Psychological Distress and Mortality in Systolic Heart Failure

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Background—Depression, anxiety, and type D (“distressed”) personality (tendency to experience negative emotions paired with social inhibition) have been associated with poor prognosis in coronary heart disease, but little is known about their role in chronic heart failure. Therefore, we investigated whether these indicators of psychological distress are associated with mortality in chronic heart failure.

Method and Results—Consecutive outpatients with chronic heart failure (n=641; 74.3% men; mean age, 66.6±10.0 years) filled out a 4-item questionnaire to assess mixed symptoms of anxiety and depression and the 14-item type D scale. End points were defined as all-cause and cardiac mortality. After a mean follow-up of 37.6±15.6 months, 123 deaths (76 due to cardiac cause) were recorded. Cumulative hazard functions for elevated anxiety/depression symptoms differed marginally for all-cause (P=0.06), but not cardiac, mortality (P=0.43); type D personality was associated with neither all-cause mortality (P=0.63) nor cardiac mortality (P=0.87). In multivariable analyses, neither elevated anxiety/depression symptoms nor type D personality was associated with all-cause mortality (hazard ratio [HR]=1.18; 95% CI, 0.76 to 1.84; P=0.45 and HR=1.09; 95% CI, 0.67 to 1.77; P=0.73, respectively) or cardiac mortality (HR=1.13; 95% CI, 0.63 to 2.04; P=0.65 and HR=1.16; 95% CI, 0.62 to 2.18; P=0.67). In secondary analyses, a 1-point increase in anxiety/depression (range, 0 to 16) was associated with an 8% increase in risk for all-cause mortality (HR=1.08; 95% CI, 1.01 to 1.15; P=0.02).

Conclusions—Neither elevated anxiety/depression symptoms nor type D personality was associated with an increased risk for all-cause or cardiac mortality. Future studies with adequate power and a longer follow-up duration are needed to further elucidate the role of psychological distress in chronic heart failure. (Circ Heart Fail. 2010;3:261-267.)

Key Words: anxiety ■ depression ■ heart failure ■ mortality ■ prognosis ■ type D personality

The incidence and prevalence of chronic heart failure (CHF) remain high despite improvements in treatment strategies. Moreover, the burden of CHF is extensive because it is associated with high mortality, frequent hospital readmissions, and impaired health status. Various clinical and demographic factors have been shown to predict poor outcome, including reduced left ventricular ejection fraction (LVEF), higher New York Heart Association (NYHA) functional class, and older age. Previous research suggests that type D personality may be associated with an increased risk for anxiety/depression symptoms, impaired health status, and cardiac mortality in patients with CHF and that this risk is independent of traditional risk factors and markers of disease severity. In this study, we examined whether symptoms of anxiety/depression and type D personality were associated with all-cause and cardiac mortality in outpatients with CHF, independent of traditional risk factors and indicators of disease severity.

Methods

Participants and Procedure

Between January 2003 and January 2008, 740 consecutive outpatients with CHF were approached for participation in hospitals in the southern regions of The Netherlands (ie, Tweesteden Hospital and St Elisabeth Hospital, Tilburg; Amphia Hospital, Breda; and Zorgsaam

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Hospital, Zeeuwse-Vlaanderen). Inclusion criteria were LVEF ≤40%, age ≤80 years, stable on medication for at least 1 month, and absence of myocardial infarction (MI) and hospital admissions in the month before inclusion. Patients were excluded in case of other life-threatening comorbidities (eg, cancer), psychiatric comorbidity (except for mood disorders), presence of evident cognitive impairments, or insufficient understanding of the Dutch language to be able to complete questionnaires. Of the 740 approached patients, 665 agreed to participate (87.0% response rate). Final analyses were based on 641 patients. A flowchart of the patient selection is shown in Figure 1. The mean age of the total sample was 66.6±10.0 years, with 476 patients (74.3%) being men. All patients were treated according to the most recent guidelines for CHF.23

Patients were approached for participation by their treating cardiologist or heart failure nurse during their outpatient visit to the cardiology department. They were contacted by telephone within 2 weeks after this visit with information about the study and were asked to fill out a questionnaire to assess sociodemographic and psychological variables. Questionnaires were returned in a stamped, prepaid envelope and checked for completeness. If patients did not return the questionnaire within 2 weeks, they received a reminder phone call or letter. The study was approved by the medical ethics committees of the participating hospitals and was conducted according to the Helsinki Declaration. All patients provided written informed consent.

Sociodemographic and Clinical Variables

Purpose-designed questions in the questionnaire assessed sociodemographic characteristics, including sex, age, educational level, current smoking, and marital status. Information on clinical variables was obtained from the patients’ medical records and comprised LVEF, NYHA functional class (I–II versus III–IV), cause (ischemic versus nonischemic), time since diagnosis, cardiac history (ie, previous MI, coronary artery bypass grafting, or percutaneous coronary intervention), and comorbidities (ie, history of stroke or transient ischemic attack, chronic obstructive pulmonary disease, kidney disease, diabetes, hypercholesterolemia, hypertension, and peripheral arterial disease). Information on prescribed medications (ie, diuretics, spironolactone, angiotensin--converting enzyme inhibitors, β-blockers, angiotensin II receptor blockers, calcium antagonists, statins, oral anticoagulants, digitalis, and aspirin) was collected from the patients’ medical records at inclusion.

Psychological Distress

Symptoms of mixed anxiety/depression were assessed with the Symptoms of Anxiety-Depression Index,24 because anxiety and depression tend to co-occur in both healthy individuals and cardiac patients.25,26 This 4-item scale, originally developed in post-MI patients, consists of 2 items assessing anxious symptoms (tension and restlessness) and 2 items assessing depressive symptoms (feeling blue and hopelessness). Items are answered on a 5-point Likert scale, ranging from 0 (not at all) to 4 (very much). Elevated anxiety/depression symptoms were defined according to a previously defined cutoff score of ≥3.24 The Symptoms of Anxiety-Depression Index is internally consistent (Cronbach α=0.86) and has been shown to independently predict a diagnosis of clinical depression and a composite of anxiety or depressive disorder.24

Type D personality was assessed with the 14-item type D scale.27 The 14-item type D scale consists of 2 subscales, negative affectivity (eg, “I often feel unhappy”) and social inhibition (eg, “I find it hard to start a conversation”), comprising 7 items each that are answered on a 5-point Likert scale (range, 0 to 4). A standardized cutoff score of ≥10 on both subscales is used to determine type D personality,27 because the interaction of negative affectivity and social inhibition, rather than negative affectivity per se, has been shown to be independently associated with poor clinical outcome.28 Both subscales have good internal consistency (Cronbach α=0.88 and 0.86, respectively).27 are not confounded by mood status or disease severity,29,30 and are stable during an 18-month period.30

End Points

All-cause mortality was the primary outcome of this study; cardiac mortality (ie, death as a result of an exacerbation of CHF, sudden cardiac death, ventricular fibrillation, or fatal MI) was the secondary outcome. Information on the cause of death was retrieved from the patients’ medical records or by contacting the general practitioner. Patients for whom the cause of death could not be unambiguously determined were assigned to the all-cause mortality group. Information on the end points was gathered in the first week of February 2009. The mean follow-up period was 37.6±15.6 months (range, 12 to 73 months). Follow-up was complete (100%) for all patients.

Statistical Analyses

Group differences were examined with χ² tests for dichotomous variables and Student t tests for independent samples for continuous variables. Cumulative survival curves for anxiety/depression symptoms (ie, high versus low) and type D personality (ie, present versus absent) were constructed by using the Kaplan–Meier method. The log-rank test was used to compare cumulative survival curves between groups. By using an etiologic approach, multivariable Cox regression models were used to examine the effect of psychological distress on all-cause and cardiac mortality adjusting for all baseline characteristics (ie, age, sex, having a partner, working status, educational level, cause, time since diagnosis, LVEF, cardiac history, New York Heart Association class, diabetes, hypercholesterolemia, hypertension, kidney disease, stroke/transient ischemic attack, chronic obstructive pulmonary disease, peripheral arterial disease, smoking status, prescribed medications, and device therapy). In these analyses, anxiety/depression symptoms and type D personality were entered as dichotomous variables. In secondary analyses, continuous variables were used for anxiety/depression symptoms, negative affectivity, social inhibition, and the interaction between negative affectivity and social inhibition. Hazard ratios (HRs) with their corresponding 95% CIs for psychological distress are reported for multivariable Cox regression analyses. Statistical analyses were performed with SPSS for Windows (version 16.0; SPSS Inc, Chicago, Ill). All tests were 2-tailed, and a P value of ≤0.05 was used to indicate statistical significance.

Post hoc power calculations for Cox regression analysis were performed with PASS 2008 (NCSS LLC, Kaysville, Utah). Power was determined for the all-cause mortality models after assuming population HRs of 1.3 and 1.5 for both anxiety/depression symptoms and type D personality, respectively, because these estimates are likely to be expected. R² for both anxiety/depression symptoms and type D personality with all other covariates was set at 0.20, which was computed by regressing the independent variable on all covari-
Psychological Distress and Mortality

Baseline Characteristics and Mortality

Participants and nonparticipants of the study differed on some baseline characteristics, with nonparticipants having higher rates of hypercholesterolemia, kidney disease, statin and nitrate prescription, and a lower prescription rate for angiotensin-converting enzyme inhibitors (4.62 < χ² < 24.30, P < 0.001).

The prevalence of psychological distress was 26% for elevated anxiety/depression symptoms and 20% for type D personality in the total sample. The mean score for negative affectivity was 7.13 ± 6.38 (range, 0 to 28), 9.14 ± 6.52 (range, 0 to 28) for social inhibition, and 2.47 ± 3.21 (range, 0 to 16) for anxiety/depression symptoms in the total sample. The prevalence of elevated anxiety/depression symptoms in type D patients was 63.3% (81 of 128).

Type D and non–type D patients differed on some baseline characteristics, with type D patients more often having a lower educational level and a lower prescription rate for oral anticoagulants but a higher prescription rate for diuretics (Table 1). In addition, some differences emerged when stratifying by anxiety/depression symptoms: patients with high levels of anxiety/depression symptoms were less likely to have a partner and a lower educational level, but they were more often classified as being in NYHA class III–IV, having a lower prescription rates for β-blockers but a higher prescription rate for nitrates, and less likely being treated with device therapy. At follow-up, 123 (19.2%) patients had died, for whom 76 (12.4%) deaths were attributable to a cardiac cause.

Psychological Distress and All-Cause Mortality

Cumulative hazard functions marginally differed for elevated versus nonelevated anxiety/depression symptoms (log-rank χ² = 3.67, P = 0.06) (Figure 2a) but not for type D versus non–type D personality (log-rank χ² = 0.24, P = 0.64; Figure 2b).

Neither elevated anxiety/depression symptoms nor type D personality was significantly associated with all-cause mortality in multivariable Cox regression analysis, after adjusting for all possible confounders (Table 2). Significant covariables in the model were older age, male sex, having no partner, current smoking, lower LVEF, and comorbid kidney disease (all P < 0.05).

In secondary multivariable analyses, by using continuous scores, a 1-point increase in anxiety/depression score (range, 0 to 16) was associated with an 8% increase in risk for all-cause mortality (HR = 1.08; 95% CI, 1.01 to 1.15; P = 0.02). Negative affectivity, social inhibition, and the interaction of negative affectivity and social inhibition were not independently associated with all-cause mortality (all P > 0.05).

Psychological Distress and Cardiac Mortality

Cumulative hazard functions differed neither for elevated versus nonelevated anxiety/depression symptoms (log-rank χ² = 0.62; P = 0.43) nor for type D versus non–type D personality (log-rank χ² = 0.03; P = 0.87).

Neither elevated anxiety/depression symptoms nor type D personality was independently associated with cardiac mortality in multivariable Cox regression analyses (Table 2). Male sex, lower LVEF, and comorbid kidney disease were significant covariables in the model for cardiac mortality (all P < 0.05).

In secondary multivariable analyses with continuous scores, neither anxiety/depression symptoms nor negative affectivity or the interaction of negative affectivity and social inhibition (all P > 0.05) was independently associated with cardiac mortality.

Post hoc power calculations for the population HRs of 1.3 and 1.5 for anxiety/depression symptoms demonstrated that the power was 0.21 and 0.42, respectively. Post hoc power calculations for these HRs for type D personality demonstrated a power of 0.18 and 0.36. Power calculations derived from bootstrapping methods yielded similar results (results not shown).

Discussion

In this study, we examined the associations between psychological distress (ie, anxious/depression symptoms and type D personality) and mortality in outpatients with CHF. Neither elevated anxiety/depression symptoms nor type D personality was associated with all-cause or cardiac mortality at a mean follow-up of 38 months. Secondary analyses, with continuous scores, showed that higher levels of anxious/depression symptoms were independently associated with all-cause but not with cardiac mortality.

The current finding that elevated anxiety/depression scores are not associated with all-cause mortality is in line with a previous study that failed to demonstrate an association between minor depression and all-cause mortality in a mixed sample of hospitalized patients with CHF and outpatients. Our findings are in contrast with those of a recent study, showing that elevated depression symptoms were independently associated with all-cause mortality in outpatients with CHF with comorbid atrial fibrillation. However, both studies used different samples and other instruments to assess psychological distress, which hampers comparability with this study.

The finding that, in secondary analyses, higher levels of anxiety/depression (continuous scores) were associated with all-cause mortality, corroborates previous studies, showing that higher levels of depressive symptoms incur an increased and independent risk for all-cause mortality in outpatients with CHF but are in contrast with a study finding no such evident association. Although 2 studies in outpatients have shown that higher levels of depressive symptoms were independently associated with cardiac mortality at 2- and 6-year follow-up, we were not able to confirm these findings.

Studies on the role of anxious symptoms in the context of mortality in outpatients with CHF have shown mixed results. Furthermore, 1 study in hospitalized patients showed that anxious symptoms were not associated with mortality at 1-year follow-up, whereas depressive symptoms were. In this study, we focused on the co-occurrence of anxiety and depression, rather than anxiety and depressive symptoms.
symptoms separately.24 Because depression and anxiety are known to frequently co-occur,26,41 this approach may serve as a more realistic representation of patient symptomatology.

The findings of this study are in line with previous studies that have demonstrated that type D personality is associated with anxiety42 and depression.16,17 In the current sample, the prevalence of elevated anxiety/depression symptoms was 63% in type D patients. However, the findings related to mortality contradict the results of previous studies, demonstrating that type D personality was independently associated with mortality in outpatients with CHF,19 post-MI patients with a decreased LVEF,20 and heart transplant recipients.43 One explanation for this discrepancy might be that most of the previous studies have focused on long-term effects, with follow-ups generally ranging from 5 to 10 years, whereas in the this study, the mean follow-up period was only 3 years. Previously, it has been argued that personality might exert its adverse effects on prognosis, especially in the long term.19,44

| Table 1. Significant Baseline Characteristics Stratified by Type D Personality and Anxiety/Depression Symptoms |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Total Sample (N = 641) | Type D (n = 128) | Non–Type D (n = 513) | P | Elevated Anxiety/Depression Symptoms (n = 169) | No Elevated Anxiety/Depression Symptoms (n = 472) | P |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Sociodemographics                                              |                                              |                                              |   |                                              |                                              |   |
| Male sex                                                       | 476 (74.3) | 93 (72.7) | 383 (74.7) | 0.64 | 123 (72.8) | 353 (74.8) | 0.61 |
| Age, mean (SD), y                                              | 66.6 (10.0) | 66.3 (10.1) | 67.8 (9.8) | 0.14 | 66.9 (10.0) | 66.5 (10.0) | 0.63 |
| Having a partner                                               | 465 (72.5) | 85 (66.4) | 380 (74.1) | 0.08 | 105 (62.1) | 360 (76.3) | 0.001 |
| Currently working                                              | 86 (13.4) | 12 (9.4) | 74 (14.4) | 0.13 | 19 (11.2) | 67 (14.2) | 0.33 |
| Lower educational level*                                        | 223 (34.8) | 55 (43.0) | 168 (32.7) | 0.03 | 73 (43.2) | 150 (31.8) | 0.008 |
| Clinical variables                                             |                                              |                                              |   |                                              |                                              |   |
| Ischemic etiology                                              | 369 (57.6) | 74 (57.8) | 295 (57.5) | 0.95 | 104 (61.5) | 265 (56.1) | 0.22 |
| Time since diagnosis, mean (SD), mo                           | 46.1 (48.4) | 50.2 (61.1) | 45.1 (44.3) | 0.29 | 47.6 (55.7) | 45.6 (45.7) | 0.64 |
| LVEF, mean (SD)                                                | 31.4 (7.2) | 31.6 (7.3) | 31.4 (7.1) | 0.83 | 31.5 (7.6) | 31.4 (7.0) | 0.86 |
| Cardiac history†                                                | 392 (61.2) | 82 (64.1) | 310 (60.4) | 0.45 | 111 (65.7) | 281 (59.5) | 0.16 |
| NYHA class III–IV                                              | 226 (30.7) | 51 (39.8) | 175 (34.1) | 0.23 | 75 (44.4) | 151 (32.0) | 0.004 |
| Diabetes mellitus                                              | 164 (25.6) | 32 (25.0) | 132 (25.7) | 0.87 | 45 (26.6) | 119 (25.2) | 0.72 |
| Hypercholesterolemia                                           | 331 (51.6) | 68 (53.1) | 263 (51.3) | 0.71 | 88 (52.1) | 243 (51.5) | 0.90 |
| Hypertension                                                   | 254 (39.6) | 51 (39.8) | 203 (39.6) | 0.96 | 75 (44.4) | 179 (37.9) | 0.14 |
| Kidney disease                                                 | 70 (10.9) | 17 (13.3) | 53 (10.3) | 0.34 | 21 (12.4) | 49 (10.4) | 0.47 |
| Stroke/TIA                                                     | 92 (14.4) | 12 (9.4) | 80 (15.6) | 0.07 | 24 (14.2) | 68 (14.4) | 0.95 |
| COPD                                                           | 102 (15.9) | 22 (17.2) | 80 (15.6) | 0.66 | 32 (18.9) | 70 (14.8) | 0.21 |
| PAD                                                            | 79 (12.3) | 21 (16.4) | 58 (11.3) | 0.12 | 23 (13.6) | 56 (11.9) | 0.55 |
| Currently smoking                                              | 154 (24.0) | 26 (20.3) | 128 (25.0) | 0.27 | 37 (21.9) | 117 (24.8) | 0.45 |
| Medication                                                     |                                              |                                              |   |                                              |                                              |   |
| ACE inhibitors                                                 | 439 (68.5) | 85 (66.4) | 354 (69.0) | 0.57 | 107 (63.3) | 332 (70.3) | 0.09 |
| β-blockers                                                     | 432 (67.4) | 85 (66.4) | 347 (67.6) | 0.79 | 102 (60.4) | 330 (69.9) | 0.02 |
| ARBs                                                           | 141 (22.0) | 32 (25.0) | 109 (21.2) | 0.36 | 41 (24.3) | 100 (21.2) | 0.41 |
| Calcium antagonists                                            | 80 (12.5) | 22 (17.2) | 58 (11.3) | 0.07 | 24 (14.2) | 56 (11.9) | 0.43 |
| Nitrates                                                       | 163 (25.4) | 40 (31.3) | 123 (24.0) | 0.09 | 53 (31.4) | 110 (23.3) | 0.04 |
| Digoxin                                                        | 143 (22.3) | 30 (23.4) | 113 (22.0) | 0.73 | 36 (21.3) | 107 (22.7) | 0.71 |
| Spironolactone                                                 | 130 (20.3) | 24 (18.8) | 106 (20.7) | 0.63 | 34 (20.1) | 96 (20.3) | 0.95 |
| Oral anti-coagulants                                           | 309 (48.2) | 51 (39.8) | 258 (50.3) | 0.03 | 77 (45.6) | 232 (49.2) | 0.42 |
| Statins                                                        | 355 (55.4) | 71 (55.5) | 284 (55.4) | 0.98 | 93 (55.0) | 262 (55.5) | 0.91 |
| Aspirin                                                        | 257 (40.1) | 54 (42.2) | 203 (39.6) | 0.59 | 64 (37.9) | 193 (40.9) | 0.49 |
| Diuretics                                                      | 469 (73.2) | 104 (81.3) | 365 (71.2) | 0.02 | 132 (78.1) | 337 (71.4) | 0.09 |
| Device therapy†                                                | 96 (15.0) | 21 (16.4) | 75 (14.6) | 0.61 | 17 (10.1) | 79 (16.7) | 0.04 |

Data are presented as n (%) unless otherwise stated. ARBs indicates angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association functional class; PAD, peripheral arterial disease; TIA, transient ischemic attack.

*Defined as primary school or lower.
†Coronary artery bypass grafting, MI, or percutaneous coronary intervention.
‡Either single, biventricular pacemaker or implantable cardioverter defibrillator.
with coronary artery disease,22 may provide another explanation. A lower prevalence of type D personality in CHF might be a consequence of type D patients being more likely to die in earlier stages of cardiac disease before developing CHF.

The current findings are generally contradictory to those of previous studies suggesting that psychological distress might predict mortality in CHF.19,33,38,39 However, both anxiety and depressive symptoms and type D personality have been consistently linked to poor patient-centered outcomes such as impaired health status,16,18,45–47 and type D personality has been shown to predict increased levels of depression16,21 and anxiety42,48 across different types and stages of cardiac disease. These patient-centered outcomes are important in their own right because they may serve as performance measures in clinical practice to optimize clinical care.49,50 Nevertheless, this study provides a new, critical perspective on the role of psychological distress in the context of cardiac disease, and CHF in particular, that warrants further exploration.

The results of this study should be interpreted with some caution. First, the observed power of this study was modest. Second, the follow-up period was relatively short, with a mean follow-up of 3 years, whereas other studies on personality have primarily focused on the long-term effects. Third, anxious and depressive symptoms were assessed by means of self-report, and no information on a clinical diagnosis of anxiety or depression was obtained. Furthermore, the generalizability of the findings to the North American setting is somewhat hampered because of the lack of minorities in this study. Finally, no systematic approach to adjudication of cardiac mortality was implemented in this study. Strengths of this study include the multicenter design, with the assessment of both chronic and episodic measures of psychological distress and the co-occurrence of anxiety/depression symptoms adding to the existing literature.

To conclude, the findings of this study indicate that neither elevated anxiety/depression symptoms nor type D personality was associated with all-cause and cardiac mortality. In secondary analyses, continuous scores of anxious/depressive symptoms were independently associated with all-cause but not with cardiac mortality. Future studies with longer follow-up and adequate power are needed to further explore the complex nature of psychological distress as a predictor of the clinical course of CHF.

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References


**CLINICAL PERSPECTIVE**

Chronic heart failure is a serious condition and a main reason for mortality and morbidity worldwide. Previous studies have suggested that psychological distress may be associated with mortality in chronic heart failure. This study examined the influence of both episodic (anxiety/depression symptoms) and chronic (type D personality—tendency to experience negative emotions and inhibit self-expression) psychological distress on all-cause and cardiac mortality during a mean follow-up period of 38 months in 641 patients enrolled in a multicenter, prospective, observational cohort study. Neither elevated anxiety/depression symptoms nor type D personality was associated with all-cause and cardiac mortality after controlling for baseline characteristics (ie, sociodemographics, clinical characteristics, disease severity, comorbidities, and prescribed medications). In contrast, higher levels of anxiety/depression symptoms were associated with a 1.08 hazard ratio (95% confidence interval, 1.01 to 1.15; \( P = 0.02 \)) for all-cause mortality, with a 1-point increase in anxious/depressive symptoms being independently associated with an 8% increased risk. The current findings are inconsistent with previous studies on the role of anxiety and depression and type D personality as predictors of mortality in different stages of cardiac disease. Because chronic heart failure represents the end stage of heart disease, psychological factors may play less of a role in survival than in patients at earlier stages of disease. Given the modest power of the study, findings should be interpreted with some caution. To conclude, although this study did not unambiguously demonstrate an effect of psychological factors on survival, they are important in their own right because they influence quality of life.
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