Psychological distress and mortality in systolic heart failure

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Abstract

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 less is known about their role in chronic heart failure (CHF). Therefore, we investigated whether these indicators of psychological distress are associated with mortality in CHF.

Method and Results: Consecutive CHF outpatients (N=641; 74.3% men; mean age 66.6±10.0 years) filled out a four-item questionnaire to assess mixed Symptoms of Anxiety and Depression (SAD4) and the 14-item Type D Scale (DS14). Endpoints were defined as all-cause and cardiac mortality. After a mean follow-up of 37.6±15.6 months, 123 deaths were recorded (76 due to a cardiac cause). Cumulative hazard functions for elevated anxiety/depression symptoms differed marginally for all-cause (p=.06) but not cardiac (p=.43) mortality; Type D personality was neither associated with all-cause (p=.63) nor cardiac mortality (p=.87). In multivariable analyses, neither elevated anxiety/depression symptoms nor Type D personality were associated with all-cause mortality (Hazard ratio (HR)=1.18, 95% Confidence Interval (CI) [0.76-1.84], p=.45 and HR=1.09, 95% CI [0.67-1.77], p=.73, respectively) or cardiac mortality (HR=1.13, 95% CI [0.63-2.04], p=.65 and HR=1.16, 95% CI [0.62-2.18], p=.67). In secondary analyses, a 1-point increase in anxiety/depression (range 0-16) was associated with a 8% increase in risk of all-cause mortality (HR=1.08, 95% CI [1.01-1.15], p=.02).

Conclusions: Neither elevated anxiety/depression symptoms nor Type D personality were associated with an increased risk of 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 CHF.

Word count: 250

Key words: Anxiety; Depression; Heart failure; Mortality; Prognosis
Psychological distress and mortality

Introduction

The incidence and prevalence of chronic heart failure (CHF) remain high, despite improvements in treatment strategies\textsuperscript{1-3}. Moreover, the burden of CHF is extensive, as it is associated with high mortality\textsuperscript{3, 4}, frequent hospital readmissions\textsuperscript{5, 6}, and impaired health status\textsuperscript{7, 8}. 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\textsuperscript{9-11}.

Some studies suggest that symptoms of psychological distress, such as anxiety and depression, have an adverse impact on prognosis. However, findings on distress as an associate of mortality in CHF remain inconclusive\textsuperscript{12, 13}. In addition, chronic psychological factors, such as Type D personality (the tendency to experience negative emotions and inhibit self-expression), might be of interest in the context of CHF\textsuperscript{14, 15}. Previous research suggests that Type D personality may be associated with an increased risk for anxiety/depression symptoms\textsuperscript{16, 17}, impaired health status\textsuperscript{18}, and cardiac mortality\textsuperscript{19} in patients with CHF, and that this risk is independent of traditional risk factors and markers of disease severity\textsuperscript{20-22}.

In the current study, we examined whether symptoms of anxiety/depression and Type D personality were associated with all-cause and cardiac mortality in CHF outpatients, independent of traditional risk factors and indicators of disease severity.

Methods

Participants and procedure

Between January 2003 and January 2008, 740 consecutive CHF outpatients were approached for participation in hospitals in the southern regions of The Netherlands (i.e., TweeSteden Hospital and St. Elisabeth Hospital, Tilburg; Amphia Hospital, Breda; and ZorgSaam Hospital, Zeeuws-Vlaanderen). Inclusion criteria were LVEF\textless;40\%, age\textgreater;=80 years, stable on medication during at least one month, and absence of myocardial infarction (MI) and hospital admissions in the month prior to inclusion. Patients were excluded in case of
other life-threatening co-morbidities (e.g., cancer), psychiatric co-morbidity (except for mood disorders), presence of evident cognitive impairments, and/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 flow-chart 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.

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 following this visit with information about the study, and were asked to fill out a questionnaire to assess socio-demographic and psychological variables. Questionnaires were returned in a stamped, pre-addressed 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.

**Socio-demographic and clinical variables**

Purpose-designed questions in the questionnaire assessed socio-demographic characteristics, including gender, age, educational level, current smoking, and marital status. Information on clinical variables were obtained from the patients’ medical records and comprised LVEF, NYHA functional class (I-II versus III-IV), etiology (ischemic versus non-ischemic), time since diagnosis, cardiac history (i.e., previous MI, coronary artery bypass grafting (CABG), or percutaneous coronary intervention (PCI)), and co-morbidities (i.e., history of stroke or transient ischemic attack, chronic obstructive pulmonary disease (COPD), kidney disease, diabetes, hypercholesterolemia, hypertension, and peripheral arterial disease (PAD)). Information on prescribed medications was collected from the patients’ medical records at inclusion (i.e., diuretics, spironolactone, ACE-inhibitors, beta-blockers,
angiotensin-II receptor blockers (ARB), calcium-antagonists, statins, oral anticoagulants, digitalis, and aspirin).

**Psychological distress**

Symptoms of mixed anxiety/depression were assessed with the Symptoms of Anxiety-Depression Index (SAD$_4$)$^{24}$, as anxiety and depression tend to co-occur in both healthy as well as cardiac samples$^{25, 26}$. This 4-item scale, originally developed in post-MI patients, consists of two items assessing anxious symptoms (*tension* and *restlessness*) and two 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 cut-off score of $\geq 3^{24}$. The SAD$_4$ is internally consistent (Cronbach’s $\alpha=.86$), 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 (DS$_{14}$)$^{27}$. The DS$_{14}$ consists of 2 subscales, *negative affectivity* (e.g. ‘I often feel unhappy’) and *social inhibition* (e.g. ‘I find it hard to start a conversation’), comprising 7 items each that are answered on a 5-point Likert scale (range 0-4). A standardized cut-off score of $\geq 10$ on both subscales is used to determine Type D personality$^{27}$, since 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’s $\alpha=.88$ and .86, respectively)$^{27}$, are not confounded by mood status or disease severity$^{29, 30}$, and are stable over an 18-month period$^{30}$.

**Endpoints**

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

**Statistical analyses**

Group differences were examined using $\chi^2$-tests for dichotomous variables and Student’s $t$-tests for independent samples for continuous variables. Cumulative survival curves for anxiety/depression symptoms (i.e., high versus low) and Type D personality (i.e., present versus absent) were constructed using the Kaplan-Meier method. The log-rank test was used to compare cumulative survival curves between groups. Using an etiological approach, multivariable Cox regression models were used to examine the impact of psychological distress on all-cause and cardiac mortality adjusting for all baseline characteristics (i.e., age, sex, having an partner, working status, educational level, etiology, time since diagnosis, LVEF, cardiac history, NYHA class, diabetes, hypercholesterolemia, hypertension, kidney disease, stroke/TIA, COPD, PAD, 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*social inhibition. Hazard ratios (HR) with their corresponding 95% confidence intervals (CI) for psychological distress are reported for multivariable Cox regression analyses. Statistical analyses were performed using SPSS for Windows 16.0 (SPSS Inc., Chicago, Illinois, USA). All tests were two-tailed and a p-value of <.05 was used to indicate statistical significance.

Post-hoc power calculations for Cox regression analysis were performed using PASS 2008 (NCSS, LLC. Kaysville, Utah). Power was determined for the all-cause mortality models assuming population hazard ratios of 1.3 and 1.5 for both anxiety/depression symptoms and Type D personality, respectively, as these estimates are likely to be expected. $R^2$ for both anxiety/depression symptoms and Type D personality with all other covariates was set at .20, which was computed by regressing the independent variable on all covariates using logistic
regression. The standard deviations of anxiety/depression symptoms and Type D personality were 0.44 and 0.40, respectively.

Results

Baseline characteristics and mortality

Participants and non-participants of the study differed on some baseline characteristics, with non-participants having higher rates of hypercholesterolemia, kidney disease, statin and nitrate prescription and a lower prescription rate for ACE-inhibitors ($4.62 < X^2 < 24.30$, $p < .001$).

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 [0-28]), 9.14±6.52 (range [0-28]) for social inhibition, and 2.47±3.21 (range [0-16]) for anxiety/depression symptoms in the total sample. The prevalence of elevated anxiety/depression symptoms in Type D patients was 63.3% (81/128).

Type D and non-Type D patients differed on some baseline characteristics, with Type D patients more often having a lower educational level, 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 more often classified as NYHA class III-IV, having a lower prescription rates for beta-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, of which 76 deaths (12.4%) were attributable to a cardiac cause.

Psychological distress and all-cause mortality

Cumulative hazard functions marginally differed for elevated versus no elevated anxiety/depression symptoms (log rank $X^2 = 3.67$, $p = .06$) (Figure 2a), but not for Type D versus non-Type D personality (log rank $X^2 = .24$, $p = .64$) (Figure 2b).
Neither elevated anxiety/depression symptoms nor Type D personality were significantly associated with all-cause mortality in multivariable Cox regression analysis, adjusting for all possible confounders (Table 2, left). Significant covariables in the model were older age, male sex, having no partner, current smoking, lower LVEF, and co-morbid kidney disease (all ps<.05).

In secondary multivariable analyses, using continuous scores, a 1-point increase in anxiety/depression score (range 0-16) was associated with a 8% increase in risk of all-cause mortality (HR=1.08, 95%CI [1.01-1.15], p=.02). Negative affectivity, social inhibition and the interaction of negative affectivity*social inhibition were not independently associated with all-cause mortality (all ps>.05).

Psychological distress and cardiac mortality

Cumulative hazard functions neither differed for elevated versus no elevated anxiety/depression symptoms (log rank $X^2=.62$, p=.43) nor for Type D versus non-Type D personality (log rank $X^2=.03$, p=.87).

Neither elevated anxiety/depression symptoms nor Type D personality were independently associated with cardiac mortality in multivariable Cox regression analyses (Table 2, right). Male sex, lower LVEF, and co-morbid kidney disease were significant covariables in the model for cardiac mortality (all ps<.05).

In secondary multivariable analyses using continuous scores, neither anxiety/depression symptoms, nor negative affectivity, nor the interaction of negative affectivity*social inhibition (all ps>.05) were independently associated with cardiac mortality.

Post-hoc power calculations for the population hazard ratios of 1.3 and 1.5 for anxiety/depression symptoms demonstrated that the power was .21 and .42, respectively. Post-hoc power calculations for these hazard ratios for Type D personality demonstrated a power of .18 and .36, respectively. Power calculations using bootstrapping methods yielded similar results (results not shown).
Discussion

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

The current finding that elevated anxiety/depression scores are not associated with all-cause mortality are 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 CHF patients 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 CHF outpatients with co-morbid atrial fibrillation. However, both studies used different samples and other instruments to assess psychological distress, which hampers comparability with the current study.

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

Studies on the role of anxious symptoms in the context of mortality in CHF outpatients have shown mixed results. Further, one study in hospitalized patients showed that anxious symptoms were not associated with mortality at one-year follow-up, whereas depressive symptoms were. In the current study, we focused on the co-occurrence of anxiety and depression, rather than anxiety and depressive symptoms separately. Since depression and anxiety are known to frequently co-occur, this approach may serve as a more realistic representation of patient symptomatology.
The findings of the current study are in line with previous studies that have demonstrated that Type D personality is associated with anxiety\textsuperscript{42} and depression\textsuperscript{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 CHF outpatients\textsuperscript{19}, post-MI patients with a decreased LVEF\textsuperscript{20}, and heart transplant recipients\textsuperscript{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 current 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\textsuperscript{19, 44}. The relatively low prevalence of Type D personality, i.e., 20\% in the current sample as compared to 25-30\% in patients with coronary artery disease\textsuperscript{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 decease in earlier stages of cardiac disease, prior to developing CHF.

The current findings are generally contradictory to those of previous studies suggesting that psychological distress might predict mortality in CHF\textsuperscript{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\textsuperscript{16, 18, 45-47}, and Type D personality has been shown to predict increased levels of depression\textsuperscript{16, 21} and anxiety\textsuperscript{42, 48} across different types and stages of cardiac disease. These patient-centered outcomes are important in their own right, as they may serve as performance measures in clinical practice to optimize clinical care\textsuperscript{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 the current 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 of depression was...
obtained. Further, the generalizability of the findings to the North American setting is somewhat hampered due to the lack of minorities in the current study. Finally, no systematic approach to adjudication of cardiac mortality was implemented in the current study. Strengths of the current 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 were associated with all-cause and cardiac mortality. In secondary analyses, continuous scores of anxious/depressive symptoms were independently associated with all-cause, but not 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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**Disclosures**

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Figure Legends

Figure 1. Flow chart of patient selection

Figure 2. Cumulative survival curves for all-cause mortality
Table 1. Significant baseline characteristics stratified by Type D personality and anxiety/depression symptoms

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<tr>
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<th>Total sample (N=641)</th>
<th>Type D (n=128)</th>
<th>non-Type D (n=513)</th>
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<th>Elevated anxiety / depression symptoms (n=169)</th>
<th>No elevated anxiety / depression symptoms (n=472)</th>
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<td><strong>Socio-demographics</strong></td>
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<td>Male sex</td>
<td>476 (74.3)</td>
<td>93 (72.7)</td>
<td>383 (74.7)</td>
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<td>123 (72.8)</td>
<td>353 (74.8)</td>
<td>.61</td>
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<td>Age, mean (SD)</td>
<td>66.6 (10.0)</td>
<td>66.3 (10.1)</td>
<td>67.8 (9.8)</td>
<td>.14</td>
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<td>66.5 (10.0)</td>
<td>.63</td>
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<td>Having a partner</td>
<td>465 (72.5)</td>
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<td>19 (11.2)</td>
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<td>Lower educational level</td>
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<td>55 (43.0)</td>
<td>168 (32.7)</td>
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<td>73 (43.2)</td>
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<td>Ischemic etiology</td>
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<td>104 (61.5)</td>
<td>265 (56.1)</td>
<td>.22</td>
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<td>Time since diagnosis, mean (SD)</td>
<td>46.1 (48.4)</td>
<td>50.2 (61.1)</td>
<td>45.1 (44.3)</td>
<td>.29</td>
<td>47.6 (55.7)</td>
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<td>LVEF, mean (SD)</td>
<td>31.4 (7.2)</td>
<td>31.6 (7.3)</td>
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<td>.83</td>
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<td>Cardiac history§</td>
<td>392 (61.2)</td>
<td>82 (64.1)</td>
<td>310 (60.4)</td>
<td>.45</td>
<td>111 (65.7)</td>
<td>281 (59.5)</td>
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<td>NYHA class III-IV</td>
<td>226 (30.7)</td>
<td>51 (39.8)</td>
<td>175 (34.1)</td>
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<td>75 (44.4)</td>
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<td>Diabetes mellitus</td>
<td>164 (25.6)</td>
<td>32 (25.0)</td>
<td>132 (25.7)</td>
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<td>45 (26.6)</td>
<td>119 (25.2)</td>
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<td>Hypercholesterolemia</td>
<td>331 (51.6)</td>
<td>68 (53.1)</td>
<td>263 (51.3)</td>
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<td>88 (52.1)</td>
<td>243 (51.5)</td>
<td>.90</td>
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<td>Hypertension</td>
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<td>51 (39.8)</td>
<td>203 (39.6)</td>
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<td>75 (44.4)</td>
<td>179 (37.9)</td>
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<td>Kidney disease</td>
<td>70 (10.9)</td>
<td>17 (13.3)</td>
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<td>21 (12.4)</td>
<td>49 (10.4)</td>
<td>.47</td>
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<td>Stroke/TIA</td>
<td>92 (14.4)</td>
<td>12 (9.4)</td>
<td>80 (15.6)</td>
<td>.07</td>
<td>24 (14.2)</td>
<td>68 (14.4)</td>
<td>.95</td>
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### Psychological distress and mortality

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<th>Condition</th>
<th>Psychological distress</th>
<th>Mortality</th>
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<tbody>
<tr>
<td>COPD</td>
<td>102 (15.9)</td>
<td>32 (18.9)</td>
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<tr>
<td>PAD</td>
<td>79 (12.3)</td>
<td>23 (13.6)</td>
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<tr>
<td>Currently smoking</td>
<td>154 (24.0)</td>
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### Medication

<table>
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<tr>
<th>Medication</th>
<th>Psychological distress</th>
<th>Mortality</th>
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<tbody>
<tr>
<td>ACE-inhibitors</td>
<td>439 (68.5)</td>
<td>107 (63.3)</td>
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<tr>
<td>Beta-blockers</td>
<td>432 (67.4)</td>
<td>102 (60.4)</td>
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<td>ARB</td>
<td>141 (22.0)</td>
<td>41 (24.3)</td>
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<tr>
<td>Calcium antagonists</td>
<td>80 (12.5)</td>
<td>24 (14.2)</td>
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<tr>
<td>Nitrates</td>
<td>163 (25.4)</td>
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<tr>
<td>Digoxin</td>
<td>143 (22.3)</td>
<td>36 (21.3)</td>
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<td>Spironolactone</td>
<td>130 (20.3)</td>
<td>34 (20.1)</td>
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<tr>
<td>Oral anticoagulants</td>
<td>309 (48.2)</td>
<td>77 (45.6)</td>
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<td>Statins</td>
<td>355 (55.4)</td>
<td>232 (49.2)</td>
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<td>Aspirin</td>
<td>257 (40.1)</td>
<td>64 (37.9)</td>
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<td>Diuretics</td>
<td>469 (73.2)</td>
<td>132 (78.1)</td>
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<tr>
<td>Device therapy†</td>
<td>96 (15.0)</td>
<td>17 (10.1)</td>
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</table>

**ARB=angiotensin-II receptor blockers; COPD=chronic obstructive pulmonary disease; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association functional class; PAD=peripheral arterial disease; TIA=transient ischemic attack.**

*Results are presented as n (%) unless otherwise stated.

† Defined as primary school or lower

§ CABG, MI, or PCI

∀ Either single, biventricular pacemaker or implantable cardioverter defibrillator

Significant findings are presented in boldface.
Table 2. Multivariable model of psychological distress and mortality\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>All-cause mortality (n=123)</th>
<th>Cardiac mortality (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95%CI</td>
</tr>
<tr>
<td>Anxiety/depression symptoms\textsuperscript{b}</td>
<td>1.18</td>
<td>0.76-1.84</td>
</tr>
<tr>
<td>Type D personality\textsuperscript{b}</td>
<td>1.09</td>
<td>0.67-1.77</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Model adjusted for age, sex, having an partner, working status, educational level, etiology, time since diagnosis, LVEF, cardiac history, NYHA class, diabetes, hypercholesterolemia, hypertension, kidney disease, stroke/TIA, COPD, PAD, smoking status, prescribed medications, and device therapy.

\textsuperscript{b} Hazard ratios for dichotomous scores.
Figure 1.

Number of patients approached for participation

- Refused to participate: n=75
- Did not return questionnaire: n=19
- Unreachable: n=2
- Too many missing items on questionnaires: n=3

Patients included in analyses: n=641
Figure 2.
2a. stratified by elevated anxiety/depression symptoms

- Elevated anxiety/depression symptoms
- No elevated anxiety/depression symptoms

2b. stratified by Type D personality

- Type D
- non-Type D

Follow-up in months

Survival (%)

p = .06

p = .63
Psychological Distress and Mortality in Systolic Heart Failure
Aline J. Pelle, Susanne S. Pedersen, Angélique A. Schiffer, Balázs M. Szabó, Jos W. Widdershoven and Johan Denollet

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