
Atrial fibrillation (%)	131 (36.7)	106 (37.3)	25 (32.1)	0.5	101 (35.2)	30 (42.9)	0.3
Hypertension (%)	155 (43.3)	121 (42.6)	34 (43.6)	1	116 (40.4)	39 (54.9)	**0.04**
Diabetes mellitus (%)	93 (25.7)	68 (23.9)	25 (32.1)	0.2	70 (24.1)	23 (32.4)	0.2
Chronic renal failure (%)	172 (47.8)	135 (47.5)	37 (47.4)	1	134 (46.4)	38 (53.5)	0.3
Medication use							
Beta blockers (%)	331 (91.7)	255 (89.8)	76 (97.4)	0.07	262 (90.3)	69 (97.2)	0.1
ACE inhibitors (%)	244 (67.6)	196 (69.0)	48 (61.5)	0.3	201 (69.3)	43 (60.6)	0.2
Angiotensin 2 receptor blockers (%)	102 (28.2)	78 (27.5)	24 (30.8)	0.7	79 (27.1)	23 (32.4)	0.5
Aldosteron antagonists (%)	277 (76.5)	215 (75.7)	62 (79.5)	0.6	222 (76.3)	55 (77.5)	0.96
Loop diuretics (%)	333 (92.0)	261 (91.9)	72 (92.3)	1	266 (91.4)	67 (94.4)	0.6
Antidepressants (%)	15 (4.2)	6 (2.1)	9 (11.5)	**0.001**	8 (2.8)	7 (9.9)	**0.02**
Intoxications							
Alcohol (%)	149 (42.0)	123 (43.3)	26 (33.3)	0.1	123 (43.2)	26 (37.1)	0.4
Smoking (%)				0.09			0.09
Never	104 (28.9)	79 (27.8)	25 (32.1)		89 (30.8)	15 (21.1)	
Current	35 (9.7)	23 (8.1)	12 (15.4)		24 (8.3)	11 (15.5)	
Former (> 30 days)	221 (61.4)	180 (63.4)	41 (52.6)		176 (60.9)	45 (63.4)	

BMI = Body Mass Index, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting.

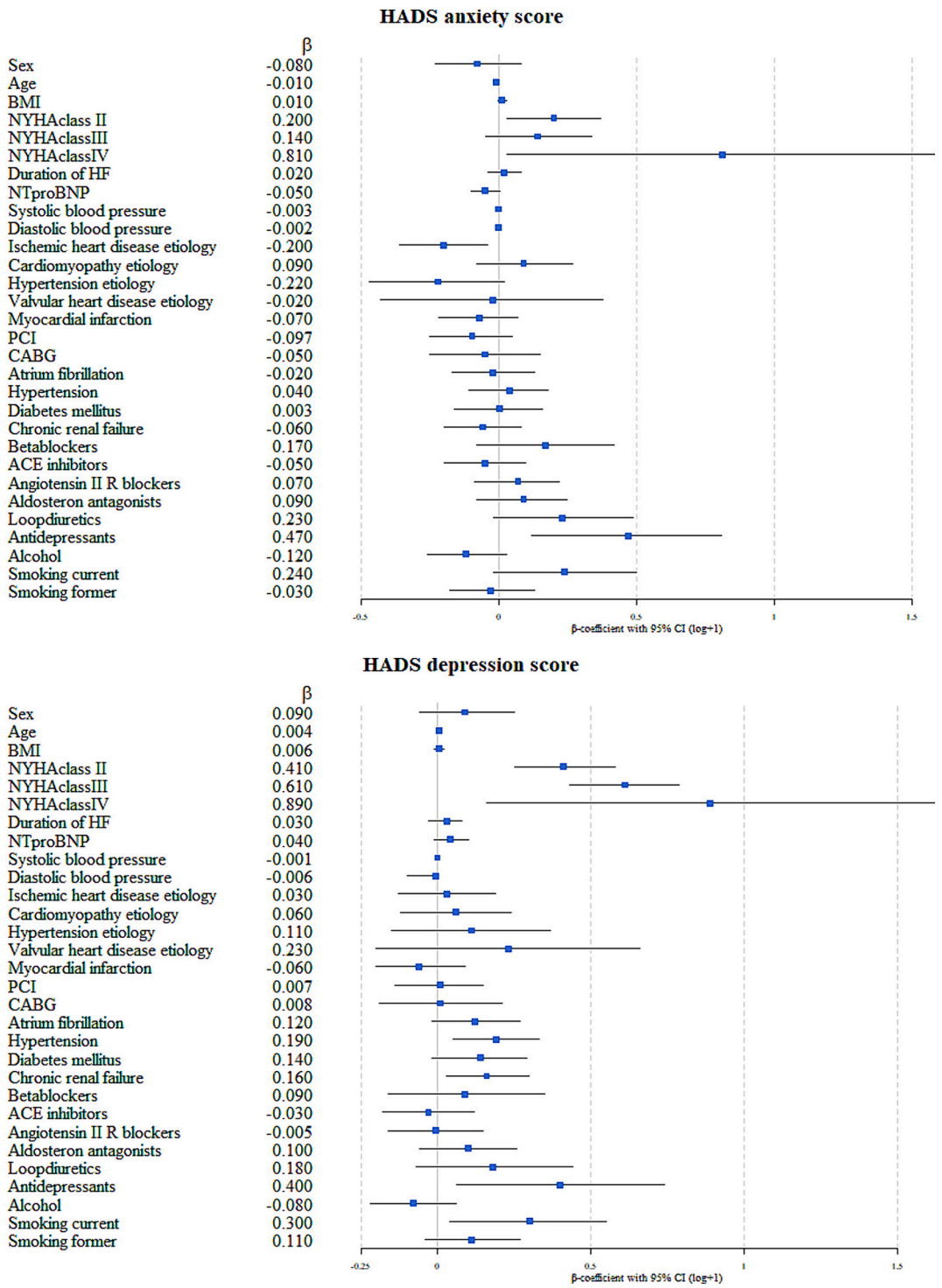

Fig. 1. Forest plot of the association of baseline characteristics with baseline HADS scores. Betas depict increase or decrease in score (log+1 transformed) when the explanatory variable is increased by 1 unit. 95% CI = 95% confidence interval.

of −0.001 (95% CI (−0.009–0.001) in log(score+1) per 3 months, $p = 0.16$).

When repeatedly measured anxiety scores were examined in relation to the endpoint by means of joint models, a positive association was found, which remained statistically significant after multivariable adjustment (Table 3). After adjustment for age, sex, NTproBNP and all the variables that were significantly different in Table 1, the HR was 1.68 (1.19–2.36), $p = 0.022$. Repeatedly measured depression scores also showed independent associations with the endpoint after multivariable adjustment (HR of 2.04 (1.39–3.06), $p < 0.001$).

For the sensitivity analysis, the results were materially the same. No important differences were seen in the baseline characteristics (Supplementary table S2 and S3, and Supplementary fig. S6). Baseline anxiety scores were significantly associated with the primary endpoint (HR 1.52 (1.08–2.15), $p = 0.024$ in the sensitivity analysis, while in the main analysis, this did not reach statistical significance (HR 1.34(0.99–1.83), $p = 0.063$) (Supplementary table S4). Furthermore, in the sensitivity analysis, the association between serially measured depression scores

Table 2
Association of baseline HADS score with primary endpoint.

	HADS anxiety score		HADS depression score	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Crude Model	1.15 (0.86–1.54)	0.34	1.97 (1.46–2.65)	**<0.001**
Multivariable Model	1.34 (0.99–1.83)*	0.06	1.68 (1.19–2.36) **	**0.003**

and the primary endpoint was borderline significant (HR 1.41 (0.996–2.03), $p = 0.052$). This most likely resulted from loss of statistical power due to the missing values (Supplementary table S5).

4. Discussion

In this prospective cohort study in chronic HF patients, baseline, as well as serially measured depression symptoms, were associated with higher risk of an adverse clinical outcome. Serially measured anxiety symptoms also showed an association with higher risk of an adverse clinical outcome. Leading up to these adverse cardiovascular events, depression symptoms increased slightly over time, while anxiety symptoms appeared to remain relatively stable.

These results confirm and extend the findings from previous studies. Freedland et al. examined 400 patients with chronic HF, and showed a significantly higher risk of all-cause readmissions with repeatedly measured higher PHQ-9 depression scores [14]. While this is in line with the findings in our study, the PHQ-9 questionnaire differs from the HADS in an important manner [21]. It contains questions regarding symptoms that could also be attributed to HF, i.e. low energy, or low appetite, making it difficult to distinguish emotional disorder from physical disorder. This, in its turn, could overestimate the emotional disorder symptoms and thus overestimate the association between depression and outcome. This is something that has been taken into account during the development of the HADS questionnaire [18]. As for anxiety, previous studies also reported statistically significantly higher risk of (re)admission in chronic HF patients in association with baseline

Table 3
Association of repeatedly measured HADS score and primary endpoint.

	HADS anxiety score		HADS depression score	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Crude Model	1.51 (1.06–2.23)	**0.02**	1.83 (1.27–2.74)	**<0.001**
Multivariable Model	1.57 (1.07–2.30)*	**0.02**	2.04 (1.39–3.06) **	**<0.001**

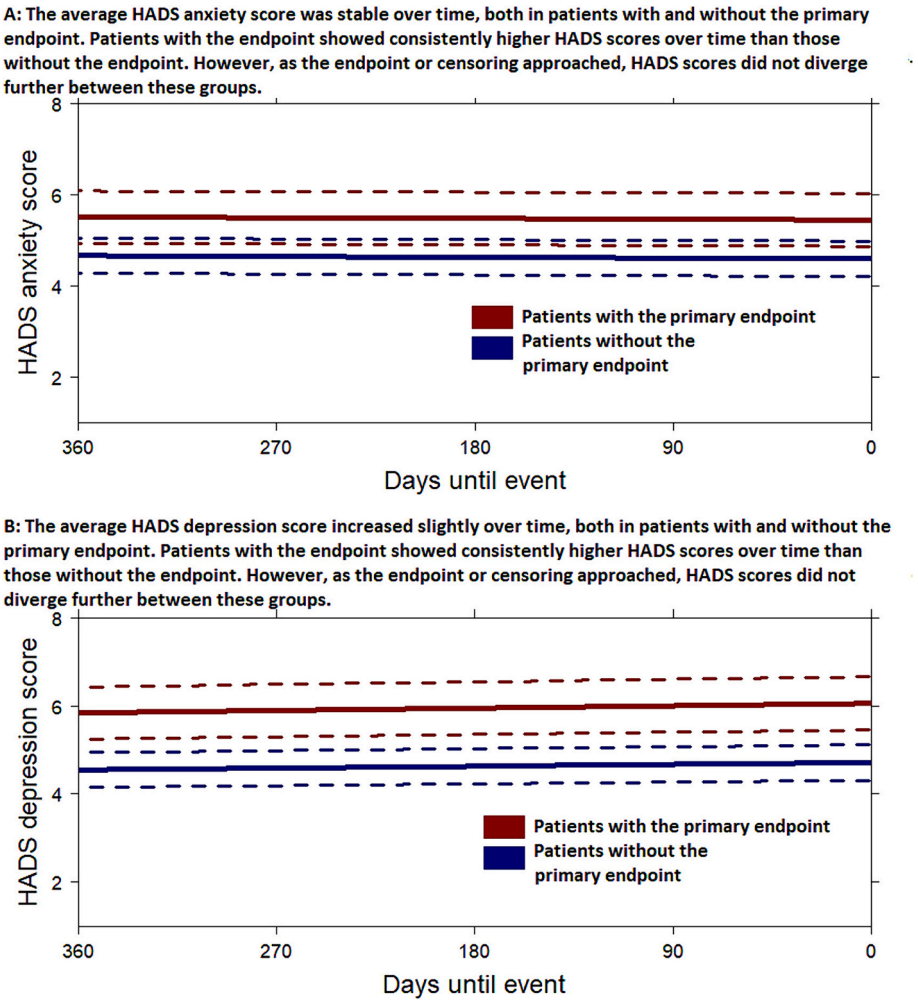

Fig. 2. Change in HADS score leading up to the primary endpoint or censoring. Continuous lines represent the scores for patients who reached the endpoint (red) and patients who did not (blue), from the joint model. Time-point zero represents the occurrence of an endpoint, or censoring in patients who remained endpoint-free. Dotted lines represent the 95% confidence intervals. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

anxiety measurements [11]. However, an association between anxiety and mortality has not yet been demonstrated in HF patients as associations were not statistically significant [7,11]. Moreover, most studies on this topic have only examined anxiety symptoms assessed at baseline in relation to adverse clinical outcomes [22–26]. A recent study by Hamatani et al. [27] measured anxiety and depression at admission and at discharge in patients admitted for HF, to determine if hospitalization improved these symptoms. Their results showed a decrease in symptoms of anxiety during admission.

Our finding that serially assessed anxiety symptoms are independently associated with clinical outcome, stresses the importance of screening for anxiety as well as depression, and treating patients accordingly. Currently, the ESC guidelines only recommend screening for depression in clinical practice when there is suspicion thereof [12]. Screening or treatment for anxiety is only mentioned in end-stage HF patients [12]. Based on the findings of this study, screening for anxiety should also be taken into consideration.

The significant correlation between anxiety and depression as shown in previous studies [13,24] underscores the substantial overlap in their affective symptoms, with depression emerging as the stronger predictor of mortality [15,24]. However, the relationship between anxiety and health outcomes in heart failure (HF) patients appears less outspoken, and studies regarding mortality have not shown significant associations after adjusting for relevant demographic and clinical variables [7,15,24]. Notably, several studies suggest that anxiety disorders may pose a greater cardiac health risk than anxiety symptoms alone [7].

These differences may in part be explained by the fact that despite their high comorbidity and shared risk factors, anxiety and depression represent distinct emotional experiences, potentially influencing coping mechanisms and prognosis differently. Phobic anxiety or panic disorder has consistently shown associations with ischemic heart disease [7,23], but the link between non-phobic anxiety and ischemic heart disease remains inconsistent. Given that phobic anxiety and panic disorder are less common than general anxiety, the nuances of the impact of anxiety on HF outcomes require further elucidation.

There are several pathophysiological mechanisms that may link depression and anxiety to HF.

First, inflammation is known to play a role in deterioration of both depression/anxiety and HF [7,28]. In HF, inflammation has been shown to contribute to cardiac remodeling and fibrosis, and elevated levels of inflammatory markers are associated with cardiovascular mortality and disease progression in HF patients. Accordingly, especially for depression, studies have shown that it is associated with elevated inflammatory activity, with studies linking depressive symptoms to increased levels of cytokines, including CRP, IL-1, and IL-6 [7,28,29]. Research suggests that the inflammatory response associated with depression contributes to the development of cardiac disease and cardiovascular mortality. However, for anxiety, this relation has not been studied extensively.

Another possible explanation for the association between depression and poor outcome in HF, is endothelial dysfunction. Characterized by impaired nitric oxide release and aberrant vascular function, this is another aspect linking depression to cardiovascular disease [7,28]. Endothelial dysfunction in atherosclerotic arteries can lead to vasoconstriction and predisposes individuals to cardiovascular events [7,28]. Depression has been associated with endothelial dysfunction, and treatment with selective serotonin reuptake inhibitors (SSRIs) has been shown to improve endothelial function in depressed patients with established coronary artery disease [7,28], suggesting a potential therapeutic avenue.

Lastly, dysfunctions in the sympathetic nervous system (SNS) are additional pathways potentially linking depression to HF. In both depressed patients and patients with severe anxiety, activation of the SNS may occur, which is also present during occurrence of HF events and mortality [7,28,30].

Limitations of this study should be addressed. Firstly, the HADS questionnaire provides a self-reported outcome. This entails potential bias, for example a non-response bias, where patients omit individual questions or do not fill out the entire questionnaire. Such missing data could influence the results and under- or overestimate the severity of symptoms, as well as the effect of anxiety and depression on adverse outcomes. In the current investigation, it is more likely that the severity of symptoms is underestimated, as patients may be more comfortable reporting better situations or uncomfortable answering some of the questions. Thus, we imputed the missing data, and as a sensitivity analysis, we performed a complete-case analysis as well.

Additionally, we did not record additional treatment during follow-up. Overall, the HADS questionnaires showed that the majority of patients had only mild symptoms, with HADS scores that usually did not necessitate action. However in some cases, the treating physician was notified of a high HADS score, and we cannot exclude the fact that this may have led to additional treatment. This may have led to an underestimation of the associations we found. Moreover, we did not structurally perform clinical assessment by a psychiatrist, and we did not register clinical diagnosis of depression during follow-up.

Moreover, since this was an observational study, residual confounding may be present. We adjusted for relevant variables including antidepressant use, duration of HF at baseline, NYHA class and NT-proBNP, however presence of residual confounding cannot fully be excluded.

Further to this, a possible contributor to the association between anxiety and depression and clinical outcome is the fact that anxiety and depression have both been associated with a higher risk of unhealthy behavior, as demonstrated in otherwise healthy adults [31]. To improve outcomes in HF, self-care is a vital part. The American Heart Association defined different parts to self-care in HF [32]. Self-care maintenance includes taking medication, adhere to a diet, exercise and actively monitor symptoms of worsening [32]. In HF, depression often causes poor medication adherence [33] and lower levels of overall self-care [34]. Anxiety has been associated with lower adherence to regular exercise, maintaining a diet, reducing stress and smoking cessation in patients with recent MI [35]. As the self-care following MI is similar to that for HF, one can speculate that anxiety is associated with similar self-care adherence. Although our study adjusted for several clinical factors, poor self-care and unhealthy behavior as mentioned above, were not taken into account.

Our results should be validated by other studies that use repeatedly measured symptoms of anxiety and depression. Not only self-reported symptoms should be used, but studies would benefit from validation of symptoms by a psychologist or psychiatrist. Such an approach could also determine whether the severity of the symptoms that is associated with adverse events, correlates with the severity for which treatment is usually started; or whether anxiety and depression have an effect on cardiovascular outcomes well before treatment is usually introduced.

Altogether, this study demonstrates that both anxiety and depression symptoms cause a higher risk of a composite endpoint of hospitalization for heart failure, cardiovascular mortality, heart transplantation and LVAD implantation. Screening for both disorders should be considered in clinical practice to detect risk of worse clinical outcome. Further research is needed to determine the effect of treatment on adverse outcomes as well as the best treatment options for both anxiety and depression.

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Authors contributions

I.K., K.M.A. and E.B. conceived and designed the study. S.A.K. and B. O. analyzed the data and wrote the manuscript. All authors were involved in interpretation of the data and revising the manuscript and

had final approval of the submitted and published versions. K.M. Akkerhuis : Conception and design of the work, the acquisition and interpretation of data, revising the manuscript. J.J. Brugts: Acquisition and interpretation of data, revising the manuscript.

CRediT authorship contribution statement

S. Abou Kamar: Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **B. Oostdijk:** Writing – original draft, Formal analysis. **K. Andrzejczyk:** Writing – review & editing. **A. Constantinescu:** Writing – review & editing, Investigation, Conceptualization. **K. Caliskan:** Writing – review & editing, Investigation, Conceptualization. **V. Umans:** Writing – review & editing, Investigation, Conceptualization. **E. Boersma:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **B. van Dalen:** Writing – review & editing, Supervision, Investigation, Conceptualization. **I. Kardys:** Writing – review & editing, Project administration, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

None declared.

Data availability

The datasets presented in this article are not readily available because anonymized data that support the findings of this study will be made available to other researchers for purposes of reproducing the results upon reasonable request and in accordance with a data-sharing agreement.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.132274.

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