Health outcomes in chronic heart failure

Schiffer, A.A.J.

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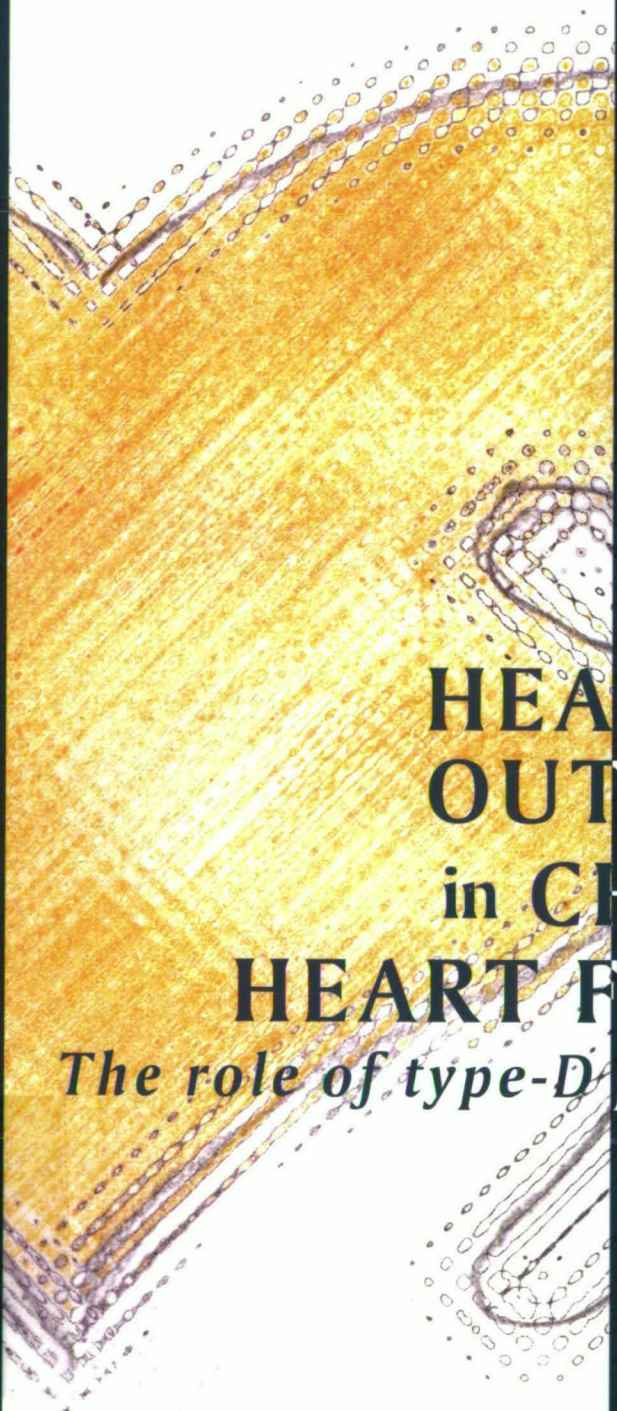

HEALTH OUTCOMES in CHRONIC HEART FAILURE

The role of type-D personality

Angélique A J J Schiffer

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HEALTH OUTCOMES in CHRONIC HEART FAILURE
THE ROLE OF TYPE-D PERSONALITY

Angélique Agnes Johanna Jozef Schiffer, April 25, 2008

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PROMOTOR

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COPROMOTORES

Dr. S.S. Pedersen
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"Que vivre est difficile, ô mon coeur fatiqué!"

Henri Frédéric Amiel (1821-1881, Swiss philosopher, poet and critic)

CONTENTS

CONTENTS

CHAPTER 1

General introduction

THE GROWING EPIDEMIC OF CHRONIC HEART FAILURE

Chronic heart failure (CHF) is one of the leading health problems in the Western World [1-4]. This chronic, progressive condition is increasing in both prevalence and incidence due to the ageing of the population, better chances of survival following myocardial infarction and the growing incidence of hypertension, hence reaching epidemic proportions [5,6]. In the United States, a total prevalence of 2.5% was reported in 2004 [7]. The Rotterdam Study, a Dutch population-based prospective cohort study of more than 7,000 patients, indicated point prevalence rates of CHF of 6.4% (1997), 6.7% (1998) and 7.0% (1999). Higher prevalence rates were found in men than in women, and there was a significant rise in prevalence with age. The study indicated that almost 1 in 3 individuals aged 55 or older will develop CHF during their life span [8]. The incidence reported in the latter study was 14.4/1000 person-years, with significantly higher incidence in men than in women [8]. By comparison, the Netherlands Heart Foundation reported a prevalence of 163,800-176,400 and an incidence of 37,400-43,400 in the Netherlands in 2000 [9].

Apart from being a common condition, CHF is also associated with high mortality and morbidity rates, despite impressive advances in treatment during the last decades [1-4,8-10]. In 2,445 patients hospitalised for CHF in the United Kingdom in the year 2000, all-cause mortality rates 1-, 2-, and 5-years after hospital discharge were 37.3%, 52.9%, and 78.5%, respectively [2]. In the United States, deaths from CHF increased between 1994 and 2004 with 28%, whereas hospital discharges rose with 175% [7]. In the Netherlands, 5,624 patients died of CHF in 2004 (12% of total cardiac mortality) and 24,460 (8% of total cardiac hospitalisation) were hospitalised [10].

Taken together, CHF is a chronic and progressive condition that is associated with high mortality and morbidity, hence deserving attention in clinical research. All the more because studies have shown that patients with CHF also report impaired quality of life [11-14].

QUALITY OF LIFE AND HEALTH STATUS AS PATIENT-CENTRED OUTCOMES

Quality of life and health status are often used synonymously; however, quality of life is a broader concept than health status, as it not only assesses the influence of the disease on the individual's functioning, but also the extent to which this is

bothersome to the individual [15]. Quality of life and health status are important outcome measures in CHF research, because in general CHF patients prefer better quality of life over prolonged survival [16]. In addition, the studying of patient-centred outcomes, such as quality of life and health status, has been advocated as a means by which to bridge the gap between scientific research and clinical practice [17]. Patient-centred outcomes are an important aspect of patient-centred care, i.e., attending to patients' needs, improving or maintaining their quality of life and giving them an opportunity to play an active role in medical decision-making [17]. Furthermore, impaired quality of life has been linked to worse prognosis in coronary artery disease (CAD) and CHF [18-20]. Thus, knowledge of the determinants of health status and quality of life in CHF may also help to identify CHF patients at high risk for worse prognosis, thereby leading to improvements in treatment and enhancements in secondary prevention.

Recent studies have identified New York Heart Association (NYHA) functional class, socio-demographic variables, somatic co morbidities and depression as potential determinants of health status in CHF, whereas clinical disease characteristics, such as left ventricular ejection fraction (LVEF), seem to play a minor role [11,21-26]. Apart from depression, little is known about psychological and psychosocial determinants of patient-centred outcomes, such as health status, in CHF.

EPISODIC VERSUS CHRONIC PSYCHOLOGICAL RISK FACTORS

The importance of psychological and psychosocial factors in heart disease has been increasingly recognised in recent years, but studies have mainly focussed on depression, also in CHF [27-35]. Depression has been shown to predict adverse prognosis and impaired health status, although some studies did not confirm a relationship between depressive symptoms and mortality [25,26,29-34]. By contrast, few studies have focused on anxiety in relation to health outcomes in CHF, with results being inconsistent [30,32,35-37]. With the primary focus on mood states, and in particular on depression, there is a risk of ignoring other potentially important psychological risk factors, such as personality.

According to the theory of Kop, psychological risk factors in heart disease can be classified into (1) acute risk factors, (2) episodic risk factors, and (3) chronic risk factors, based on their duration [38,39]. Acute risk factors, such as a fit of anger, may act as a trigger of cardiac events within a time period of one hour, whereas

episodic risk factors exert an influence from several months up to two years and tend to reoccur, with depression and anxiety comprising examples of this category of risk factors. Finally, chronic risk factors, such as personality traits and socioeconomic status, have an impact of longer than two years [38,39].

A paucity of studies has investigated the role of personality as a chronic psychological risk factor in CHF, probably because of inconsistencies in research findings on the Type A Behaviour Pattern (TABP) [40]. However, personality is an important explanatory factor of individual differences in distress and health outcomes in CAD, and probably also in CHF [41-43]. The type-D, or distressed, personality has been related to poor health status and adverse prognosis in patients with CAD [e.g. 36,40-42,44-47]. Given that CAD patients are at risk of developing CHF, type-D personality may also be associated with deleterious health outcomes in this patient group. Thus, it may be of importance to examine both episodic as well as chronic psychological risk factors in the context of CHF.

THE NATURE OF TYPE-D PERSONALITY

Personality refers to the organisation of traits, which reflect consistencies in affect and behaviour of persons [48,49]. Negative affectivity and social inhibition are two normal and stable personality traits that are relevant in the context of CAD [50,51]. Negative affectivity and social inhibition are theoretically sound major domains of personality. Negative affectivity refers to the tendency to experience negative emotions (such as anger, irritability and dysphoria), have a negative view of self, and scan the world for impending trouble [50]. Social inhibition is the tendency to inhibit the expression of emotions and behaviours in social interactions, because of fear of rejection or disapproval [51]. Persons with a type-D personality have elevated scores on both negative affectivity and social inhibition. This means that they have a tendency to experience a broad range of negative feelings that they are not going to share with others, because they fear rejection or disapproval [48,52,53].

Both statistical procedures (cluster analysis) and specific theoretical assumptions underlie the construction of the type-D personality concept [48,54]. Research using cluster analysis yielded a number of coping subtypes in patients with CAD, under which the specific personality subtype that was characterised by high negative affectivity and high social inhibition [48,54,55]. The theoretical deduction followed the empirically based personality profile by using a median split of scores on self-report measures of negative affectivity and social inhibition [48,53]. This median split was used following the coping subtypes model developed by

Weinberger [56]. A recent study using item response theory confirmed that all items of the Type-D Scale (DS14), the instrument used to assess type-D, have the highest measurement precision around this cut-off [57].

Evidence shows that negative affectivity and social inhibition, as measured by the DS14, are not the same as neuroticism and introversion/extraversion, respectively [53]. In the validation study of the DS14, evidence on the construct validity of the scale in both the general population as well as in cardiac patients and in patients with hypertension was provided. The DS14 was validated against the NEO-Five Factor Inventory (NEO-FFI), which assesses the Big-five personality traits, namely neuroticism, extraversion, openness, agreeableness and conscientiousness [53,58]. In subjects from the general population, the DS14 negative affectivity subscale correlated r=.68 with NEO-FFI neuroticism, while the correlation between the DS14 social inhibition subscale and NEO-FFI extraversion was r=-.59. In other words, the traits were related but not identical. The above-mentioned findings were replicated in cardiac patients. Negative affectivity correlated r=.68 with neuroticism, whereas social inhibition correlated r=-.65 with extraversion [53].

Taken together, these results show that the DS14 negative affectivity and social inhibition sub domains are related to NEO-FFI neuroticism and extraversion, respectively, but that the NEO-FFI and the DS14 measure different constructs [53]. In addition, the type-D construct represents the interaction of traits whereas the NEO-FFI assesses single traits. A recent study confirmed that it is the interaction of the two DS14 personality traits that is toxic, with social inhibition moderating the effect of negative affectivity on prognosis [59]. Furthermore, neuroticism may have negative connotations, such as "neurotic disorder" [48]. Although type-D personality is an important determinant of emotional distress, such as anxiety and depression, and type-D may therefore predispose to psychopathology, the personality configuration itself is not psychopathological given that it is based on normal traits [48].

TYPE-D PERSONALITY: AN EMERGING RISK FACTOR IN CAD

In recent years, several studies have examined the detrimental effects of type-D personality on prognosis and other health outcomes in CAD. Among the first was a study published in the Lancet in 1996 [60]. In this study, type-D personality predicted mortality over a 6-10 year follow-up period in CAD patients, independently of biomedical risk factors and measures of disease severity, such as impaired LVEF and three-vessel-disease [60]. These findings were replicated in 1998, 2000, 2004,

2006 and 2007, also in coronary patients with an impaired LVEF, and in patients treated with percutaneous coronary intervention with drug-eluting stents [36,44,59,61-63]. Very recently was shown that type-D personality was also predictive of worse prognosis in heart transplantation recipients [64]. Apart from being associated with "hard medical outcome", type-D personality has also been associated with impaired health status and increased psychological distress (i.e., depression, anxiety, post-traumatic stress disorder, and vital exhaustion) in cardiac patients [e.g. 40,45,47,65-68].

Recently, some studies have investigated possible physiological and behavioural mechanisms in explaining the impact of type-D personality on health outcomes. One very recent study, for example, investigated the association between type-D and the cortisol awakening response in patients hospitalised for acute coronary syndrome [69]. Furthermore, two cross-sectional studies have examined the associations between type-D personality and the cytokines TNF-α and its soluble receptors sTNFR1 and sTNFR2, and one recent study focused on type-D and health-related behaviours in physically healthy persons [70-72]. Although the first two studies were conducted in patients with CHF [70,71], the potential impact of type-D personality on patient-centred outcomes, such as impaired health status and increased psychological distress (depression and anxiety), and prognosis in CHF is not known, nor have any prospective studies examined possible physiological and behavioural mechanisms that may explain the adverse effects of type-D personality on health outcomes in CHF.

For a more extensive review of the literature on the type-D personality construct, readers are referred to Chapter 2 of this thesis. Furthermore, a review article on type-D personality in Dutch is included in the Appendix.

PRESENT RESEARCH AND AIMS OF THIS THESIS

The present thesis examines the role of type-D personality as a chronic risk factor for patient-centred outcomes and prognosis in CHF, and reports on findings of a longitudinal follow-up study. Patients for the study were recruited from the cardiology department of the TweeSteden hospital in Tilburg, the Netherlands. All patients were consecutive CHF outpatients. The study was approved by the medical ethics committee. The data for the cross-sectional study described in Chapter 3 were collected at the heart failure outpatient clinic of the TweeSteden hospital as part of daily clinical practice.

As mentioned before, until now no studies have reported on the impact of type-D personality on adverse patient-centred outcomes and prognosis in CHF. Furthermore, no prospective studies have examined possible physiological and behavioural mechanisms explaining the adverse effects of type-D personality on these outcomes in CHF. Therefore, the focuses in the present thesis are on the role of type-D personality as a determinant of patient-centred outcomes and prognosis, i.e., health outcomes, in CHF, and on possible mechanisms explaining the adverse effects of type-D personality on these outcomes. In Figure 1, a schematic overview of the outline and aims of the present thesis is presented.

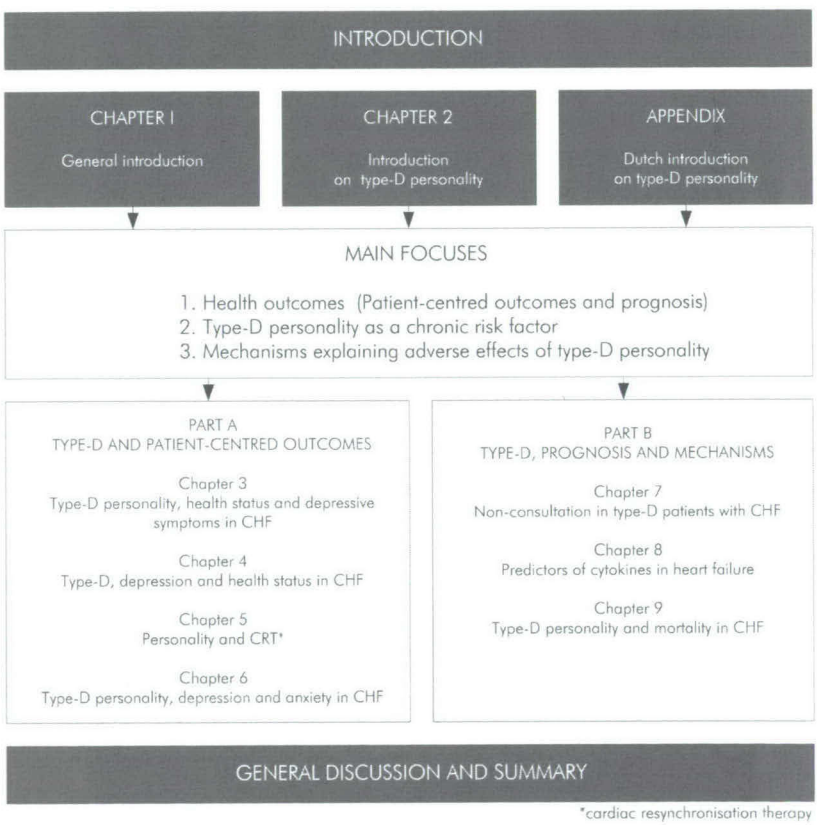

Figure 1. Outline and aims of the thesis

OUTLINE OF THE THESIS

PART A

TYPE-D PERSONALITY AS A PREDICTOR OF PATIENT-CENTRED OUTCOMES IN CHF

After a general introduction on type-D personality (Chapter 2), the first part of this thesis (Part A) focuses on type-D personality and its traits, and patient-centred outcomes in CHF.

An exploratory, cross-sectional study (n=84) on the association between type-D personality on the one hand, and health and mood status, and depressive symptoms on the other hand will be described in Chapter 3. This is the first study to examine the influence of type-D personality on health status, depressive symptoms and mood status in patients with CHF.

In a second, prospective study in 166 CHF patients, the findings of the cross-sectional study reported in Chapter 3 will be replicated. However, in this study, health status will be assessed using a broader approach, that is, using both disease-specific and generic (mental and physical) health status as patient-centred outcome measures. Furthermore, the aim of this study is to examine whether type-D personality would predict impaired health status above and beyond depressive symptoms (Chapter 4).

The relationship between negative affectivity, one of the type-D traits, health status, cardiac symptoms, perceived disability and functional capacity will be investigated in an exploratory study of 31 CHF patients who underwent cardiac resynchronisation therapy (CRT) (Chapter 5). To the best of our knowledge, no previous study has reported on the influence of personality traits on a broad range of patient-centred outcomes in patients treated with CRT.

Since anxiety and its determinants are in general less investigated in CHF than for instance depression, and the predictive role of type-D personality on anxiety in CHF has not been investigated, Chapter 6 will focus on type-D personality as a predictor of clinically relevant anxiety, measured with a clinical interview. In this study, 149 CHF patients are included.

PART B

TYPE-D PERSONALITY AS A PREDICTOR OF PROGNOSIS IN CHF AND MECHANISMS EXPLAINING THE ADVERSE EFFECTS ON HEALTH OUTCOMES

The second part of the thesis (Part B) reports on the relationship between type-D personality and mortality in CHF, and on possible mechanisms explaining adverse relationships between type-D personality and health outcomes.

Chapter 7 will prospectively investigate the association between type-D personality and impaired self-management, or more specifically, impaired consultation behaviour, in 178 CHF patients. Given their high level of social inhibition, type-D CHF patients may be at risk for inadequate self-management in terms of poor consultation behaviour. This failure to consult for cardiac symptoms is paradoxical given their tendency to experience high levels of negative feelings and to worry.

A possible physiological mechanism explaining adverse relationships between type-D personality and mortality is neurohormonal activation (cytokines). The relationship between type-D personality and chronic kidney disease on the one hand, and pro- and anti-inflammatory cytokine levels on the other hand, will be prospectively investigated in 125 CHF patients in Chapter 8.

Finally, the role of type-D personality in cardiac prognosis will be described in Chapter 9, as no study has reported on the relationship between type-D personality and prognosis in the context of CHF. The prognostic value of type-D personality will be examined in 232 CHF patients.

In the general discussion and summary of the thesis (Chapter 10), the main findings will be summarised and integrated. Implications for clinical research and practice will be described and reflections on limitations and strengths of the present research will be given. Finally, a review article on type-D personality in Dutch is included in the Appendix.

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INTRODUCTION
ON TYPE-D PERSONALITY

CHAPTER 2

Type-D personality and cardiovascular disease: evidence and clinical implications

Angélique A. Schiffer[a], Alessia Pavan[a], Susanne S. Pedersen[a], Paola Gremigni[b], Marinella Sommaruga[c], Johan Denollet[a]

[a]CoRPS – Center of Research on Psychology in Somatic diseases, Tilburg University, Tilburg, the Netherlands
[b]Department of Psychology, University of Bologna, Italy
[c]Servizio di Psicologia, Fondazione Salvatore Maugeri, IRCCS, Tradate, Italia; Maugeri Foundation, Care and Research, Psychology Unit, Tradate (Italy)

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ABSTRACT

Despite significant reductions in morbidity and mortality in recent years due to improved treatment strategies, cardiovascular disease is the leading cause of death in the Western World. Psychosocial factors, such as depression, have been shown to impact adversely on the prognosis of patients with coronary artery disease, but personality factors have to a large extent been ignored since the controversial findings surrounding the Type A Behaviour Pattern. This review on type-D personality highlights the importance of including personality factors in research and clinical practice, as personality may be an important explanatory factor of individual differences in multiple clinical outcomes. Type-D personality is defined as a high score on negative affectivity (a tendency to experience increased negative emotions) and social inhibition (a tendency not to express these emotions when together with others). Type-D has been associated with increased depression, fatigue, poor (health-related) quality of life, and increased risk of cardiac morbidity and mortality, independent of established biomedical risk factors. Type-D personality can be assessed with the Type-D 14-item Scale (DS14). The scale is a brief, valid and standardised instrument that comprises little burden to patients and to clinical practice. The DS14 has recently been validated in Italian cardiac patients.

RIASSUNTO

Nonostante negli ultimi anni si sia verificata una notevole diminuzione di morbilità e mortalità, grazie anche al miglioramento nella diagnostica e nella cura, le malattie cardiovascolari rimangono la causa principale di morte nelle popolazioni occidentali.
Si è dimostrato che fattori psicosociali, come ad esempio la depressione, giocano un ruolo negativo nella prognosi delle malattie cardiovascolari; tuttavia, i fattori legati alla personalità, a causa dei risultati a volte contraddittori delle ricerche sul Tipo A (Type A Behaviour Pattern), sono stati trascurati. Questa rassegna sulla personalità di Tipo D mette in luce l'importanza dell'inclusione dei fattori di personalità nella ricerca e nella pratica clinica, poichè la personalità può essere un importante fattore esplicativo di differenze individuali in molteplici esiti clinici.
La personalità di Tipo D è una combinazione di due dimensioni : affettività negativa (tendenza ad esperire emozioni negative nel tempo e in diverse situazioni) ed inibizione sociale (tendenza ad inibire emozioni e comportamenti nelle interazioni sociali. La personalità di Tipo D è stata associata ad un aumento di depressione, spossatezza cronica, insoddisfacente qualità della vita connessa alla salute e aumentato rischio di morbilità e mortalità per malattie cardiovascolari, indipendentemente da altri fattori di rischio biomedici. La personalità di Tipo D è misurabile con la Scala DS14 costituita da 14-item, uno strumento conciso, valido e standardizzato che richiede poco tempo a pazienti e operatori. La DS14 è stata recentemente validata anche in pazienti cardiopatici italiani.

INTRODUCTION

Several studies have shown that psychological distress is associated with the pathogenesis of cardiovascular disease (CVD) [1,2], but a paucity of studies include an appraisal of the contribution of personality to the link between distress and CVD prognosis. Personality factors may have much explanatory power in terms of individual differences in psychological distress, morbidity and mortality following somatic disease such as CVD, as will be shown in this review. In part, the exclusion of personality factors in psychosomatic research can be attributed to inconsistent results on the Type A Behaviour Pattern (TABP) and CVD.

The type-D (distressed) personality construct, derived from theoretical and empirical research, is characterised by a high score on two stable personality traits, i.e., negative affectivity and social inhibition [3-5]. Negative affectivity denotes the tendency to experience negative emotions (such as anxiety, sadness, anger) across time and situations, with individuals high on this trait scanning the world for signs of impending trouble [6,7]. Social inhibition refers to the tendency to inhibit the expression of these negative emotions in social interactions, i.e., individuals high on this trait fear the negative judgment of others and belittle or hide their difficulties, thereby generating a condition of social isolation [7,8]. In general, individuals with a type-D personality present with few positive emotions, have low self-esteem, and are generally dissatisfied with life [5]. In addition, type-D persons are more likely to suffer from depression, chronic tension, anger, pessimism, poor social support, and low levels of perceived well-being [3-5,9].

The present review reports on research on type-D personality in relation to CVD conducted between 1995 and 2004. For clarity, the studies have been categorised according to the levels of evidence in medical experimentation proposed by the Italian National Program for Guidelines Ministry of Health (Table 1) [10]. These levels range from I to V, with level I (e.g. randomised controlled trials and meta-analyses) being the highest, i.e., the best, level of evidence, and level V (e.g. case studies without a control group) being the lowest. To date, no studies have looked at interventions targeting type-D personality. Therefore, evidence from level I and II studies is not available.

EVIDENCE LEVEL III STUDIES

The study that can be considered a precursor to the type-D personality construct was published in 1995 [11]. It was based on a small sample of 105 male survivors of

myocardial infarction (MI), and investigated the association between personality and mortality. The results of the study showed that personality traits might play a role in the adverse effect of emotional distress on prognosis in post-MI patients. Patients with a type-D personality had a 6-fold increased risk of cardiac mortality compared with non type-D patients, adjusting for biomedical factors, including low exercise tolerance, previous MI, smoking, and age. Furthermore, adding the personality variable to biomedical factors in a logistic regression model more than doubled the sensitivity of the model in terms of its ability to predict mortality. In the latter study, depression, social alienation, somatisation and the use of benzodiazepines were also related to prognosis in post-MI patients. The findings indicated a higher prevalence of the various psychosocial risk factors in the distressed than in the non-distressed. However, the factors did not add to the level of prediction of mortality above and beyond that of the distressed personality type [11].

Table 1. Levels of evidence

Levels of evidence as provided by the Italian ministry of health	
I	*Randomised controlled trials (RCTs) and/or systematic reviews of RCTs*
II	*One RCT*
III	*Cohort non-randomised studies with concurrent or historical controls or their meta-analyses*
IV	*Retrospective studies (such as case control) or their meta-analyses*
V	*Case series without control group*
VI	*Expert opinion (such as guidelines or consensus conference)*

In 1996, an extension of the 1995 study was published [9]. The number of patients included was increased in order to enhance the power of the study, and the follow-up was extended. Type-D personality was associated with a significantly increased risk of mortality (type-Ds=27% versus non type-Ds=7%;$p< 0.00001$). The influence of type-D on cardiac and non-cardiac death remained substantial (OR=4.1;95%CI:1.9-8.8), even after adjusting for left ventricular ejection fraction (LVEF), multi-vessel disease, low exercise tolerance, and lack of thrombolytic therapy after MI. As shown in Figure 1, type-D personality was a predictor of all-cause mortality, independent of the two well-known risk factors for coronary heart disease

(CHD), i.e., LVEF and multi-vessel disease [9]. Another important result of this (and the previous) study was that neither negative affectivity nor social inhibition alone, but the synergistic effect of these two traits had deleterious effects on cardiovascular health; death rates for patients scoring high on only one of these traits did not differ from patients scoring low on both traits.

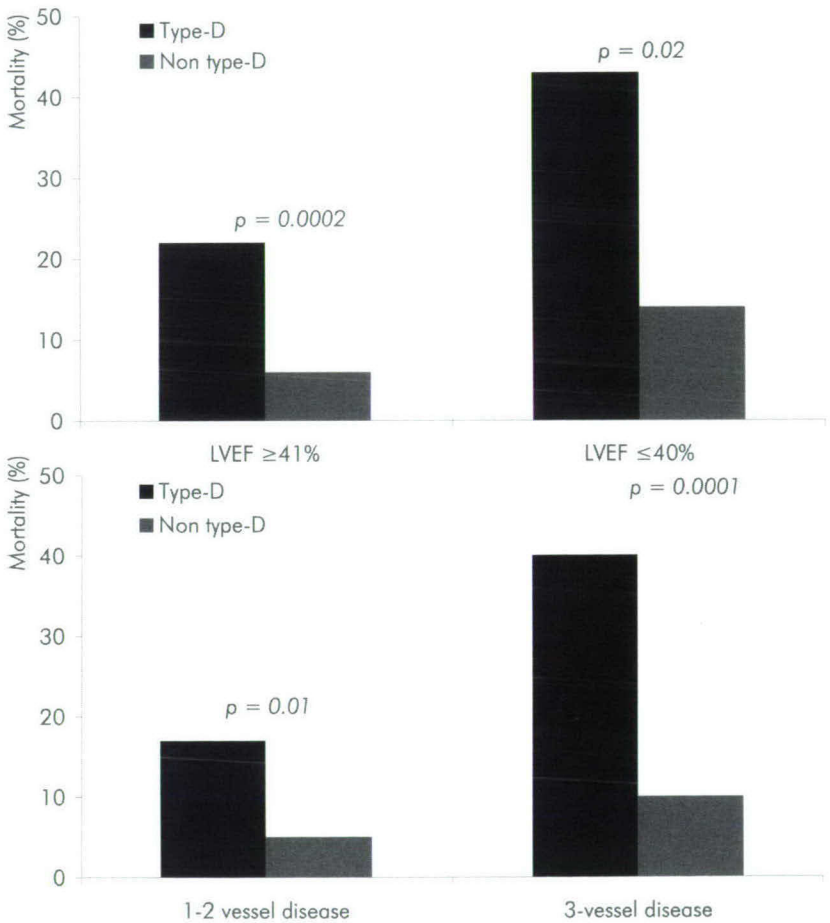

Figure 1. Left ventricular ejection fraction (LVEF) and multi-vessel disease stratified by personality type

In 2000, the above-mentioned results were confirmed in a 5-year follow-up study of 319 patients with established CHD [12]. In a multivariate model, type-D personality (OR=8.9;95%CI:3.2-24.7), LVEF<50% (OR=3.9;95%CI:1.4-11.1) and age<55 (OR=2.6;95%CI:1.0-6.6) were identified as independent predictors of cardiac mortality and non-fatal MI at 5-year follow-up. Type-D personality was also a risk factor for a combined endpoint, defined as cardiac mortality, non-fatal MI, coronary bypass graft surgery (CABG) and percutaneous transluminal coronary angioplasty (PTCA) (OR=4.5;95%CI:2.3-8.5) [12].

Two studies have investigated the relation between type-D and prognosis in special interest groups. The first study was undertaken in patients with a poor LVEF [13]; the second in patients with established CHD who developed cancer [14]. The first study, focused on 87 patients with MI and a LVEF≤50%. Type-D (RR=4.7; 95%CI:1.9-11.8) and LVEF≤30% (RR=3.0;95%CI:1.2-7.7) were identified as independent risk factors for cardiac events in a follow-up period of 6-10 years (mean=7.9 years) [13]. The second study, that examined the association between type-D personality and the development of cancer in male CHD patients, found that 13% of type-D patients developed cancer versus 2% of non type-D patients [14]. Type-D personality (OR=7.2;95%CI:2.9-18.1) and age (OR=4.6;95%CI:1.5-14.3) were identified as independent predictors of the development of cancer. There was no association between development of cancer and cardiac disease severity as measured by LVEF [14].

A recent sub-study of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry evaluated the impact of type-D personality on prognosis at 9-month follow-up in 875 consecutive patients with ischemic heart disease (IHD) following percutaneous coronary intervention (PCI) [15]. The patients had either received a sirolimus-eluting stent (SES) or a conventional bare stent. In univariate analysis, patients with a type-D personality had a higher risk of a composite of death or MI (5.6%) compared with non type-Ds (1.3%) (OR=4.7;95%CI:1.9-12.0). Type-D personality remained an independent risk factor for mortality or MI (OR=5.3;95%CI:2.1-13.7) after adjusting for all other clinical variables, including stent type. The results of the above-mentioned RESEARCH sub-study suggest that type-D personality is an independent predictor of prognosis in CHD, even when patients are treated with the latest advent in interventional cardiology [15].

Taken together, the consistency of these results suggests that type-D personality is an independent risk factor for hard medical outcomes in patients with established CHD.

EVIDENCE LEVEL IV STUDIES

A study by Appels and colleagues in 2000 considered the association between vital exhaustion (VE) and the inhibition of emotions in patients having suffered a sudden cardiac arrest (SCA) [16]. This study, based on 99 patients with SCA and 119 controls, identified VE as an antecedent of SCA. Furthermore, the effect of VE was modified by the inhibition of emotions, with patients who did not express their emotions being at a 7-fold increased risk of SCA [16].

In 2001, a study of 171 patients with IHD focused on the relation between type-D personality, gender, VE, and symptoms of angina [17]. Patients scheduled for coronary angiography (CAG) completed a questionnaire at baseline and 6 weeks following invasive or medical therapy. Univariate analysis yielded type-D as an independent predictor of VE at baseline and at follow-up. Compared with non type-Ds, type-D patients were at increased risk of VE both at baseline (OR=6.4;95%CI:3.0-9.7) and follow-up (OR=4.7;95%CI:0.7-8.8). At follow-up, type-Ds also reported more symptoms of angina pectoris than non type-Ds.

A recent contribution to type-D research was conducted in Denmark [18]. The objectives of this study were to investigate whether the Type-D Personality Scale (DS16) is a valid and reliable measure in other than Belgian populations, and to investigate whether individuals with a type-D personality may be at increased risk of developing posttraumatic stress disorder. The study was based on 112 first MI patients and 115 healthy controls, selected at random from the general population. The study confirmed the validity of the DS16, and identified type-D (OR=4.5;95%CI:1.4-14.6), neuroticism (OR=1.3;95%CI:1.1-1.5) and diagnosis of MI (OR=4.0;95%CI:1.4-11.4) as independent predictors of posttraumatic stress disorder adjusting for several other variables [18].

In another study, Pedersen and colleagues [19] investigated the prevalence of symptoms of anxiety and depression, and the association between type-D personality, social support and distress in patients with an implantable cardioverter defibrillator (ICD) (n=182) and their partners (n=144). The results showed a higher prevalence of anxiety symptoms in partners (42%) than in patients (31%), whereas levels of depression were similar (29% versus 28%). Both in patients (OR=7.0; 95%CI:2.3-21.3) and in partners (OR=8.8;95%CI:3.2-24.1), type-D was an independent determinant of symptoms of anxiety. Type-D was also independently associated with depressive symptoms in patients (OR=7.4;95%CI:2.5-21.9) and partners (OR=4.4;95%CI:1.8-11.01).

The results of the level IV studies indicate that the type-D construct also has value in arrhythmia research, and again support the notion that personality is an important explanatory factor of individual differences in distress.

EVIDENCE LEVEL V STUDIES

In 1998, the first level V study on type-D was published [5]. The focus of the study was on the two traits that define type-D, i.e., negative affectivity and social inhibition, and the development of a brief self-report measure for identifying type-Ds. The aim of the study was to replicate the 1996 finding that the synergistic effect of these two traits, i.e., type-D personality, is a risk factor in CHD patients [9]. The results showed that the Type-D Scale was a valid and reliable measure with type-Ds reporting more depressive feelings, lower self-esteem, and more dissatisfaction with life than non type-Ds [5].

A study of 734 patients with hypertension again focused on the synergetic effect of negative affectivity and social inhibition that is known as a risk factor in CHD [7]. First, the results showed that negative affectivity and social inhibition and their lower order traits could be assessed reliably in this patient group. This means that the type-D construct is not only applicable in patients with established CHD. Furthermore, there was an association between type-D personality and depressive affect; 49% of the type-Ds scored high on depressive affect versus 23% of the non type-Ds [7].

A preliminary cross-sectional study of 42 male patients with chronic heart failure (CHF) suggested that immune-activation may comprise one link between type-D personality and cardiac events [20]. Denollet and colleagues found that type-D was independently associated with higher levels of the pro-inflammatory cytokine TNFα and its soluble receptors TNFR1 and TNFR2, which comprise important prognostic indicators in CHF [20,21]. In the Denollet et al. study, type-D was as important as ischemic aetiology in immune activation [20]. It has previously been shown that negative emotions are associated with increased levels of pro-inflammatory cytokines [22]. The results of another study in healthy subjects ($n=173$) on the relationship between type-D personality and physiological indices, indicated a relationship between increased blood pressure and social inhibition, and between reduced heart rate and negative affectivity, in male subjects [23]. Furthermore, both negative affectivity and social inhibition turned out to be correlated with increased cortisol levels as a result of stress. These results suggest that the sympathic nervous

system may comprise another pathway in the relationship between type-D and outcomes in CVD [23].

An American study took into consideration type-D personality and other risk factors that have been associated with an increased risk of mortality in patients with CVD, using age at initial diagnosis as a proxy for prognosis. Type-D personality was found not to be significantly correlated with age at initial diagnosis; however, type-D persons reported more symptoms of depression and anxiety compared to non type-Ds [24]. A sequel to the latter study, which increased the number of participants by including more women, identified a significant relation between type-D and younger age at initial diagnosis of CVD in men [25].

Publications on type-D personality based on the level of evidence in medical experimentation as proposed by the Italian Ministry of Health are shown in Table 2.

Table 2. Publications on type-D personality based on the level of evidence in medical experimentation as proposed by the Italian Ministry of Health

Author	*Publication*	*Evidence level*	*Reference number*
Denollet et al.	*1996, Lancet*	*3*	*9*
Denollet & Brusaert	*1998, Circulation*	*3*	*13*
Denollet	*1998, Psychol Med*	*3*	*14*
Denollet	*1998, Ann Behav Med*	*5*	*5*
Denollet et al.	*2000, Circulation*	*3*	*12*
Denollet	*2000, J Psychosom Res*	*5*	*7*
Appels et al.	*2000, J Psychosom Res*	*4*	*16*
Pedersen & Middel	*2001, J Psychosom Res*	*4*	*17*
Denollet et al.	*2003, Brain Behav Immun*	*5*	*20*
Habra et al.	*2003, J Psychosom Res*	*5*	*23*
Pedersen & Denollet	*2004, J Psychosom Res*	*4*	*18*
Pedersen et al.	*2004, Psychosom Med*	*4*	*19*
Pedersen et al.	*2004, J Am Coll Cardiol*	*3*	*15*
Ketterer et al.	*2004, J Psychosom Res*	*5*	*25*

TYPE-D PERSONALITY, QUALITY OF LIFE, AND RESPONSE TO TREATMENT

Quality of Life

Until now, we have mainly considered the levels of evidence related to hard endpoints in CVD, i.e., morbidity and mortality, but response to treatment and quality of life (QoL) comprise other important endpoints. As emphasised by the World Health Organization (WHO), the target for the next millennium in terms of public health is a general improvement in QoL; all health-care professionals are required to devote attention to this aspect which to date only has been considered secondary [26]. Furthermore, in medical research, patients have rated quality of life as more important than extended survival [27]. As a consequence, QoL is an important outcome measure in medical research, also since impaired QoL has been associated with adverse prognosis [28,29].

Two studies have investigated the association between type-D personality and QoL in CVD patients. In the already cited study by Denollet and colleagues, type-Ds reported poorer subjective health compared to non type-Ds at 5-year follow-up [12]. QoL was measured with the Health Complaints Scale (HCS) and the Global Mood Scale (GMS), two psychometrically sound and sensitive measures of QoL [30,31]. It must be emphasised, however, that the above-mentioned results are based on a relatively small sample ($n=104$), and that further studies are warranted to confirm these associations. A cross-sectional study of 84 patients with CHF found an association between type-D personality and impaired health status [32]. In univariate analysis, type-D was associated with impaired health status (OR=2.8;95%CI:1.1-7.3); after adjusting for clinical and demographic variables, type-D remained an independent risk factor for impaired health status (OR=3.3;95%CI:1.2-9.1) [32].

Response to treatment

The already mentioned results of the Pedersen and Middel study on patients scheduled for CAG ($n=171$) showed that type-Ds reported more symptoms of angina pectoris than non type-Ds following CABG/PTCA or conservative treatment, despite reduction in symptoms of angina [17]. This means that type-D patients benefit from treatment, but not to the same extent as non type-D patients, as their levels of distress and somatic complaints remain significantly higher. Furthermore, another study showed that the convergence of decreased LVEF, younger age and type-D personality predicts absence of an expected therapeutic response [12].

Taken together, these results show that type-D personality is not only associated with an increase in emotional distress, more cardiac events and poor QoL, but also seems to moderate the effects of pharmacological and invasive treatment.

CROSS-CULTURAL RESULTS ON TYPE-D PERSONALITY: PRELIMINARY RESULTS ON THE DS14

During the third conference on the (Non-) Expression of Emotions in Health and Disease in Tilburg, the Netherlands (October 2003), a symposium was organised on the cross-cultural applicability of the type-D construct. Results of five studies on the validation of the Type-D Scale (DS14) in different countries, i.e., Belgian, Hungary, Germany, Denmark, and Italy were presented [18,33-36]. The DS14 comprises two subscales, i.e., negative affectivity and social inhibition, containing seven items each [33]. Both subscales have good test-retest validity and high internal validity, with Cronbach's α of .88 and .86 for the negative affectivity and social inhibition subscales, respectively. The items are answered on a 5-point Likert scale from "false" (0) to "true" (4). A pre-determined cut-off ≥ 10 on both subscales is used to determine those with a type-D personality [33].

The results of the Hungarian study in the general population ($n=12570$) identified type-D personality as a risk factor for cardiovascular disorder, MI, and cardiovascular morbidity, especially in subgroups in whom more traditional risk factors were absent (i.e., hypertension, diabetes and smoking) [34]. The German study ($n=2417$) confirmed the validity and reliability of the German DS14 in cardiac patients, psychosomatic patients and healthy factory workers (preliminary data) [35]. The prevalence of type-D in cardiac patients was 24%, in psychosomatic patients 62%, and in healthy factory workers 32% [35]. The Danish study, which has been mentioned previously, was conducted in first MI patients and healthy controls. The DS16 was found to be a valid instrument in both MI patients and healthy persons. Type-D also was associated with a more than 4-fold increased risk of posttraumatic stress disorder in this population, confirming that it is a marker of general distress [18]. The validation study of the Italian version of the DS14 included 145 cardiac patients [36]. The study confirmed the validity of the Italian DS14, of with Cronbach's α .82 and .80 for the negative affectivity and social inhibition subscale, respectively, and found type-D to be a predictor of psychological distress [36].

TYPE-D OR NOT TYPE-D: DO WE NEED ANOTHER PERSONALITY TYPE?

The emergence of non-psychopathological personality types and their association with somatic disease dates back to the 1950s when Friedman and Rosenman discovered that behavioural factors influenced serum cholesterol levels independent of diet [37]. Their observations led to the derivation of the TABP, or Type A as it is often referred to. The TABP is probably the most well known "personality" construct, and is defined as a competitive achievement orientation, a sense of urgency, and hostility; Type B typifies individuals with the absence of TABP. Following identification of TABP as an aetiological risk factor for CHD, independent of established biomedical risk factors, TABP was formally recognised as a risk factor of CVD on par with traditional biomedical risk factors [38,39]. However, later studies have shown mixed findings, and it seems that sub components of TABP (hostility) rather than global TABP have deleterious effects on health [2,40,41]. The following personality taxonomy that emerged was Type C personality, or the cancer-prone personality [42]. Type C defines those individuals who are cooperative, unassertive, and who suppress negative emotions [4,42]. Type-D personality is the most recent addition to these non-psychopathological personality dispositions, and may revive research in personality factors per se.

As a final remark, it is important to note that, although TABP is often regarded as a personality type, it was defined so as to avoid any association with general and stable features of personality [43]. Hence, it is particularly paradoxical that inconsistent results in relation to TABP have led to the general exclusion of personality factors in CVD. By contrast, type-D is a personality construct that is based on two stable traits, i.e., negative affectivity and social inhibition. So far, this personality type has been related consistently to hard and soft endpoints in CVD and other chronic conditions, thereby identifying patients at risk for important events and impaired QoL.

CONCLUDING REMARKS

The identification of cardiac patients at risk of recurrent cardiac events and impaired QoL, and the modification of this risk comprise important targets for secondary prevention. Since psychosocial risk factors have shown to cluster together within individuals, hence increasing the risk of adverse prognosis substantially, it is imperative to be able to identify this subgroup of patients. A recent review on the role

of psychological factors in CVD has suggested that focus on chronic stress in research and in clinical practice may facilitate the identification of these patients [1]. Chronic psychological risk factors are believed to promote the development of episodic and acute risk factors [44,45]. Type-D personality comprises a chronic psychological risk factor in so far as Type-D individuals deal with stress in a particular way. As shown in this review, type-D has substantial explanatory power of individual differences in cardiac morbidity and mortality. It has been associated with increased morbidity and mortality in patients with established CVD, comprising a risk factor on par with traditional biomedical risk factors. Furthermore, it has been associated with increased psychological distress and impaired QoL, and it has been shown to moderate the effects of pharmacological and invasive treatment. Type-D personality has also been shown to be important in other chronic conditions and diseases, including hypertension [7], cancer [14], and arrhythmias [19].

An important question remains, however, namely whether it is at all possible to modify the impact of type-D personality given its stable effect on behaviour. Although two recent trials have produced mixed findings [46,47], psychosocial interventions successful at reducing emotional distress, depression, TABP and anger/hostility, have proven to reduce morbidity and mortality in patients with CVD [48-51]. Type-D patients match this psychological profile and may therefore benefit from similar psychosocial interventions, even though this needs to be confirmed in future intervention studies.

In conclusion, the DS14 could be used in research and in clinical practice in order to identify patients at risk of future cardiovascular events. The scale is a brief and valid measure that comprises little burden to patients and to clinical practice. Although the scale was developed in Belgian cardiac patients, its applicability in other cultures has been demonstrated in recent studies in Denmark, Hungary Germany, and Italy [18,34-36].

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PART A

TYPE-D PERSONALITY AS A PREDICTOR OF PATIENT-CENTRED OUTCOMES IN CHRONIC HEART FAILURE

CHAPTER 3

The distressed (type-D) personality is independently associated with impaired health status and increased depressive symptoms in chronic heart failure

Angélique A. Schiffer[ab], Susanne S. Pedersen[a], Jos W. Widdershoven[b], Eric H. Hendriks[b], Jobst B. Winter[b], Johan Denollet[a]

[a]CoRPS – Center of Research on Psychology in Somatic diseases, Tilburg University, Tilburg, the Netherlands
[b]Department of Cardiology, TweeSteden Hospital, Tilburg, the Netherlands

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ABSTRACT

Background

Chronic heart failure (CHF) is a serious condition that is associated with impaired health status and a high prevalence of depressive symptoms. To date, little is known about the determinants of health status and depressive symptoms in CHF. Therefore, the aim of this study was assessing whether type-D personality is associated with impaired health status and increased depressive symptoms in CHF patients, independent of disease characteristics.

Methods

Eighty-four patients (63 men and 21 women, mean age=65.9±12.1 years) with systolic CHF completed four questionnaires to assess type-D personality (DS14), health status (MLWHFQ), depressive symptoms (CES-D) and mood status (GMS) when visiting an outpatient heart failure clinic. Information on clinical variables was obtained from the patients' medical records.

Results

Type-D patients were more likely to experience impairment in health status (18/38=47%) as compared to non type-Ds (11/46=24%), p=.027. They also more often reported symptoms of depression, i.e. 18/38=47% versus 6/46=13%, p=.001. When controlling for severity and aetiology of CHF, and age and gender, type-D remained a significant associate of health status (OR=3.3;95%CI:1.21-9.09) and depressive symptoms (OR=7.1;95%CI:2.23-22.39).

Conclusions

Type-D personality was associated with impaired health status and increased depressive symptoms in CHF patients. These preliminary findings demonstrate the value of including personality factors in CHF research.

INTRODUCTION

Chronic heart failure (CHF), which is the end-stage of most heart diseases, is an important cause of cardiac morbidity and mortality, and has been labelled as an emerging epidemic [1,2]. CHF has also been related to impaired health status and quality of life, and to co morbid depression [3-7]. Quality of life is a frequently used outcome measure in medical research and some patients have rated it as more important than extended survival [8]. Depression has been associated with increased risk of morbidity, mortality, (re)hospitalisation, and poor health status in CHF [3,6,9,10].

However, most studies have focused on the prevalence of depressive symptoms in hospitalised patients with CHF [6]. Gottlieb and colleagues were among the first to determine the prevalence of depression in outpatients with heart failure, and found depression to be a common co morbid condition [6]. Moreover, little is known about the determinants of health status and depression in CHF, although studies have shown that markers of CHF severity cannot explain differences in quality of life [4,6,11]. Furthermore, to our knowledge, the determinants of mood status have not been examined in CHF. Taken together, these findings suggest that we may need to expand our focus beyond looking at traditional risk factors, as knowledge of these determinants may lead to an expansion and refocusing of the treatment strategies used in CHF.

Personality may be an important determinant of individual differences in health status and depression in CHF that largely has been overlooked. Neuroticism, for example, has been shown to be an independent predictor of increased mortality in patients with CHF [12]. The adverse affect of type-D, or distressed, personality on health outcomes in patients with coronary heart disease (CHD), including high-risk patients with decreased left ventricular function following myocardial infarction, is also well-documented [13-15]. A high score on two stable personality traits, i.e., negative affectivity (the stable tendency to experience negative emotions and affect across time and situations) and social inhibition (the stable tendency to inhibit the expression of these negative emotions in social situations), defines type-D personality [e.g. 13,16]. Type-D personality is associated with increased risk of morbidity, mortality and impaired quality of life in patients with acute coronary syndromes (ACS) [13-17]. A recent study also showed that type-D individuals with an implantable cardioverter defibrillator (ICD) suffered from more anxiety and depressive symptoms compared with patients with non type-D personality [18]. Although patients with CHD

are at risk of developing CHF, to our knowledge no study has examined the effect of type-D personality on health and mood status in patients with CHF.

Thus, the objective of the current study was to examine whether type-D personality is associated with impaired health and mood status, and increased depressive symptoms in unselected outpatients with CHF.

METHODS

Study population

Consecutive unselected patients ($n=121$) with a diagnosis of systolic heart failure, visiting the heart failure outpatient clinic of the TweeSteden teaching hospital in Tilburg, the Netherlands, were asked to participate in the current study, and 84 patients agreed. Patients (1) with other life threatening co morbidities (e.g. cancer), (2) older than 80 years, (3) with a history of diastolic heart failure, (4) incapable of understanding and reading Dutch, or (5) with cognitive impairments , were excluded from this study.

Clinical variables

Socio-demographic variables included gender and age. Information on severity (New York Heart Association (NYHA) functional class and left ventricular ejection fraction (LVEF)) and aetiology (ischemia) of heart failure was obtained from the specialised heart failure nurse or the treating cardiologist. Information on clinical variables (hypertension, diabetes mellitus, smoking, hypercholesterolemia, and adipositas) and medication was obtained from the patients' medical records.

Type-D personality

Type-D personality was measured with the 14-item Type-D Scale (DS14) [19]. The scale comprises two subscales, negative affectivity and social inhibition, containing seven items each. Examples of items measuring negative affectivity are "I often make a fuss of unimportant things", and "I often feel unhappy". "I often feel inhibited in social interactions", and "I find it hard to start a conversation" are examples of items of the social inhibition subscale. The items are answered on a 5-point Likert scale from 0 ("false") to 4 ("true"). A pre-determined cut-off ≥ 10 on both subscales is used to determine those with a type-D personality [19]. Both subscales have good test-retest validity and high internal validity with Cronbach's α of .88 and .86 for the negative affectivity and social inhibition subscales, respectively [19].

Health status

The Minnesota Living with Heart Failure Questionnaire (MLWHFQ), a disease specific instrument, was used to assess health status [20]. This questionnaire consists of 21 items that are answered on a 6-point scale. The reliability of the scale is good with Cronbach's α of .95 [20]. A higher score on the MLWHFQ represents a poorer health status. The MLWHFQ is a frequently used measure to assess health status in CHF patients.

Depression and mood status

Depressive symptomatology was assessed with the Center for Epidemiologic Studies Depression Scale (CES-D), a measure that frequently has been used to measure depressive symptoms in CHF [21,22]. The 20 items are answered on a 4-point Likert scale ranging from 0 ("rarely or none of the time") to 3 ("most or all of the time"). A higher score on the CES-D indicates more depressive symptoms, with a score $\geq$16 indicating likely depressive symptomatology. The CES-D has a high internal consistency, as measured by Cronbach's α (ranging from .85-.90), and scores correlate highly with other self-report measures of depressive symptoms [23].

The 20-item Global Mood Scale (GMS) was used to evaluate mood status, defined as negative and positive affect [24]. Each subscale consists of 10 items that are answered on a 5-point Likert scale ranging from 0 ("false") to 4 ("true"). The scale has a high internal consistency with Cronbach's α of .90 [24].

Procedure

Patients were approached by letter and asked to fill in the four questionnaires. Patients who had not returned the questionnaires within two weeks received a reminder telephone call. This study was conducted at the heart failure outpatient clinic of the TweeSteden hospital as part of daily clinical practice. Patient participation was voluntary.

Statistical analyses

Discrete variables were compared with the chi-square test and continuous variables with the Student's *t* test. Univariate and multivariate logistic regression analyses were used to assess the association between type-D personality and the outcome measures health status, depressive symptoms and mood status. Prior to running logistic regression analyses, the scores on the questionnaires were recoded into discrete variables. The highest tertile on the MLWHFQ indicated impaired health status, whereas the highest tertiles of the both subscale of the GMS indicated increased negative affect and increased positive affect, respectively. In multivariate

analyses, we adjusted for NYHA functional class, LVEF, aetiology of CHF, gender and age. All statistical tests were two-tailed; $p<0.05$ was used for all tests to indicate statistical significance. Odds ratio (OR) with 95% confidence intervals (CI) are reported. All statistical analyses were performed using *SPSS 11.5* for Windows.

RESULTS

Patient characteristics

Patient characteristics are listed in Table 1. No significant differences were found between type-D and non type-D patients on demographic and clinical variables ($p<0.05$). Thus, type-D personality was not a function of NYHA functional class, LVEF, or aetiology of heart failure. Furthermore, no significant differences were found between type-Ds and non type-Ds on the prescription of drugs ($p<0.05$; results not shown).

Table 1. Patient characteristics

	Type-D	*Non type-D*	*p*
Male gender	*26*	*37*	*.21*
Age (mean±SD)	*66.7±13.2*	*65.2±11.2*	*.55*
Ischemic aetiology	*22*	*27*	*.94*
NYHA[a] Class III and IV	*14*	*23*	*.23*
LVEF[b] (mean±SD)	*27±8*	*24±10*	*.20*
Smoking	*10*	*9*	*.46*
Hypertension	*15*	*22*	*.44*
Diabetes Mellitus	*8*	*8*	*.67*
Hyperlipidemia	*16*	*18*	*.78*
Adipositas	*9*	*16*	*.27*

[a]*NYHA, New York Heart Association functional class.*
[b]*LVEF, Left ventricular ejection fraction.*
Data are presented as n unless otherwise stated

Type-D patients reported impairment in health status more often than non type-Ds (18/38=47% versus 11/46=24%, $p=.027$). They were also more likely to suffer from depressive symptomatology, i.e. 18/38=47% versus 6/46=13%, $p=.001$ (Figure 1).

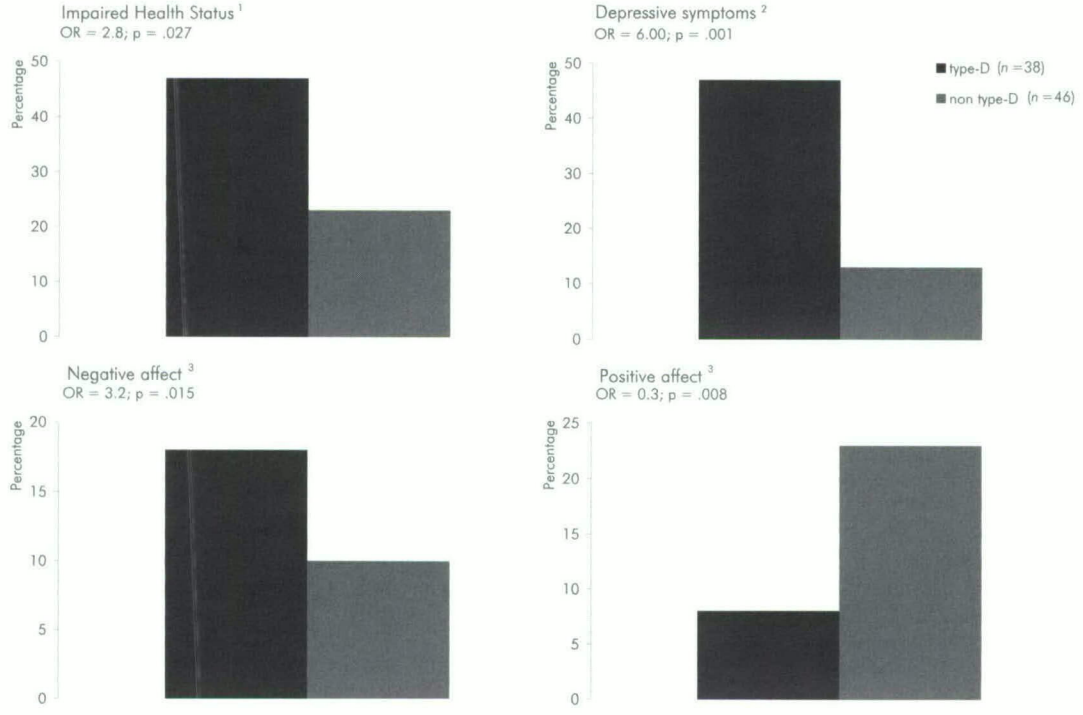

Figure 1. Type-D personality, impaired health and mood status, and depressive symptoms in heart failure (unadjusted analyses)

[1]Minnesota Living with Heart Failure Questionnaire (MLWHFQ); a high score indicates impaired health status
[2]Center for Epidemiologic Studies Depression Scale (CES-D); a high score indicates more depressive symptoms
[3]Global Mood Scale (GMS), subscale negative affect; a high score indicates more negative affect
[3]Global Mood Scale (GMS), subscale positive affect; a high score indicates more positive affect

Type-D personality, health status and depressive symptoms

In univariate analysis, type-D personality was associated with impaired health status and more depressive symptoms (Figure 1). Age, gender, NYHA classification, LVEF and aetiology of CHF were not significantly related to these endpoints in univariate analyses (Table 2).

Table 2. Relationship between clinical and demographic factors, health status and depressive feelings (unadjusted analyses)

	Impaired health status		*Depressive feelings*	
	OR	*p*	*OR*	*p*
NYHA[a] class	*1.3*	*0.571*	*1.1*	*0.835*
LVEF[b]	*0.97*	*0.190*	*0.98*	*0.636*
Aetiology	*0.6*	*0.334*	*1.3*	*0.625*
Male gender	*1.6*	*0.356*	*1.8*	*0.268*
Age	*1.0*	*0.610*	*1.0*	*0.938*

[a]*NYHA, New York Heart Association functional class*
[b]*LVEF, Left ventricular ejection fraction*

When adjusting for severity and aetiology of CHF, age, and gender, type-D personality was independently related to health status (OR=3.3;95%CI:1.21-9.09) and depressive symptoms (OR=7.1;95%CI:2.23-22.39) (Table 3).

Type-D personality and mood status

In univariate analyses, type-D patients were more likely to experience negative affect and less likely to experience positive affect (Figure 1). Type-D personality remained a significant associate of negative affect (OR=3.4;95%CI:1.26-9.23) and positive affect (OR=0.3;95%CI:0.09-0.81) when controlling for severity and aetiology of CHF, and demographic variables (Table 3). However, lower NYHA functional class (OR=3.7;95%CI:1.07-12.61) and younger age (OR=0.9;95%CI:0.91-1.00) were also independently associated with more positive affect in multivariate analysis (Table 3).

Table 3. Type-D personality as a determinant of health status, depressive symptoms and mood status (adjusted analyses)

	Impaired health status[1]		*Depressive feelings*[2]		*Negative affect*[3]		*Positive affect*[3]	
	OR (95%CI)	*p*	*OR (95%CI)*	*p*	*OR (95%CI)*	*p*	*OR (95%CI)*	*p*
Type-D	*3.32 (1.21-9.09)*	*.02**	*7.07 (2.23-22.39)*	*.001***	*3.41 (1.26-9.23)*	*.02**	*0.26 (0.09-0.81)*	*.02**
NYHA[a] *III & IV*	*1.19 (0.39-3.59)*	*.76*	*1.15 (0.34-3.90)*	*.82*	*0.69 (0.22-2.10)*	*.51*	*3.67 (1.07-12.61)*	*.04**
LVEF[b]	*0.96 (0.90-1.03)*	*.25*	*0.96 (0.89-1.04)*	*.33*	*0.97 (0.91-1.04)*	*.39*	*1.04 (0.97-1.12)*	*.23*
Aetiology	*0.58 (0.21-1.65)*	*.58*	*1.29 (0.43-3.94)*	*.65*	*0.68 (0.24-1.91)*	*.47*	*2.52 (0.82-7.72)*	*.11*
Male gender	*1.54 (0.49-4.84)*	*.46*	*1.26 (0.37-4.28)*	*.72*	*1.15 (0.37-3.60)*	*.81*	*0.27 (0.06-1.13)*	*.07*
Age	*1.00 (0.96-1.04)*	*.91*	*0.99 (0.94-1.03)*	*.50*	*1.00 (0.96-1.04)*	*.99*	*0.95 (0.91-1.00)*	*.04**

[a]*NYHA, New York Heart Association functional class*
[b]*LVEF, Left ventricular ejection fraction*
[1]*Minnesota Living with Heart Failure Questionnaire (MLWHFQ); a high score indicates impaired health status*
[2]*Center for Epidemiologic Studies Depression Scale (CES-D); a high score indicates more depressive symptoms*
[3]*Global Mood Scale (GMS), subscale negative affect; a high score indicates more negative affect*
[3]*Global Mood Scale (GMS), subscale positive affect; a high score indicates more positive affect*

*$p<.05$;**$p\leq.001$

DISCUSSION

As mentioned by Albus et al., there is evidence that psychological factors such as type-D personality contribute to the development and adverse outcomes in CHD [25]. To our knowledge, this is the first study to examine the influence of personality on health status and mood status in patients with CHF. Type-D patients were more likely to have poor health status, increased depressive symptoms, and impaired mood status compared with non type-Ds. These associations remained significant when adjusting for severity (NYHA functional class and LVEF) and aetiology of CHF, gender, and age. Characteristics of CHF, i.e., NYHA functional class and LVEF, were not related to any of the outcome measures. This means that clinical measures of CHF are not related to health and mood status, and depressive symptoms, but type-D personality is.

The results of the current study concur with studies having investigated the role of personality on quality of life in patients with ACS. These patients are at risk of developing CHF. In a prospective study of patients with ACS, type-D personality was found to be a predictor of impaired quality of life at 5-year follow-up [13]. In ACS patients, personality factors, such as type-D, have also been related to hard medical outcome [13-15], as has neuroticism in patients with CHF ([12]. Furthermore, a recent study showed that type-D patients treated for arrhythmia with ICD therapy experienced more anxiety and more depressive symptoms than non type-Ds treated with ICD [18].

In previous research on depression and CHF, there has been a focus on the prevalence of depressive symptoms, and on the association between depression and prognosis in CHF [9,11,26]. Only one study has examined the role of depressive symptoms as a predictor of health status in patients with CHF [3]. Rumsfeld and colleagues found depressive symptoms to be a strong predictor of worsened health status in CHF, adjusting for baseline health status and over 20 patient variables [3]. Ruo and colleagues found similar results among patients with CHD [27]. Recently, Gottlieb et al. found the presence of depression in patients with CHF to be associated with reduced quality of life scores [6]. No study, however, examined which factors are important in determining the depressive feelings that are so common in CHF.

Furthermore, although some studies have suggested an association between depression and personality traits such as neuroticism [28] or alexithymia [29], and between depression and personality pathology [30], no study has examined the role of a normal personality construct as a possible determinant of

depressive feelings in CHF patients specifically. We found type-D personality, a personality type that is not characterised as psychopathology, to be an important associate of depressive feelings in patients with heart failure.

This study has a number of limitations. First, the cross-sectional design of the study does not allow for determination of cause and effect. Second, the number of patients was relatively small, which limits generalisation of the results and the number of variables that can be controlled for in statistical analyses. Third, we did not include information on pacing techniques and other types of CHF treatment, because all patients included in this study were optimally treated by a cardiologist and a specialised heart failure nurse. Fourth, there is an overlap between symptoms of heart failure and depression. A diagnostic interview with a psychologist would provide better information on this issue.

Despite these limitations, this study is the first to investigate the role of type-D personality as an associate of health and mood status in heart failure patients. Moreover, the study was based on an unselected group of outpatients.

In conclusion, these preliminary findings suggest that type-D personality may be associated with adverse health status, increased depressive symptoms, and impaired mood status in patients with CHF. The results also demonstrate that it may be worthwhile to include personality factors in future studies of patients with CHF, as personality may be an important explanatory factor of individual differences in outcome. Large-scale studies are now warranted to confirm these results.

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CHAPTER 4

Type-D personality and depressive symptoms are independent predictors of impaired disease-specific and generic health status in chronic heart failure over time

Angélique A. Schiffer[abc], Susanne S. Pedersen[a], Jos W. Widdershoven[b], Johan Denollet[a]

[a]CoRPS – Center of Research on Psychology in Somatic diseases, Tilburg University, Tilburg, the Netherlands
[b]Department of Cardiology, TweeSteden Hospital, Tilburg, the Netherlands
[c]Department of Medical Psychology, TweeSteden Hospital, Tilburg, the Netherlands

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ABSTRACT

Background

Little is known about the role of personality as a determinant of health status in chronic heart failure (CHF). We examined whether type-D personality exerts a stable, independent effect on health status in CHF over 12 months, controlling for depressive symptoms.

Methods

Consecutive systolic CHF patients ($n=166$; 75% men; mean age 66±9) completed the DS14 and the BDI at baseline, and the MLWHFQ (disease-specific health status) and SF-36 (generic health status) at baseline and 12 months.

Results

There was a general improvement in disease-specific ($p=.008$) and mental ($p=.06$) health status over 12 months, but type-D patients reported significantly lower disease-specific ($p<.001$) and mental ($p<.001$) health status as compared to non type-Ds. Type-D personality was not related to generic physical health status. The negative impact of type-D personality on disease-specific ($p=.89$) and mental ($p=.69$) health status was stable, as indicated by the non-significant interaction effects. In multivariable analyses, type-D personality was an independent predictor of disease-specific ($\beta=.20;p=.003$) and mental ($\beta=-.25;p=.001$) health status, controlling for depressive symptoms, disease characteristics, socio-demographic variables, relevant medication, and baseline health status. Depressive symptoms was an independent predictor of disease-specific ($\beta=.20;p=.012$) and generic physical health status ($\beta=-.24;p=.001$). In logistic regression analyses, type-Ds had a more than 2-fold risk of impaired disease-specific health status and a close to 4-fold risk of impaired mental health status.

Conclusions

Type-D personality and depression were independent, stable predictors of impaired health status over 12 months. Because health status is an important patient-centred outcome and related to prognosis in CHF, counselling of patients at high risk for impaired health status is indicated.

INTRODUCTION

Chronic heart failure (CHF) is a serious condition, with increasing incidence and prevalence, and deleterious effects on prognosis and health status [1-4]. Impaired health status is a predictor of poor prognosis in CHF [5], but it is also emphasised by patients as an important treatment goal on its own, with patients generally preferring better health status over prolonged survival [6]. Hence, the study of health status, representing a patient-centred outcome, and its determinants is important for secondary prevention in order to identify high-risk patients. The study of patient-centred outcomes has also been advocated by others, as a means by which to bridge the gap between research and clinical practice [7].

Several studies have focused on functional status, as indicated by (self-rated) New York Heart Association (NYHA) class [8,9], age [8,10,11], sex [8,11,12], and somatic co morbidity [8] as important determinants of health status in patients with CHF. Depression has also been identified as a potential determinant [e.g. 13,14]. By contrast, a paucity of studies has investigated personality in the context of health status and CHF, probably because of the inconsistencies in findings in research on the Type A Behaviour Pattern (TABP) [15]. However, personality factors may explain individual differences in health outcomes above and beyond demographic and clinical risk factors [16].

Type-D personality is an emerging risk factor that has been associated with poor prognosis and health status across different cardiovascular patient groups [17,18]. Type-D personality is defined by a high score on the two stable personality traits negative affectivity and social inhibition [16]. Type-D patients tend to experience increased levels of anxiety, irritation, and depressed mood across situations and time, while not sharing these emotions with others because of fear of rejection or disapproval [16]. Type-D personality has been associated with impaired health status in patients with coronary artery disease, and in heart transplantation recipients [15,19,20]. Preliminary findings from a cross-sectional study suggested that type-D may also affect health status in CHF patients [21], but no prospective studies have examined whether this effect remains stable over time. Furthermore, it is unknown whether type-D personality predicts disease-specific and generic health status in CHF above and beyond depressive symptoms.

Therefore, the aims of this study were to examine (1) whether type-D personality has a stable effect on both disease-specific and generic health status in CHF over a 12-month period, and (2) whether type-D personality is an independent

determinant of disease-specific and generic health status at 12-month follow-up, when adjusting for depressive symptoms.

METHODS

Patient population, design and procedure

Between October 2003 and October 2005, consecutive CHF patients from the cardiology unit of the TweeSteden teaching hospital in Tilburg, the Netherlands, were recruited for the current study. Of 287 patients, 228 (79.4%) agreed to participate. However, since we used a prospective design and patients died and left the study during follow-up, final analyses are based on 166 out of 228 patients (Figure 1).

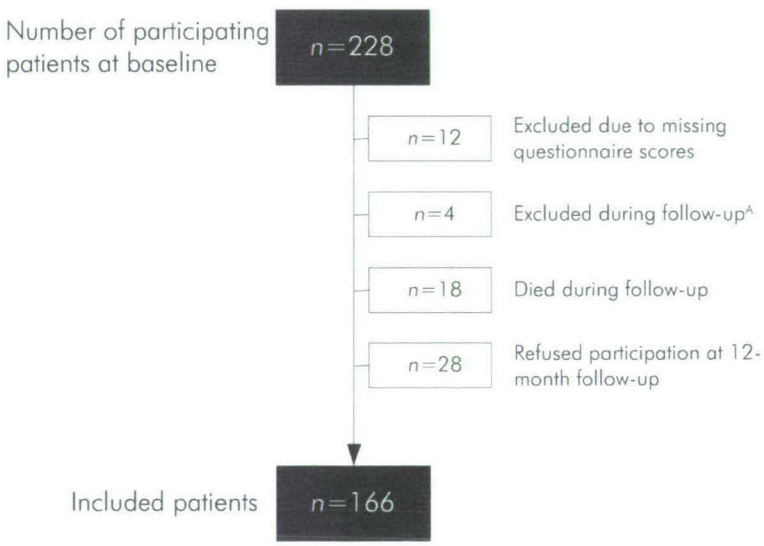

Figure 1. Flow chart of patient selection

[A] *These patients were excluded due to medical (e.g. cerebrovascular accident during the study) or logistic reasons (e.g. moving abroad).*

All patients were treated following the most recent guidelines for CHF [1,2,22]. Inclusion criteria were: (1) diagnosis of systolic CHF with a left ventricular ejection fraction (LVEF) ≤40%, (2) ≤80 years of age, and (3) stable on medication for at least one month prior to inclusion. We excluded patients with (1) a diagnosis of diastolic heart failure, (2) who were unable to read, write or understand Dutch, and (3) who had life-threatening co morbidities (e.g. cancer or a myocardial infarction (MI) one month preceding inclusion), or (4) severe cognitive impairments (e.g. dementia).

The study was approved by the hospital medical ethics committee and carried out conform to the Helsinki Declaration. Every patient received oral and written information about the study and provided written informed consent. Participation was voluntary and patients were free to withdraw at any time during the study.

The treating cardiologist or CHF nurse informed patients about the study and asked them to participate. If they agreed, they were called by the investigator in the same week to make an appointment for assessment. During the first visit, patients were given additional information about the study and were asked to complete a set of questionnaires at home and return them in a self-addressed envelope. At 12-month follow-up, patients were invited to the hospital again and received a set of questionnaires to complete at home once more. All questionnaires were checked for completeness. Patients who had left open several questions were called to obtain the answers or they were mailed a copy of the items and were asked to complete them. In case the questionnaires were not returned within two weeks, patients received a reminder telephone call or letter.

Measures

Health status.

In the current study, both disease-specific as well as generic health status were assessed at baseline and at 12-month follow-up.

We used the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) to assess disease-specific health status [23,24]. The MLWHFQ is a 21-item measure of health status that is frequently used in CHF patients [24]. The 21 items are answered on a 6-point Likert scale, ranging from "no" (0) to "very much" (5). A higher score on the MLWHFQ represents a poorer health status [23]. The MLWHFQ has solid psychometric properties, with good internal consistency (Cronbach's α=.91-.96) [23,24].

The Short-Form Health Survey (SF-36) is a 36-item measure of generic health status, with higher scores indicating better generic health status, except for the bodily pain subscale where a high score indicates the absence of pain [25-27]. The SF-36 can be divided into eight subscales, namely (1) physical functioning, (2) role limitations due to physical functioning, (3) role limitations due to emotional functioning, (4) mental health, (5) vitality, (6) social functioning, (7) bodily pain, and (8) general health. Subscale scores can be obtained by summing the items together, dividing the outcome by the range of scores, and finally transforming the raw scores to Z-scores, ranging from 0 to 100. The subscales can be summarised into a physical component summary score (PCS) and a mental component summary score (MCS) [27]. In a recent study, the two-factor structure of the SF-36 was validated in patients with somatic diseases [28], and therefore the two component summary scores were used in this study. The Dutch version of the SF-36 is a reliable and valid instrument for use in chronic disease populations. The mean Cronbach's α across the eight subscales is .84 [26].

Type-D personality.
Type-D personality was measured with the Type-D Scale (DS14) [16]. The questionnaire consists of 14 items that are divided into two subscales, namely negative affectivity and social inhibition. Items are answered on a 5-point Likert scale from "false" (0) to "true" (4). A standardised cut-off ≥ 10 on both subscales indicates type-D caseness [16]. Emons and colleagues showed recently that the items of the DS14 had highest measurement precision around the mentioned cut-off [29]. The two DS14 subscales have good psychometric qualities, with Cronbach's α=.88/.86 and 3-month test-retest reliability r=.72/.82 for the negative affectivity and social inhibition subscale, respectively [16]. Recently, the stability of type-D personality over 18 months was shown in post-MI patients [30]. The DS14 was administered at baseline.

Depressive symptoms.
The presence of depressive symptoms was assessed at baseline with the Beck Depression Inventory (BDI), a commonly used questionnaire to measure depressive symptoms in clinical research and in patients with cardiovascular disease (CVD) [31,32]. The 21 items are answered on a 4-point scale, ranging from "0" to "3". A higher total score on the BDI indicates more depressive symptoms. A standardised cut-off ≥ 10 denotes those with likely depressive symptomatology [31]. The BDI is a

valid and reliable measure of depressive symptoms, with Cronbach's α=.81 in non-psychiatric samples [32].

Socio-demographic and clinical characteristics.
Socio-demographic variables, including sex, age, marital status, and educational level, were obtained through four purpose-designed questions in the questionnaire. Information on clinical variables, including LVEF, NYHA functional class, aetiology of CHF (ischemic/non-ischemic), co morbidities (diabetes mellitus, renal insufficiency, hypertension and hyperlipidemia), and medication (ACE inhibitors, ARB's, diuretics, spironolactone, digitalis, beta-blockers, long-acting nitrates, aspirin, statins, and psychopharmaca) were obtained from the medical records or the treating cardiologist/CHF nurse. Smoking status was assessed by means of self-report.

Statistical analyses

Discrete variables were compared with the chi-square test and continuous variables with Student's *t* test for independent samples. In order to adjust for multiple comparisons, multivariate analyses of variance (MANOVA) for repeated measures were performed to examine whether there were differences in disease-specific health status (MWLHFQ), mental health status (SF-36) and generic physical health status (SF-36), and between type-D and non type-D patients and depressed and non depressed patients on these outcomes, over a 12-month period. Post-hoc ANOVA's for repeated measures were performed to evaluate differences in mean scores on disease-specific and generic health status at baseline and at 12-month follow-up. Type-D personality and depressive symptoms were entered (separately) into the ANOVA's to compare type-D and non type-D patients, and depressed and non-depressed patients on both disease-specific and generic health status over a 12-month period. Univariable and multivariable linear regression analyses were used to examine predictors of disease-specific and generic health status at 12 months. Prior to regression analyses, independent continuous variables were recoded into dichotomous variables. In the multivariable linear regression analyses, we entered type-D personality [e.g. 15,19-21], depressive symptoms [13,14], age [8,10,11], sex [8,11,12], NYHA functional class [8,9], diuretics, spironolactone, long-acting nitrates and psychopharmaca, since these variables have been identified as potential determinants of impaired health status in the CVD literature, or were significant in univariable analyses in the current study. Since LVEF is a measure of disease severity and may be a potential confounder of health status, LVEF was added as a covariate in the multivariable analyses. Finally, we controlled for baseline health status. To

enhance clinical interpretability, multivariable logistic regression analyses were performed as secondary analyses, dichotomising the health status scores using the highest tertile. All analyses were performed using *SPSS 12.0.1* for Windows.

RESULTS

Of 287 patients, 228 (79.4%) agreed to participate. There were significant differences between participants and non-participants on age, sex, hyperlipidemia and use of aspirin. Participants were younger (mean age=65.6±9.2 versus 70.6±8.3;$p<.001$), more often male (75.3% versus 50.9%;$p=.001$), more likely to have hyperlipidemia (53.6% versus 32.1%;$p=.004$), but less likely to be prescribed aspirin (45.2% versus 64.3%;$p=.010$) as compared to non-participants.

Baseline characteristics

Of 166 patients, 38 (23%) patients had a type-D personality, and 52 patients (31%) had significant depressive symptoms. Baseline characteristics, stratified by type-D personality, are shown in Table 1. There were no significant differences between type-D and non type-D patients on any of the demographic and clinical baseline characteristics (all $ps>.05$).

Type-D personality, depressive symptoms and health status

The results of the MANOVA for repeated measures indicated a significant overall improvement in disease-specific, mental, and generic physical health status over time ($F(1,165)=13.040;p<.001$). When including type-D personality and depressive symptoms as covariates, we found a main effect for both type-D personality ($F(1,164)=28.820;p<.001$) and depressive symptoms ($F(1,164)=81.160;p<.001$) on these outcomes.

In posthoc analyses, ANOVA's for repeated measures showed a significant general improvement in disease-specific health status ($F(1,164)=7.101;p=.008$) over 12 months. However, type-D patients reported significantly lower disease-specific health status compared with non type-D patients ($F(1,164)=25.482;$ $p<.001$) (Figure 2). The interaction effect type-D by time was not significant ($F(1,164)=.020;p=.89$), indicating that type-D personality exerted a stable effect on disease-specific health status over a 12-month period. There was also a significant main effect for depressive symptoms ($F(1,164)=72.315;p<.001$), and the negative effect of depressive symptoms on disease-specific health status was stable over time, as indicated by the non-significant interaction effect depressive symptoms by time ($F(1,164)=2.688;p=.103$).

Table 1. Baseline characteristics stratified by type-D personality

	Total sample	Type-D (n=38)	Non Type-D (n=128)	p
Demographics				
Age, Mean (SD)	66 (9)	67 (9)	65 (9)	0.30
Male sex	125 (75)	31 (82)	94 (73)	0.39
Living with a partner	123 (74)	27 (71)	96 (75)	0.68
Lower Education	54 (33)	17 (45)	37 (29)	0.08
Clinical variables				
LVEF[1] %, mean (SD)	30 (7)	31 (7)	30 (8)	0.44
NYHA[2] class III and IV	76 (46)	22 (58)	54 (42)	0.09
Ischemic aetiology	89 (54)	19 (50)	70 (55)	0.71
Smoking	38 (23)	7 (18)	31 (24)	0.52
Co morbidities				
Diabetes	43 (26)	10 (26)	33 (26)	1.00
Renal insufficiency	21 (13)	6 (16)	15 (12)	0.58
Hypertension	56 (34)	14 (37)	42 (33)	0.70
Hyperlipidemia	89 (54)	22 (58)	67 (52)	0.58
Medication				
ACE-inhibitors	127 (77)	31 (82)	96 (75)	0.52
ARB's	22 (13)	5 (13)	17 (13)	1.00
Diuretics	127 (77)	33 (87)	94 (73)	0.13
Spironolactone	38 (23)	8 (21)	30 (23)	0.83
Digitalis	52 (31)	13 (34)	39 (31)	0.69
Beta-blockers	110 (66)	25 (66)	85 (66)	1.00
Long-acting nitrates	31 (19)	9 (24)	22 (17)	0.35
Aspirin	75 (45)	19 (50)	56 (44)	0.58
Statins	84 (51)	21 (55)	63 (49)	0.58
Psychopharmaca	24 (15)	7 (18)	17 (13)	0.43

Numbers are presented as n (%) unless otherwise stated
[1]*LVEF=Left ventricular ejection fraction*
[2]*NYHA=New York Heart Association functional class*

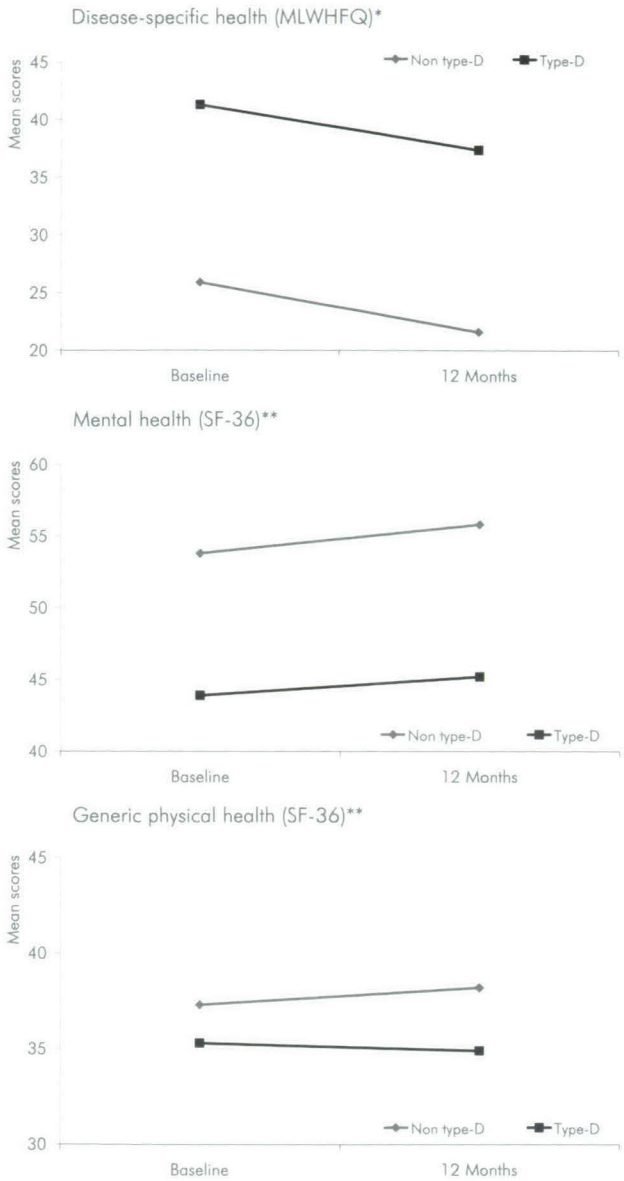

Figure 2. Mean health status scores at baseline and 12-month follow-up stratified by type-D personality

* *a higher score means worse disease-specific health status*
** *a lower score means worse generic (mental and physical) health status*

Furthermore, scores on mental health status (the MCS of the SF-36) did not change significantly over time, although there was a trend ($F(1,164)=3.648;p=.06$) for an improvement in mental health status over 12 months. The main between-subjects effect for type-D on mental health status was significant ($F(1,164)=45.311$; $p<.001$), with type-D patients reporting worse mental health status as compared to non type-D patients (Figure 2). The interaction effect for type-D by time was not significant ($F(1,164)=.164;p=.69$), again indicating a stable effect of type-D personality on the MCS scale over time. The main effect of depressive symptoms on mental health status was significant ($F(1,164)=34.459;p<.001$) and stable over time, as indicated by the non-significant interaction-effect depressive symptoms by time ($F(1,164)=1.660;p=.20$).

Scores on generic physical health status (the PCS of the SF-36) did not change significantly over time ($p=.79$), neither was there a significant main between-subjects effect for type-D personality ($p=.12$) (Figure 2). The interaction effect for type-D by time was also not significant ($F(1,164)=.833;p=.36$). However, there was a significant main between-subjects effect for depressive symptoms ($F(1,164)=38.970;p<.001$). This main effect was stable over time, as the interaction-effect depressive symptoms by time was not significant ($F(1,164)=.244;p=.62$).

Independent predictors of health status at 12 months

In univariable linear regression analyses, type-D personality, depressive symptoms, NYHA functional class, diuretics, spironolactone, long-acting nitrates, psychopharmaca, and baseline health status were significant predictors of disease-specific and/or generic health status (Table 2). In multivariable linear regression analyses, type-D personality remained an independent predictor of disease-specific ($\beta=.20;t=3.0$, $p=.003$) and mental ($\beta=-.25;t=-3.5$, $p=.001$) health status, adjusting for depressive symptoms, NYHA class, diuretics, spironolactone, long-acting nitrates, psychopharmaca, baseline health status, age, sex, and LVEF. Type-D personality was not an independent predictor of generic physical health status ($p=.82$). Depressive symptoms independently predicted disease-specific and generic physical health status (Table 3).

In secondary analyses, we dichotomised health status as an outcome measure in order to enhance clinical interpretability as advocated by others [33], and to compare the results with those of other studies on type-D personality [e.g. 34]. The results of the logistic regression analyses are displayed in Table 4.

Table 2. Significant predictors of impaired disease-specific and generic health status at 12 months (univariable analyses)

	Disease-specific health (MLWHFQ)		Mental health (SF-36;MCS)		Generic physical health (SF-36;PCS)	
	β	p	β	p	β	p
Type-D personality	.34	< .001	-.44	< .001	n.s.	n.s.
Depressive symptoms	.46	< .001	-.34	< .001	-.43	< .001
NYHA functional class	.23	.003	n.s.	n.s.	-.31	< .001
Diuretics	.19	.015	-.21	.006	-.16	.039
Spironolactone	n.s.	n.s.	n.s.	n.s.	-.16	.041
Long-acting nitrates	.19	.012	n.s.	n.s.	-.27	< .001
Psychopharmaca	.29	< .001	n.s.	n.s.	-.23	.003
Baseline health status	.48	< .001	-.48	< .001	-.49	< .001

MLWHFQ=Minnesota Living with Heart Failure Questionnaire;SF-36=Short-Form Health Survey;MCS=Mental Component Scale; PCS=Physical Component Scale;NYHA=New York Heart Association classification;n.s.=not significant

Table 3. Independent predictors of impaired disease-specific and generic health status at 12 months (multivariable linear analyses)

	Disease-specific health (MLWHFQ)		Mental health (SF-36;MCS)		Generic physical health (SF-36;PCS)	
	β	p	β	p	β	p
Type-D personality	.20	.003	-.25	.001	n.s.	n.s.
Depressive symptoms	.20	.012	n.s.	n.s.	-.24	.001
NYHA functional class	n.s.	n.s.	n.s.	n.s.	-.18	.009
Diuretics	n.s.	n.s.	-.14	.042	n.s.	n.s.
Spironolactone	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Long-acting nitrates	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Psychopharmaca	.14	.045	n.s.	n.s.	n.s.	n.s.
Baseline health status	.27	.001	-.33	< .001	-.33	< .001
Age	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Sex	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
LVEF	.14	.033	n.s.	n.s.	n.s.	n.s.

LVEF=Left ventricular ejection fraction;MLWHFQ=Minnesota Living with Heart Failure Questionnaire;SF-36=Short-Form Health Survey; MCS=Mental Component Scale;PCS=Physical Component Scale;NYHA=New York Heart Association classification;n.s.=not significant

Table 4. Independent predictors of impaired disease-specific and generic health status at 12 months (multivariable logistic analyses)

	Disease-specific health (MLWHFQ)		*Mental health (SF-36;MCS)*		*Generic physical health (SF-36;PCS)*	
	OR (95%CI)	*p*	*OR (95%CI)*	*p*	*OR (95%CI)*	*p*
Type-D personality	*2.5 (.98-6.61)*	*.06*	*3.8 (1.4-10.2)*	*<.001*	*n.s.*	*n.s.*
Depressive symptoms	*3.2 (1.3-8.1)*	*.01*	*n.s.*	*n.s.*	*3.2 (1.3-7.8)*	*.009*
NYHA functional class	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*2.4 (1.0-5.5)*	*.04*
Diuretics	*3.3 (1.1-9.9)*	*.04*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Spironolactone	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Long-acting nitrates	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Psychopharmaca	*n.s*	*n.s*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Baseline health status	*3.4 (1.4-8.1)*	*.007*	*9.6(3.7-24.8)*	*< .001*	*3.9 (1.7-9.0)*	*.002*
Age	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Sex	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
LVEF	*1.1 (1.0-1.2)*	*.02*	*n.s.*	*n.s.*	*n.s.*	*n.s.*

LVEF=Left ventricular ejection fraction;MLWHFQ=Minnesota Living with Heart Failure Questionnaire;SF-36=Short-Form Health Survey; MCS=Mental Component Scale;PCS=Physical Component Scale;NYHA=New York Heart Association classification;n.s.=not significant

DISCUSSION

This is the first prospective study to examine the effect of type-D personality and its stability over time on disease-specific and generic health status in patients with CHF, while adjusting for depressive symptoms. Although there was a general improvement in health status over time, type-D patients reported significantly poorer disease-specific and mental health status as compared to non type-D patients. Thus, type-D personality exerted a stable, negative effect on disease-specific as well as on mental health status over a 12-month period. When controlling for potential confounders, including depressive symptoms, measures of disease severity, and baseline health status, type-D personality remained a significant independent predictor of disease-specific and mental health status. We found type-D patients to have a more than 2-fold risk of impaired disease-specific health status, and a close to 4-fold risk of impaired mental health status. In this study, we found no general improvement in generic physical health status over time; neither was there a significant relation between type-D personality and this outcome measure.

Personality as a determinant of individual differences in CHF patients' health status has largely been overlooked, as there is only one cross-sectional study on the relationship between type-D personality and health status in this patient group [21]. This study found that type-D was a significant associate of impaired health status adjusting for disease severity [21]. In the current study, this finding was replicated in a larger sample, using a more broad measure of health status and a prospective design.

Apart from type-D personality, we also found depressive symptoms to be an important predictor of impaired health status. This result is consistent with other studies focusing on depression as a determinant of health status in CHF [e.g. 13,14,35,36]. However, in the current study was shown that personality was also an important determinant that predicted individual differences in health status above and beyond depressive symptoms. Therefore, our results elaborate on findings from previous studies on determinants of health status in CHF. Furthermore, the results also support the notion that depressive symptoms and type-D personality are different forms of psychological distress. A recent sub study of the Myocardial Infarction and Depression Intervention Trial (MIND-IT) showed that type-D personality was less confounded by disease severity than post-MI depression [37]. This may help to explain why type-D personality has predictive value above and beyond depressive symptoms.

In previous studies, type-D personality has been associated with impaired health status and quality of life, for instance in patients surviving heart transplantation, and in patients treated with percutaneous coronary intervention or coronary artery bypass surgery [15,17-20,34]. Although the studies by Pedersen and colleagues [15,20], and Al-Ruzzeh and colleagues [34] found that type-D personality was an independent predictor of mental and physical health, we found no association between type-D personality and generic physical health status in the current study. Our sample of patients with CHF may be different from the patient samples in other studies in that patients in the present study are chronically ill with hardly any options left concerning invasive interventions. Hence, the generic physical health status may have been largely a function of the severity of CHF in the current study.

There was an overall significant improvement in disease-specific and mental health status over time, which suggests general treatment benefits or better adjustment to the disease. However, the subgroup type-D patients reported significantly lower health status as compared to non type-D patients, with this negative effect being stable over a 12-month period. These results indicate that type-D personality is not a temporal psychological risk factor for impaired health status in CHF, but an enduring one, and that type-D patients do not only need optimal pharmacological treatment but also more intensive psychological coaching and intervention. Vulnerable patients, such as type-D patients (but also patients with significant depressive symptoms) should be offered coaching, with the aims of improving self-management abilities [38], learning to better adjust to their disease, and extending their social network and sources of social support. Impaired self-management [38], maladjustment to the condition of CHF, and low social support [39] could be possible behavioural mechanisms explaining the relationship between type-D personality and impaired health status in CHF. Since impaired health status has been associated with death and (re)hospitalisation in patients with heart disease [5,33,40], efforts such as counselling of subgroups of patients at high risk for impaired health status are warranted.

A number of limitations must be considered in interpreting the results of this study. First, study participants were required to visit the outpatient clinic to be included in the study, and hence the sample could be biased by mobility and younger age. Second, there were several differences on clinical variables between participants and non-participants, as participants were more often male, younger, had more often hyperlipidemia and used less often aspirin. Third, we used self-report measures to assess health status and self-report may be prone to socially desirable

behaviour. Strengths of the study are its prospective design, the use of a broad measure of health status, since a disease-specific as well as a generic instrument was used, and the controlling for confounders, including depressive symptoms, disease severity, and baseline health status.

In conclusion, we found type-D personality to be a stable, independent predictor of disease-specific and mental health status in patients with CHF over a 12-month period, also when adjusting for depressive symptoms. Since health status is an important patient-centred outcome, with patients generally preferring better health status over prolonged survival, and impaired health status being associated with poor prognosis [5-7,33,40], high-risk patients, such as type-D patients, require a form of behavioural and psychosocial intervention in addition to their management of CHF. Furthermore, it seems timely now to include personality factors in cardiovascular research, as we need more studies that lead to a fuller understanding of the influence of personality factors on health outcomes [41].

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CHAPTER 5

Health status in patients treated with cardiac resynchronisation therapy: modulating effects of personality

Angélique A. Schiffer[ab], Johan Denollet[a], Susanne S. Pedersen[a], Herman Broers[b], Jos W. Widdershoven[b]

[a]CoRPS – Center of Research on Psychology in Somatic diseases, Tilburg University, Tilburg, the Netherlands
[b]Department of Cardiology, TweeSteden Hospital, Tilburg, the Netherlands

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ABSTRACT

Background

Cardiac resynchronisation therapy (CRT) is a promising treatment in chronic heart failure (CHF). However, a subgroup of patients still report impaired health status, cardiac symptoms and feelings of disability following CRT. The aims of this study were to examine (1) whether CHF patients treated with CRT improved in patient-centred outcomes and functional capacity, and (2) whether personality traits exert a stable effect on these outcomes over 2 months.

Methods

Analyses are based on 31 patients (65% male; mean age 70±8) with CHF treated with CRT. Two weeks before and 2 months after CRT, patients completed the Type-D Scale (negative affectivity, i.e. tendency to experience negative emotions, and social inhibition, i.e. tendency to inhibit self-expression), the Minnesota Living with Heart Failure Questionnaire (disease-specific health status) and the Health Complaints Scale (cardiac symptoms and perceived disability), and performed the 6-minute walking test (functional capacity).

Results

There was an improvement in disease-specific health status ($p<.001$), cardiac symptoms ($p=.001$), perceived disability ($p<.001$), and functional capacity ($p=.007$) in all patients over 2 months. However, high negative affectivity patients reported significantly lower disease-specific health status ($p=.046$), and more cardiac symptoms ($p=.035$) and perceived disability ($p=.015$) as compared to low negative affectivity patients. There was no significant main effect for negative affectivity on functional capacity. High negative affectivity patients still reported lower disease-specific health status ($p=.06$) and significantly more perceived disability ($p=.04$) when adjusting for left ventricular ejection fraction, gender and age. The effects for negative affectivity on patient-centred outcomes, as measured by Cohen's effect size index, were moderate to large.

Conclusions

Patient-centred outcomes improved over a 2-month period in patients treated with CRT, but negative affectivity exerted a stable, negative effect on health status, cardiac symptoms and perceived disability. Personality traits should be taken into account when evaluating effects of CRT.

INTRODUCTION

Cardiac resynchronisation therapy (CRT) has been used extensively over the last years in patients with advanced systolic chronic heart failure (CHF) and a prolonged QRS interval. Such patients commonly have a delayed myocardial activation, leading to a dyssynchronic contraction pattern of the left ventricle. This dyssynchrony results in hemodynamic alterations and ensures symptoms to the patients, such as dyspnoea [1,2]. Large-scale clinical trials have shown that CRT exerts positive effects on mortality, morbidity, quality of life, functional status, and exercise capacity in CHF [1-7]. However, a subgroup of patients still report significant symptoms and high levels of disability following CRT, and are labelled as non-responders [8,9].

When evaluating the effects of CRT, New York Heart Association (NYHA) class and health status are most frequently used as indicators [e.g. 2,5,10], whereas the effects on a more broad range of patient-centred outcomes have not been reported. Little is also known about improvements in patient-centred outcomes following CRT. Patient-centred care refers to attending to patients' needs, improving or maintaining their quality of life and giving them an opportunity to play an active role in medical decision-making [11]. One key component of patient-centred care is assessment of patient-centred outcomes. Examples of such outcomes are health-related quality of life and symptom burden [11].

The distressed, or type-D, personality has been shown to influence a number of health outcomes in patients with heart disease, including mortality, morbidity, quality of life and health status [12-15]. Type-D personality is defined by two normal and stable personality traits, namely negative affectivity (the tendency to experience a broad range of negative feelings) and social inhibition (the tendency not to share these feelings in social interaction) [16-19]. Thus, patients with this disposition experience increased negative emotions, while not expressing these emotions in social interaction because of fear of rejection or disapproval [16,17]. Not only type-D personality, but also its two traits negative affectivity and social inhibition have been shown to be determinants of individual differences in health outcomes [12-26]. To date, no study has reported on the association between negative affectivity, social inhibition and type-D personality, and patient-centred outcomes in patients treated with CRT.

Therefore, the aims of the present study were to examine (1) whether CHF patients treated with CRT experience general improvements in patient-centred outcomes (disease-specific health status, cardiac symptoms, perceived disability) and functional capacity (6-minute walking test performance) over a 2-month period, and

(2) whether negative affectivity, social inhibition, or both (i.e., type-D personality) exert a stable negative effect on these outcomes.

METHODS

Patient population, design and procedure

Between October 2003 and December 2006, all CHF patients who were eligible for CRT at the cardiology department of the TweeSteden teaching hospital in Tilburg, the Netherlands, were approached for participation in the current study. All patients were treated according to the most recent guidelines for CHF [27,28]. These patients received either an Insync-III® (Medtronic) or Frontier-II® (St Jude) device. These devices provide atrial-driven biventricular pacing with the use of a standard right ventricular lead and a left ventricular lead.

Inclusion criteria for CRT, and thereby for the current study, were (1) diagnosis of systolic CHF, (2) being on optimal medical therapy, (3) NYHA functional class III or IV, with a QRS duration $\geq$120msec, and (4) left ventricular ejection fraction (LVEF)$\leq$40%. In addition, (5) at least one of the following echocardiographic criteria had to be fulfilled: an aortic pre-ejection delay$>$140msec, an interventricular mechanical delay$>$40 msec, or delayed activation of the posterolateral left ventricular wall [3,29]. For the current study, patients who were unable to read, write or understand Dutch, who had life-threatening co morbidities (e.g. cancer or a myocardial infarction one month preceding inclusion), severe cognitive impairments (e.g. dementia), or who participated in another study on psychological determinants of health outcomes in CHF, were excluded.

Of 91 patients, 55 fulfilled all criteria and were asked to participate in the current study, of whom 41 (74.5%) agreed. However, since we used a prospective design, final analyses are based on 31 patients who had complete data at baseline and follow-up (Figure 1).

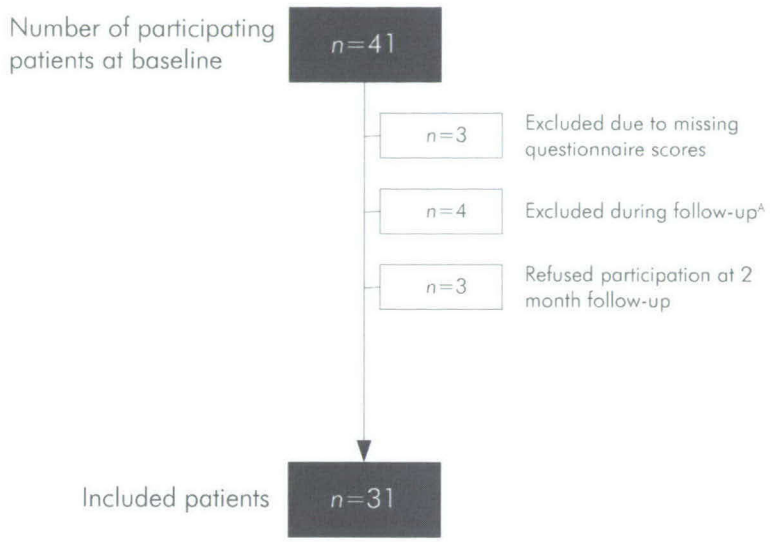

Figure 1. Flow chart of patient selection

[A]These patients were excluded because of diagnosis of dementia after inclusion (n=2), no resynchronisation therapy after all (n=1), and failure of successful implementation (n=1)

The study was approved by the hospital medical ethics committee and carried out according to policies to protect human subjects formulated by the World Medical Association and described in the Helsinki Declaration. Every patient received verbal and written information about the study and provided written informed consent. Participation was voluntary and patients were free to withdraw at any time during the study without further explanation or consequences. The specialised heart failure nurse informed patients about the current study and asked them to participate. If they agreed, they were called by the investigator in the same week to make an appointment for assessment (mean time between assessment and CRT=2 weeks;SD=2 weeks). During the first visit, patients were given additional information about the study and the CRT implantation procedure. They were asked to perform the 6-minute walking test (6MWT) and complete a set of questionnaires at home. The questionnaires were returned in self-addressed envelopes. Two months following CRT (mean time between CRT and follow-up assessment=8 weeks;SD=3 weeks), patients were asked to return to the hospital and the assessment procedure was repeated.

All questionnaires were checked for completeness, and patients who had left open several questions were called to obtain the answers. In case the

questionnaires were not returned within one week after assessment, patients received a reminder telephone call or letter.

Instruments (patient-centred outcomes)

The Minnesota Living with Heart Failure Questionnaire (MLWHFQ) was used to assess disease-specific health status from the patient's perspective [30]. The MLWHFQ is a subjective measure that is frequently used to measure disease-specific health status in CHF patients [31]. The 21 items are answered on a 6-point scale, ranging from "no" (0) to "very much" (5), with a higher score on the MLWHFQ representing a poorer disease-specific health status [30]. The items ask about the impact of physical and psychological symptoms and the effect of heart failure on physical and social functioning. In addition, medication side effects are captured [32]. The MLWHFQ has solid psychometric properties, with Cronbach's α ranging from .91-.96 [30-32]. The total score is the best measure of the patient's health status [32].

Cardiac symptoms and perceived disability were measured with the Health Complaints Scale (HCS). Originally, the scale was developed to create a sensitive outcome measure in the context of coronary heart disease [33]. This questionnaire consists of two 12-item subscales, measuring cardiac symptoms that frequently occur in patients with heart disease, and perceived disability, respectively. The cardiac symptom subscale contains items measuring cardiac and pulmonary symptoms, fatigue and sleep problems, whereas the perceived disability subscale contains items focusing on health worry (anxious concerns about ones health) and illness disruption (concerns about the extent to which illness interferes with ones life). The items are answered on a 5-point Likert scale ranging from "not at all" (0) to "extremely" (4) [33]. The HCS is a valid, internally consistent (Cronbach's $\alpha \geq .89$), and stable (test-retest reliability$\geq .69$) measure, and has good construct validity [33,34]. Furthermore, it has been shown that the HCS is sensitive to detect treatment effects [33]. A higher score on the subscales of the HCS means more symptoms and more perceived disability.

Disease-specific health status and health complaints were measured at baseline and 2 months following CRT.

Functional capacity

We used the 6MWT as a measure of the patient's functional capacity. The 6MWT has good intrasubject reproducibility and reliability [35,36]. Patients were asked to walk six minutes at their own pace, without talking to the investigator. The

investigator encouraged patients with standardised statements, such as "You are doing well." Other conversation was not allowed. The walking test was interrupted when patients were too tired or reported too many symptoms to walk any further. The patients were permitted to stop and rest when necessary during the test [35,37]. Functional capacity was measured at baseline and 2 months following CRT.

Personality traits

Negative affectivity, social inhibition, and type-D personality were assessed with the Type-D Scale (DS14) [17]. The questionnaire consists of two subscales of seven items each, measuring the two normal and stable personality traits negative affectivity and social inhibition [17]. The 14 items are answered on a 5-point Likert Scale ranging from "false" (0) to "true" (4). Examples of items measuring negative affectivity are "I often feel unhappy" and "I am often irritated". Examples of items measuring social inhibition are "I often feel inhibited in social interactions" and "I am a closed kind of person". Type-D personality is defined as a standardised cut-off ≥ 10 on both subscales of the DS14, i.e., the negative affectivity as well as the social inhibition subscale. High negative affectivity and high social inhibition are defined as a score of ≥ 10 on the negative affectivity or social inhibition subscale, while scoring low on the other scale [17]. Recently was shown that the items of the DS14 had highest measurement precision around the mentioned cut-off [38]. The negative affectivity and social inhibition subscales have good internal consistency (Cronbach's α=.88/.86) and good 3-month test-retest reliability (r=.72/.82) [17]. The construct validity of negative affectivity and social inhibition has been confirmed against the Big-Five personality traits neuroticism and extraversion, respectively [17]. Furthermore, a recent study in 475 patients with myocardial infarction indicated that type-D personality was a stable construct over an 18-month period [39]. The DS14 was administered at baseline.

Clinical variables and socio-demographic characteristics

Information on clinical variables (aetiology, LVEF, NYHA, co morbidities, current medication, height and weight) was collected at baseline and obtained from the medical records or the treating cardiologist/heart failure nurse. Socio-demographic variables included gender, age, marital status, educational level and work status, and were measured by purposed-designed questions in the questionnaire. Life style variables (i.e. smoking and exercising) were also measured by means of self-report.

Statistical analyses

Discrete variables were compared with the chi-square test and continuous variables with Student's *t* test for independent samples. In order to adjust for multiple comparisons, multivariate analyses of variance (MANOVA) for repeated measures were performed to examine whether there were differences in (a) patient-centred outcomes, i.e., disease-specific health status (MLWHFQ), cardiac symptoms and perceived disability (HCS), and (b) between low/high negative affectivity (cut-off $\geq$10), low/high social inhibition (cut-off $\geq$10) and type-D personality (yes/no) [17] on these outcomes over time. Differences on 6MWT performance over time were evaluated with an analysis of variance (ANOVA). Post-hoc ANOVA's for repeated measures were performed to evaluate differences in mean scores on the patient-centred outcomes at baseline and 2 months following CRT. Personality traits were entered into the ANOVA's to examine between-group differences on all outcome measures. Analyses of covariance (ANCOVA) were used to examine whether negative affectivity exerted a stable effect on disease-specific health status, cardiac symptoms, perceived disability and functional capacity, adjusting for baseline LVEF, gender and age.

Finally, Cohen's effect size index (d) was used to evaluate the influence of negative affectivity and gender on all outcome measures [40]. Gender is an individual difference variable that is often included in cardiovascular research [41]. An effect size (ES) of 0.20 is considered small, of 0.50 moderate, and of $\geq$0.80 large [40]. All analyses were performed using *SPSS 14.0* for Windows.

RESULTS

Baseline characteristics

Of 31 patients, 11 (36%) had elevated scores on negative affectivity and 18 patients (58%) were significantly socially inhibited. The prevalence of type-D personality in this sample was 26% (8/31).

Baseline characteristics for the complete sample and stratified by negative affectivity are shown in Table 1. High negative affectivity patients differed from low negative affectivity patients on educational level in that patients high on negative affectivity were more often on lower educational level.

CRT and patient-centred outcomes

The results of the MANOVA for repeated measures indicated a significant overall improvement in disease-specific health status, cardiac symptoms and perceived disability ($F(1,30=25.150; p<.001)$).

Table 1. Baseline characteristics stratified by negative affectivity

	Total sample (n=31)	High NA[1] (n=11)	Low NA (n=20)	p
Demographics				
Age, Mean (SD)	70 (8)	70 (8)	70 (9)	.95
Male sex	20 (65)	6 (55)	14 (70)	.39
Living with a partner	23 (74)	8 (73)	15 (75)	.89
Lower Education	9 (29)	6 (55)	3 (15)	.02
Retired	23 (74)	9 (82)	14 (70)	.47
Working	3 (10)	1 (9)	2 (10)	.94
Clinical variables				
NYHA[2] class III	28 (90)	9 (82)	19 (95)	.23
LVEF[3] %, mean (SD)	27 (8)	28 (11)	26 (6)	.71
Ischemic aetiology	20 (65)	9 (82)	11 (55)	.14
Life style				
Smoking	7 (23)	3 (27)	4 (20)	.64
Physical activity	12 (39)	3 (27)	9 (45)	.33
BMI[4], mean (SD)	28 (4)	30 (5)	27 (3)	.55
Co morbidities				
COPD[5]	11 (36)	5 (46)	6 (30)	.39
Diabetes mellitus	7 (23)	4 (36)	3 (15)	.17
Renal insufficiency	6 (19)	2 (18)	4 (20)	.90
Hypertension	19 (61)	6 (55)	13 (65)	.57
Hyperlipidemia	17 (55)	8 (73)	9 (45)	.14
PAD[6]	6 (19)	3 (27)	3 (15)	.41
Medication				
ACE-inhibitors	24 (77)	7 (64)	17 (85)	.17
ARB's	12 (39)	6 (55)	6 (30)	.18
Diuretics	23 (74)	9 (82)	14 (70)	.47
Spironolactone	5 (16)	1 (9)	4 (20)	.43
Digitalis	8 (26)	4 (36)	4 (20)	.32
Beta-blockers	18 (58)	6 (55)	12 (60)	.77
Long-acting nitrates	11 (36)	4 (36)	7 (35)	.94
Aspirin	20 (65)	6 (55)	14 (70)	.39
Statins	14 (45)	5 (46)	9 (45)	.98
Psychopharmaca	9 (29)	4 (36)	5 (25)	.51

Data are presented as n (%) unless otherwise indicated

[1]Negative affectivity; [2]New York Heart Association functional class; [3]Left ventricular ejection fraction; [4]Body mass index; [5]Chronic obstructive pulmonary disease; [6]Peripheral artery disease

ANOVA for repeated measures showed a significant general improvement in disease-specific health status, as measured with the MLWHFQ over 2 months in patients treated with CRT ($F(1,30)=25.665;p<.001$). There was also a main effect for time on both subscales of the HCS, indicating an improvement in cardiac symptoms ($F(1,30)=13.789;p=.001$) and in perceived disability ($F(1,30)=15.685;$ $p<.001$) over time.

In Table 2, mean scores on the patient-centred outcomes at baseline and 2 months following CRT are shown.

Table 2. Mean scores on patient-centred outcomes and functional capacity at baseline and 2 months following CRT

	Mean (SD) Baseline	Mean (SD) 2 months	F	p
Health status[1]	47.5 (16.4)	32.2 (17.7)	25.665	<.001
Cardiac symptoms[2]	21.0 (12.6)	13.9 (12.7)	13.789	.001
Perceived disability[2]	23.8 (11.6)	17.0 (13.7)	15.685	<.001
Functional capacity[3]	120.0 (95.2)	200.0 (160.0)	8.538	.007

[1]Minnesota Living with Heart Failure Questionnaire
[2]Health Complaints Scale
[3]6-minute walking test (in meters)

Personality and patient-centred outcomes in CRT

When including personality traits (that is negative affectivity, social inhibition, and type-D personality) as between-subjects factors in the MANOVA's for repeated measures, we found a main effect for negative affectivity on disease-specific health status, cardiac symptoms and perceived disability ($F(1,29=6.810;p=.01$). This effect for negative affectivity was (a) stable over time, given the fact that the negative affectivity by time interaction effect was non-significant ($p=.70$), and (b) the same for all patient-centred outcome measures used, i.e., the negative affectivity by scale interaction was also non-significant ($p=.85$). Neither social inhibition nor type-D personality were significantly associated with any of the outcome measures.

In the ANOVA for repeated measures, we found that high negative affectivity patients treated with CRT reported significantly lower disease-specific health status compared to low negative affectivity patients ($F(1,29)=4.363;p=.046$) (Figure 2). The interaction effect negative affectivity by time was not significant ($F(1,29)=.050;p=.82$), indicating that negative affectivity exerted a stable effect on disease-specific health status over a 2-month period. Compared to low negative

affectivity patients, high negative affectivity patients also reported more cardiac symptoms ($F(1,29)=4.879;p=.035$) and more perceived disability ($F(1,29)=6.715;$ $p=.015$), as measured with the HCS over 2 months (Figure 2). The non-significant interaction effects for negative affectivity by time for both cardiac symptoms ($F(1,29)=.970;p=.33$) and perceived disability ($F(1,29)=.022;p=.88$) indicated a stable negative effect for negative affectivity on cardiac symptoms as well as on perceived disability over the follow-up period.

Effects on functional capacity

Functional capacity, as measured with the 6MWT, improved significantly during the course of 2 months ($F(1,30)=8.538;p=.007$) (Table 2). However, there was no significant between-subjects difference between high and low negative affectivity patients on the 6MWT ($p=.33$) (Figure 2), neither was there an interaction effect for negative affectivity by time ($p=.36$). There were also no main effects for social inhibition or type-D personality on functional capacity.

Effect of negative affectivity on outcomes (adjusted analyses)

When adjusting for LVEF, gender and age (ANCOVA), high negative affectivity patients still reported lower disease-specific health status ($F(1,1)=3.813;p=.06$) and significantly more perceived disability ($F(1,1)=4.894;p=.04$) as compared to low negative affectivity patients. There were no significant main between-subjects effects for negative affectivity on cardiac symptoms ($p=.11$) nor on functional capacity ($p=.37$), when adjusting for disease severity, gender and age (Table 3). There were no significant between-subjects effects for LVEF, gender and age, but male patients had near significant better functional capacity as compared to female patients ($F(1,1)=3.833;p=.06$) (Table 3).

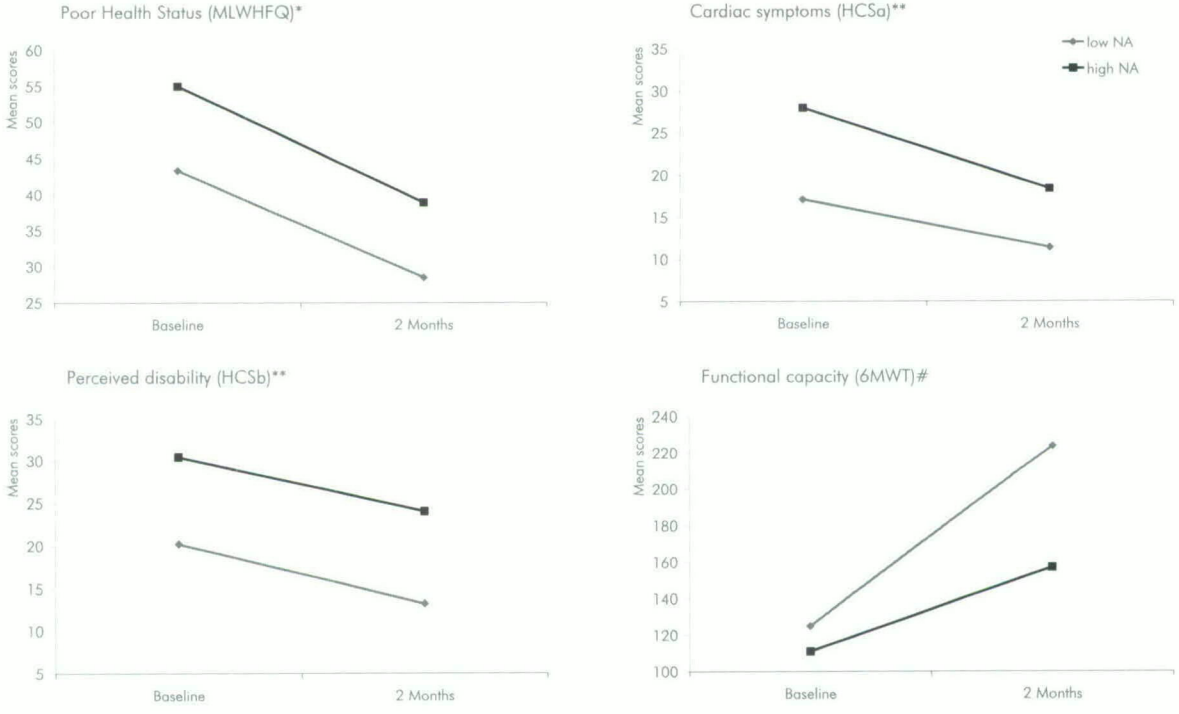

Figure 2. Mean health status, symptom and functional capacity scores at baseline and 2-month follow-up stratified by negative affectivity

* *a higher score means worse health status*
** *a higher score means more health complaints/perceived diasbility*
 # distance walked in meters

Table 3. Effect of negative affectivity on patient-centred outcomes and functional capacity (adjusted analyses)

	Health Status[a]		Cardiac symptoms[b]		Perceived disability[b]		Functional capacity[c]	
	F	*p*	*F*	*p*	*F*	*p*	*F*	*p*
NA[1]	3.813	0.06	2.802	0.11	4.894	0.04	0.839	0.37
LVEF[2]	1.319	0.26	0.053	0.82	0.151	0.70	1.005	0.32
Gender	0.129	0.72	1.314	0.26	0.809	0.38	3.833	0.06
Age	0.039	0.85	0.755	0.39	0.003	0.96	0.259	0.62

[1]*Negative affectivity*
[2]*Left ventricular ejection fraction*
[a]*Minnesota Living with Heart Failure Questionnaire*
[b]*Health Complaints Scale*
[c]*6-minute walking test*

Effects of negative affectivity versus gender

Negative affectivity had moderate to large effects on the patient-centred outcomes at baseline and 2-month follow-up, but a small effect on functional capacity, as measured by Cohen's effect size index. The effects of negative affectivity on disease-specific health status, cardiac symptoms and perceived disability were larger than the effect of gender on these outcomes (Figure 3).

DISCUSSION

To our knowledge, this is the first study to examine the influence of personality traits on a broad range of patient-centred outcomes in patients treated with CRT. We found a general improvement in patient-centred outcomes, i.e., disease-specific health status, level of cardiac symptoms, perceived disability, and in functional capacity over a 2-month period in these patients. However, negative affectivity had a stable, negative effect on patient-centred outcomes, with patients high on negative affectivity reporting lower disease-specific health status, more cardiac symptoms and more perceived disability as compared to low negative affectivity patients. There was no difference between high and low negative affectivity patients on functional capacity. When adjusting for disease severity (LVEF) and socio-demographics, negative affectivity still exerted a substantial negative effect on disease-specific health status and perceived disability. The effects of negative affectivity on the patient-centred outcomes were moderate to large, as indicated by

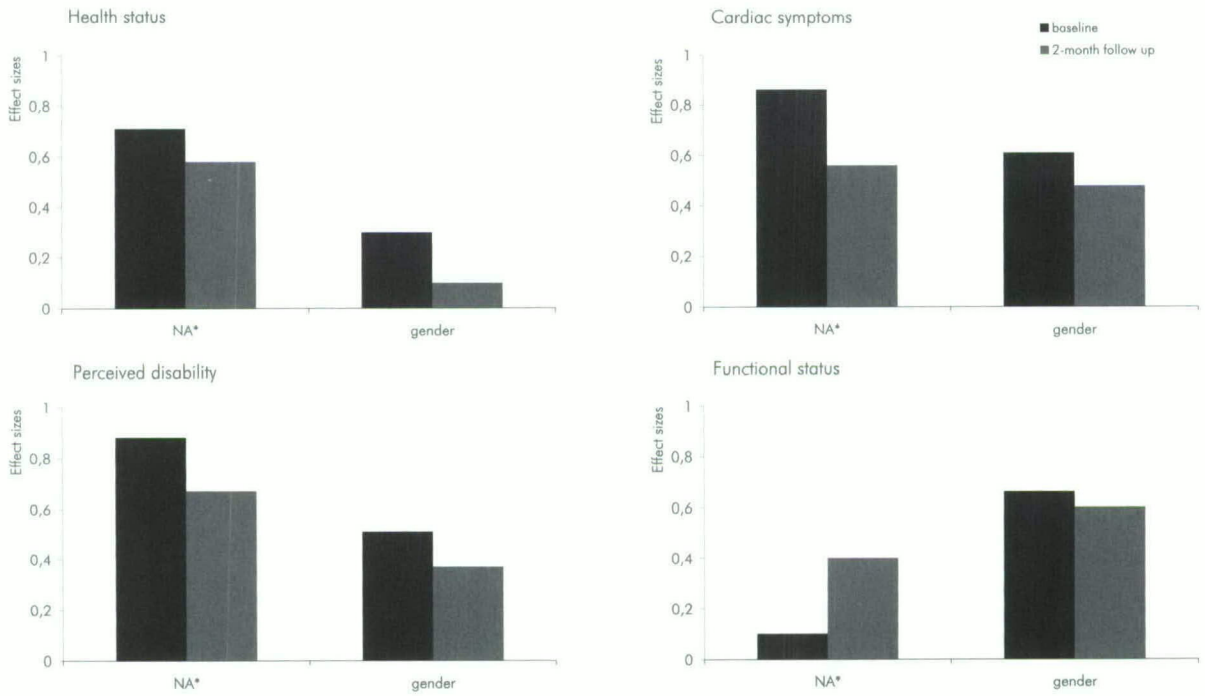

Figure 3. Effect sizes for negative affectivity and gender on patient-centred outcomes and functional capacity

**Negative affectivity*

Cohen's effect size index [40]. Type-D personality (concurrent high negative affectivity and social inhibition) and social inhibition were not associated with the patient-centred outcomes or functional capacity.

CRT is a promising treatment option for patients with advanced CHF, as it has been shown in prospective clinical trials to reduce mortality and morbidity, and to improve quality of life and functional status [1-7,42-45]. However, not all patients experience improvement following CRT [44]. In this context, it is important to identify which clinical parameters predict poor treatment response [45,46], but it might be of equal importance to gain knowledge about those patients that still report cardiac symptoms and perceived disability following CRT. Furthermore, it has been shown in previous research in patients with an implantable cardioverter defibrillator that psychological variables are at least as important as disease-characteristics in predicting quality of life [47].

Some authors stress that soft endpoints (such as measures of complaints and 6MWT performance) are less appropriate for measuring effects of CRT [44], whereas others emphasise that there is an urgent need to focus on patient-centred outcomes in cardiovascular research, such as health status and symptoms [11]. Negative affectivity is a stable personality trait that is defined as the tendency to experience a broad range of negative feelings even in the absence of overt stress. High negative affectivity persons focus on the negative side of others and the world, and have a negative self-view [18]. Research has shown that persons high on negative affectivity report more symptoms, although the relationship between negative affectivity and actual morbidity or mortality is not clear [17,48,49]. As Kroenke points out, subjective symptoms may guide diagnosing and treatment in medical settings [50]. Therefore, the subgroup of high negative affectivity post-CRT patients, who report more impaired disease-specific health status and more health complaints as compared to low negative affectivity patients, may incorrectly be labelled as "non-responder" or "having no benefit from CRT". However, these patients do improve on outcome following CRT, although they do not reach the same level as low negative affectivity patients, as they report more health complaints. Furthermore, there were no differences between high and low negative affectivity patients on functional capacity, whereas high negative affectivity patients do perceive more disability as compared to low negative affectivity patients. Therefore, it may be that persons high on negative affectivity are sensitive for the encouraging statements that the investigator is allowed to give during 6MWT performance, but in general feel more disabled. An alternative may be that these patients report more impaired disease-specific health status, more symptoms, and feel more disabled both before

and after CRT, but are not different from low negative affectivity patients on more objective measures, such as 6MWT performance. In a recent study in patients with atrial fibrillation (AF) was shown that negative emotions influenced patients' AF symptoms report more than objective indicators of AF [51]. Taken together, it is possible that high negative affectivity patients report more health complaints, although they do not differ on clinical measures of disease severity. Further research is warranted to explore this.

In previous research, type-D personality has been shown to predict negative outcome [e.g. 12-15,20-22,52,53]. In this study, no differences between type-D and non type-D patients on any of the outcome measures over a 2-month period was found. This may be due to the relatively small sample size, with only eight patients being identified as type-D, and the relatively short follow-up period of two months.

Limitations and strength

This study is exploratory and has several limitations. First, there was no control group and it is not possible to attribute the general improvements in disease-specific health status, cardiac symptoms, perceived disability, and functional capacity to CRT. Second, the sample size was small, which may be a reason for not finding an effect of negative affectivity on cardiac symptoms in adjusted analyses. Third, the follow-up period was relatively short. Fourth, we had only information on LVEF and NYHA class at baseline and were therefore not able to study the influence of personality traits on LVEF and other echo parameters over time. We were therefore also not able to assess whether CRT had resulted in changes in echo parameters. However, the focus of the study was on patient-centred outcomes.

Despite these limitations, this is the first study examining the effect of personality traits on patient-centred outcomes in patients treated with CRT. Furthermore, the study focuses on patient-centred outcomes and their determinants, which may help to close the gap between research and clinical practice [11].

Conclusions

In conclusion, we found general improvements in disease-specific health status, cardiac symptoms, perceived disability and functional capacity over a 2-month period in patients treated with CRT. However, patients high on negative affectivity reported lower disease-specific health status, and more cardiac symptoms and perceived disability as compared to patients low on negative affectivity. Large-scale studies with a longer follow-up period are needed to further explore the relationship between personality traits and outcomes in patients treated with CRT.

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CHAPTER 6

Type-D personality but not depression predicts severity of anxiety in heart failure patients at 1-year follow-up

Angélique A. Schiffer[ab], Susanne S. Pedersen[a], Herman Broers[b], Jos W. Widdershoven[b], Johan Denollet[a]

[a]CoRPS – Center of Research on Psychology in Somatic diseases, Tilburg University, Tilburg, the Netherlands
[b]Department of Cardiology, TweeSteden Hospital, Tilburg, the Netherlands

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ABSTRACT

Aims

Chronic heart failure (CHF) is a debilitating condition associated with poor outcome, including increased anxiety. However, anxiety and its determinants have not yet been studied systematically in CHF. We examined whether type-D personality and depressive symptoms would predict clinically significant anxiety at 1-year follow-up.

Methods

Consecutive patients with systolic CHF ($n=149$; 79% men; mean age 66 ± 8.6) completed the Type-D Scale (DS14), the Beck Depression Inventory, and the Anxiety Sensitivity Index at baseline. A clinical interview (Hamilton Anxiety Rating Scale) was used to assess clinically significant anxiety at 1-year follow-up.

Results

At 12-month follow-up, 26% (9/35) of type-D patients had clinically significant anxiety versus only 6% (7/114) of the non type-Ds ($p=0.001$).

In univariable analyses, type-D personality (OR=5.3;$p=0.002$) and anxiety sensitivity (OR=4.5;$p=0.009$), but not depressive symptoms ($p=0.27$), predicted clinically significant anxiety. Type-D remained an independent predictor of anxiety at 1-year (OR=5.7;$p=0.01$), controlling for depressive symptoms, anxiety sensitivity, socio-demographic and clinical variables. Adding type-D in a hierarchical logistic regression model, comprising standard and psychological risk factors, enhanced the level of prediction of clinically significant anxiety substantially (-2LL=75.16 $X^2=26.46$;$p=0.009$).

Conclusion

Type-D personality, but not depressive symptoms, predicted

1-year clinically significant anxiety. The Type-D Scale could be used to identify CHF patients at high risk of anxiety, as these patients may be at increased risk of adverse prognosis and impaired quality of life.

INTRODUCTION

Chronic heart failure (CHF) is a major health problem, with the incidence and prevalence of this potentially fatal disorder increasing tantamount to an epidemic [1,2]. Despite an impressive development of various treatment options, CHF is still associated with poor prognosis and functional capacity, frequent (re)hospitalisation, and escalating health costs [1,3,4]. Importantly, CHF is also associated with increased psychological distress [5,6], and there is an urgent need to focus on this patient-centred outcome and its determinants in CHF [7].

Depression has received the most attention in CHF, with only few studies focusing on anxiety [8,9]. However, there is evidence to suggest that 8-16% of CHF patients suffer from clinically significant anxiety, such as generalised anxiety disorder or panic disorder [10,11]. Moreover, anxiety in heart patients is frequently under-recognised in clinical practice [12]. Although anxiety has been linked in some (although not all) studies to prognosis, morbidity, and functional status in CHF [13-16], few studies have investigated the determinants of anxiety, and all of these have been cross-sectional [10,17,18]. In these cross-sectional studies, higher New York Heart Association (NYHA) functional class [10,18], co morbid physical conditions [10], and lower perceived control [17] were associated with increased levels of anxiety.

The distressed (type-D) personality may be another important, but over-looked, determinant of anxiety in CHF patients. Type-D patients have elevated scores on two normal and stable personality traits, namely negative affectivity (tendency to experience negative emotions) and social inhibition (tendency to inhibit self-expression in social interaction) [19] (Table 1). Type-D personality has been associated with several negative outcomes in patients with cardiac disease, such as worse prognosis and impaired quality of life [e.g. 20-22]. Type-D personality is also independently associated with an increased risk of depressive symptoms and anxiety in patients with an impaired pumpfunction, in patients with an implantable cardioverter defibrillator (ICD), and in coronary patients [e.g. 6,23-25].

Increasing our knowledge of the prevalence and determinants of anxiety may enhance secondary prevention and further improve management of CHF [9,10]. However, to date no prospective study has directly examined the relationship between type-D personality and anxiety in CHF patients. Hence, the objective of this 1-year follow-up study was to examine whether type–D personality would predict clinically significant anxiety in CHF patients.

Table 1. Definition, symptoms and assessment of negative affectivity (NA) and social inhibition (SI)

	NA	SI
Definition	*tendency to experience negative emotions across time and situations*	*tendency to inhibit negative emotions in social contact, because of fear of disapproval*
Symptoms (examples)	*frequent worrying, scanning the world for danger, low self-esteem*	*inhibited, insecure when with others*
Assessment	*NA subscale of the DS14**	*SI subscale of the DS14*
Items (examples)	*"I often make a fuss about unimportant things" "I often feel unhappy"*	*"I am a closed kind of person" "I find it hard to start a conversation"*
Type-D	*Persons who score ≥10 on the NA and the SI subscale of the DS14.*	

**Type-D Scale*

METHODS

Study population and procedure

Consecutive CHF outpatients visiting the cardiology clinic of the TweeSteden teaching hospital in Tilburg, the Netherlands, were approached for inclusion in the current study. CHF patients with a left ventricular ejection fraction (LVEF) ≤40% and pharmacologically stable one month preceding inclusion were asked to participate in this study. Patients older than 80 years, with diastolic heart failure, incapable of understanding and reading Dutch, or with cognitive impairments or life-threatening co-morbidities were excluded. The patients were treated following the most recent guidelines for the treatment of CHF [26], and were informed about the study by a cardiologist or a specialised heart failure nurse. If patients agreed to participate, they were called the same week to set up a first appointment to complete a set of psychological questionnaires. All patients provided written informed consent and participation was voluntary. The hospital's medical ethics committee approved the study protocol, and the study was carried out according to the Helsinki Declaration.

During the first visit, patients were given a booklet with a series of self-report questionnaires asking about psychological and socio-demographic

information. Patients were asked to fill out the questionnaires at home and return them in a self-addressed envelope. At 1-year follow-up, patients were interviewed about their anxiety levels in the past week, and again received a set of questionnaires to complete at home. All questionnaires were checked for completeness. Patients who had left open several questions were called to obtain the answers or they were mailed a copy of the items and asked to complete them. In case the questionnaires were not returned within two weeks, patients received a reminder telephone call.

In total we asked 231 patients for participation in this study. The response rate was 82%, as 190 patients agreed to participate. However, because patients died and left the study during follow-up, final analyses are based on 149 patients (Figure 1).

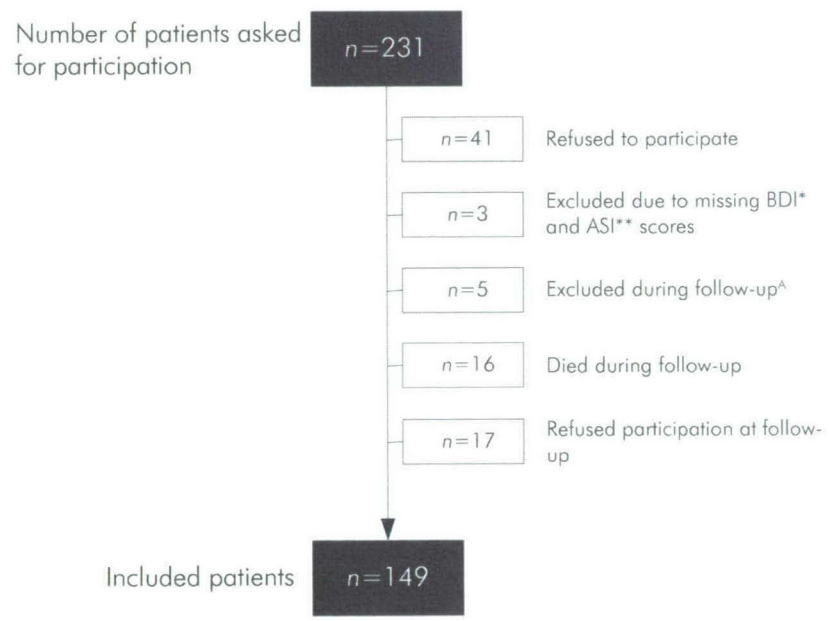

Figure 1. Flow chart of patient selection

^AThese patients were excluded due to medical (e.g. cerebrovascular accident during the study) or practical reasons (e.g. moving abroad).
**Beck Depression Inventory*
***Anxiety Sensitivity Index*

Type-D personality

The Type-D Scale (DS14), consisting of two seven-item subscales, i.e., negative affectivity and social inhibition, was used to assess type-D personality [19]. The 14 items are answered on a 5-point Likert scale from "false" (0) to "true" (4). Patients are defined as type-D when scoring ≥10 on both subscales. The DS14 has good internal consistency with Cronbach's α=.88/.86 for the negative affectivity and the social inhibition subscale, respectively. The DS14 measures two temporally stable personality traits, indicated by good test-retest reliability (r=.72 for the negative affectivity subscale and r=.82 for the social inhibition subscale). Furthermore, the two subscales are independent from changes in mood [19]. Finally, the construct validity of negative affectivity and social inhibition against neuroticism and extraversion, two important personality traits, has been confirmed [19]. The DS14 was administered at baseline.

Potentially confounding variables

We also assessed depressive symptoms and anxiety sensitivity at baseline to control for any confounding effects of these psychological variables on clinically significant anxiety. The Beck Depression Inventory (BDI) was used to measure depressive symptoms [27]. This 21-item questionnaire is a commonly used self-report measure of depressive symptoms in clinical research. There are four response options for each item, ranging from 0-3. The scale has good internal consistency with Cronbach's α=.81 in non-psychiatric samples [5]. Using a cut-off ≥10, the BDI has sensitivity and average specificity against a clinical diagnosis of depression [28].

Anxiety sensitivity may also be associated with anxiety in chronic conditions [29]. Anxiety sensitivity refers to the extent to which a person experiences anxiety-related sensations as fearful or to have a catastrophic outcome [30-32]. The 16-item Anxiety Sensitivity Index (ASI) was used to measure anxiety sensitivity [30,32]. The 16 items are answered on a 5-point Likert scale from "very little" (0) to "very much" (4) [30,32]. The internal consistency of the ASI is acceptable with Cronbach's α ranging from .80-.90 [30].

Clinically significant anxiety at follow-up

The severity of anxiety symptoms was rated by a clinical interview, namely the Hamilton Anxiety Rating Scale (HARS), a standardised psychiatric interview that is widely used in research and in clinical trials for the evaluation of anxiety [33,34]. This 14-item interview rating scale assesses and quantifies severity of anxiety along two symptom dimensions, i.e. psychic anxiety and somatic anxiety [35]. Each item is rated

on a 5-point scale by a clinical psychologist [33]. The interrater reliabilities of the HARS are 0.74, 0.73 and 0.70 for the total, psychic, and somatic subscales, respectively [35]. A cut-off ≥17 on the HARS indicates mild to severe anxiety, that is clinically significant anxiety [33]. The interview was conducted at 1-year follow-up.

Demographic and clinical characteristics.

Socio-demographic information was obtained from separate questions in the questionnaire and comprised sex, age, marital status, and educational level. Smoking status (yes/no) was also assessed by means of self-report. Information on LVEF, NYHA class, aetiology of CHF, risk factors, co morbidities and medication was obtained from the patients' records or treating cardiologist.

Statistical analyses

Discrete variables were compared with the chi-square test, whereas Student's *t* test for independent samples was used to compare continuous variables. Logistic regression analyses were performed to assess the impact of type-D personality, depressive symptoms, anxiety sensitivity, and clinical and demographic variables on clinically significant anxiety at 1-year follow-up. Prior to logistic regression analyses, NYHA class, aetiology of CHF, marital status, and educational level were recoded into dichotomous variables. Furthermore, BDI-scores and ASI-scores were also used as dichotomous variables, using the pre-determined cut-off of 10 for the BDI [5,36], and the highest tertile for the ASI. Finally, HARS scores were dichotomised using a cut-off ≥17, indicating mild to severe anxiety [33,35]. Dichotomisation was used in order to enhance clinical interpretability [37,38]. In secondary analysis, multivariable linear regression analysis with continuous variables was performed. Finally, a hierarchical logistic regression model was used to identify the model that best predicted outcome. All analyses were performed using *SPSS 12.0.1* for Windows.

RESULTS

Patient characteristics

At baseline, 35 patients (23.5%) were classified as type-D and 47 patients (31.5%) as having probable depression (BDI≥10). There were no significant differences (all *ps*>0.05) between type-D and non type-D patients on baseline characteristics, including medication (Table 2). The mean score was 8.6±6.2 (range 0-34) for self-reported depression and 12.1 ± 9.7 (range 0-47) for anxiety sensitivity.

Table 2. Baseline characteristics stratified by type-D personality

	Total sample	Type-D (n=35)	Non type-D (n=114)	p
Demographics				
Age, mean (SD)	66 (8.6)	68 (8.1)	66 (8.8)	0.22
Male sex, n (%)	118 (79)	29 (83)	89 (78)	0.54
Primary school, n (%)	54 (36)	16 (46)	38 (33)	0.18
Living with a partner, n (%)	113 (76)	27 (77)	86 (75)	0.84
Clinical variables				
LVEF[1] %, mean (SD)	30 (7)	29 (7)	30 (7)	0.32
NYHA[2] class III and IV, n (%)	72 (48)	22 (63)	50 (44)	0.05
Ischemic aetiology, n (%)	81 (54)	18 (51)	63 (55)	0.69
Smoking	36 (24)	6 (17)	30 (26)	0.27
Co morbidities				
Precious cardiac history[3], n (%)	85 (57)	19 (54)	66 (58)	0.71
Diabetes, n (%)	36 (24)	9 (26)	27 (24)	0.81
Renal insufficiency, n (%)	18 (12)	5 (14)	13 (11)	0.65
Hypertension, n (%)	49 (33)	11 (31)	38 (33)	0.83
Hyperlipidemia, n (%)	80 (54)	20 (57)	60 (53	0.64
Medication				
ACE-inhibitors, n (%)	118 (79)	27 (77)	91 (80)	0.73
All-antagonists, n (%)	22 (15)	5 (14)	17 (15)	0.93
Diuretics, n (%)	119 (80)	32 (91)	87 (76)	0.05
Spironolactone, n (%)	36 (24)	6 (17)	30 (26)	0.27
Digitalis, n (%)	49 (33)	13 (37)	36 (31)	0.54
Beta-blockers, n (%)	98 (66)	24 (69)	74 (65)	0.69
Long-acting nitrates, n (%)	32 (22)	9 (26)	23 (20)	0.49
Aspirin, n (%)	67 (45)	17 (49)	50 (44)	0.62
Statins, n (%)	71 (48)	18 (51)	53 (47)	0.61
Psychopharmaca, n (%)	21 (14)	7 (20)	14 (12)	0.25

[1]*LVEF=Left ventricular ejection fraction*
[2]*NYHA=New York Heart Association functional class*
[3]*Previous cardiac history=myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention*

Prevalence of mild to severe anxiety

The prevalence of clinically significant anxiety at 1-year follow-up in this sample was 11%. A significantly greater proportion of type-D patients displayed clinically

significant levels of anxiety (i.e., HARS rating ≥17) at 1-year follow-up ($X^2=10.7$; $p=0.001$) compared with non type-Ds. Of type-D patients, 26% (9/35) had clinically significant anxiety versus only 6% (7/114) of the non type-Ds. One-year anxiety levels, stratified by type-D personality and depressive symptomatology, are displayed in Figure 2.

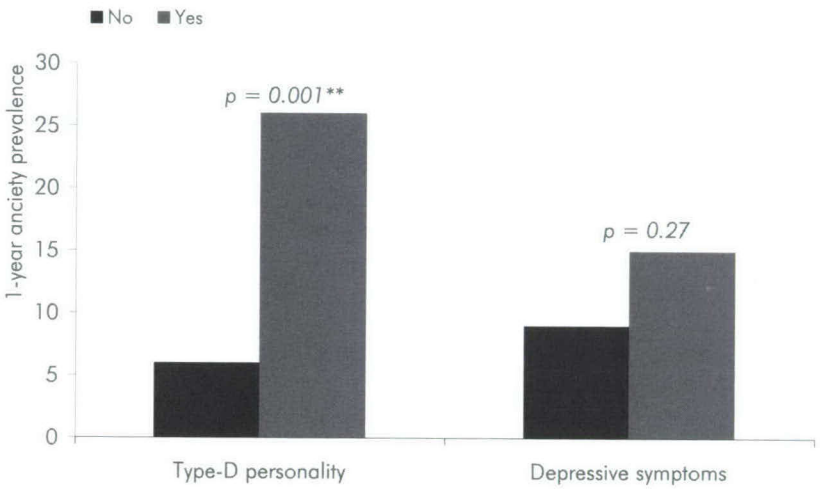

Figure 2. Clinically significant anxiety at 1-year follow-up, stratified by type-D personality and self-reported depressive symptoms at baseline

***p<0.01*

Univariable predictors of anxiety at one year

In logistic regression analyses, hypertension was the only clinical baseline characteristic that was associated with severity of anxiety at 1-year follow-up (OR=3.0;$p=0.04$). None of the other socio-demographic or clinical variables were associated with clinically significant anxiety at follow-up (Table 3). Type-D personality and anxiety sensitivity were significant predictors of clinically significant anxiety, with type-D patients having a more than 5-fold risk (OR=5.3) and patients with increased anxiety sensitivity a more than 4-fold risk (OR=4.5) of being anxious at follow-up (Table 3). In contrast, depressive symptoms were not associated ($p=0.27$) with clinically significant anxiety at 1-year follow-up.

Table 3. Univariable predictors of clinically significant anxiety at 1-year follow-up

	Odds ratio	95%CI	p
Type-D personality	**5.3**	**1.80 – 15.53**	**0.002****
Depressive symptoms	1.8	0.63 – 5.19	0.27
Anxiety sensitivity	**4.5**	**1.46 – 13.60**	**0.009****
Age	1.0	0.96 – 1.09	0.47
Male sex	1.8	0.60 – 5.85	0.28
Low educational level	0.5	0.19 – 1.50	0.23
Living with a partner	0.4	0.09 – 1.93	0.26
LVEF[A]	1.1	0.96 – 1.13	0.29
NYHA[B] classification	0.6	0.21 – 1.77	0.36
Ischemic aetiology	1.6	0.57 – 4.59	0.37
Smoking	1.1	0.32 – 3.49	0.93
Previous cardiac history	1.8	0.58 – 5.33	0.32
Diabetes	0.7	0.19 – 2.61	0.59
Renal insufficiency	1.1	0.28 – 5.01	0.96
Hypertension	**3.0**	**1.04 – 8.59**	**0.04***
Hyperlipidemia	2.0	0.67 – 6.20	0.21

[A]*Left ventricular ejection fraction*
[B]*New York Heart Association functional class*
Significant odds ratios are presented in bold face
*$p<0.05$
**$p<0.01$

Multivariable predictors of anxiety at one year

In multivariable logistic regression analysis, type-D personality was an independent predictor of clinically significant anxiety at 1-year follow-up (OR=5.7;p=0.01), adjusting for LVEF, NYHA class, aetiology of CHF, smoking, hypertension, age, sex, educational level, marital status, depressive symptoms, and anxiety sensitivity (Table 4). None of the other variables was associated with clinically significant anxiety, including depressive symptoms and anxiety sensitivity, although there was a trend for living with a partner (p=0.08) to reduce anxiety and for hypertension (p=0.09) to enhance it (Table 4). When performing multivariable linear regression analysis with continuous variables, we also found type-D to be the only significant determinant of clinically significant anxiety at 1-year follow-up (β=.35, p<.001).

Table 4. Multivariable predictors of clinically significant anxiety at 1-year follow-up

	Odds ratio	95%CI	p
Type-D personality	*5.7*	*1.45 – 22.73*	*0.01**
Depressive symptoms	*1.1*	*0.24 – 4.91*	*0.92*
Anxiety sensitivity	*2.9*	*0.72 – 12.02*	*0.13*
Age	*1.1*	*0.96 – 1.14*	*0.30*
Male sex	*2.4*	*0.52 – 10.71*	*0.27*
Low educational level	*0.6*	*0.17 – 2.14*	*0.44*
Living with a partner	*0.2*	*0.03 – 1.26*	*0.08*
LVEF[A]	*1.1*	*0.97 – 1.20*	*0.18*
NYHA[B] classification	*0.5*	*0.13 – 2.06*	*0.36*
Ischemic aetiology	*1.8*	*0.50 – 6.27*	*0.38*
Smoking	*1.6*	*0.36 – 7.07*	*0.54*
Hypertension	*3.1*	*0.85 – 11.49*	*0.09*

[A]Left ventricular ejection fraction
[B]New York Heart Association functional class
Significant odds ratios are presented in bold face
**p<0.05*

In order to examine whether the addition of psychosocial variables increased the level of prediction of anxiety severity at 1-year above and beyond demographic and clinical factors, we conducted a hierarchical logistic regression analysis, entering socio-demographic and clinical variables in the first step (-2LL=89.40 X^2=12.22;p=0.20). In the second step, we added depressive symptoms, but this addition did not enhance the predictive level of the model (-2LL=87.69 X^2=13.93;p=0.18), whereas the addition of anxiety sensitivity in the third step significantly improved the prediction of anxiety (-2LL=81.84 X^2=19.78;p=0.048). In the final step, the addition of type-D personality enhanced the level of prediction of anxiety severity at 1-year substantially (-2LL=75.16 X^2=26.46;p=0.009).

DISCUSSION

This is the first study examining the relative impact of type-D personality, depressive symptoms, and anxiety sensitivity on severity of anxiety at 1-year follow-up in patients with CHF. We found that type-D personality incurred an almost 6-fold increased risk

of clinically significant anxiety at 1-year follow-up, adjusting for depressive symptoms, anxiety sensitivity, and socio-demographic and clinical baseline characteristics, including LVEF, NYHA class and aetiology of CHF. Only type-D personality and anxiety sensitivity, but not depressive symptoms, added to the level of prediction of clinically significant anxiety at 1-year follow-up compared with socio-demographic and clinical baseline characteristics. Previous studies in ICD patients and coronary patients (with a reduced pump function) also found a relationship between type-D personality and anxiety [21,23-25].

Type-D personality is defined as having a high score on the two stable personality traits negative affectivity and social inhibition. Inhibited individuals are more vulnerable for developing anxiety [39], and given that negative affectivity already increases the risk of anxiety, the combined effect with inhibition may further exacerbate the anxiety-risk.

In CHF patients, severe anxiety has been related to reduced physical activity [40]. Furthermore, in other groups of heart patients, anxiety has been associated with impaired quality of life [41,42], more symptoms [12], and self-reported recurrent cardiac events [12]. With respect to the relationship between anxiety and mortality, mixed results have been found as some [21,43-45], but not all [13,14,41,42] studies have found a higher mortality risk in anxious heart patients. More research to clarify these inconsistent results is warranted, also in CHF patients.

According to Norman and Lang, anxiety sensitivity may be a contributor to anxiety in patients suffering from chronic disease [29]. However, in our study of chronically ill patients, anxiety sensitivity was a significant predictor of anxiety in univariable analysis, but not in multivariable analysis. It might be that type-D personality explained away the association between anxiety sensitivity and anxiety in this sample, and that anxiety sensitivity mediates the relationship between type-D and anxiety. Further research on this topic is needed.

Previous studies have shown that higher NYHA class is associated with increased levels of anxiety and a higher prevalence of anxiety disorders [10,18]. However, in the current study we did not find a relationship between any of the clinical variables and severity of anxiety at 1-year follow-up in multivariable analysis. These differences in results may be attributed to differences in study design, with previous studies being cross-sectional, whereas we used a prospective design. In addition, the above-mentioned studies did not take into account the influence of personality, although type-D personality has in several previous studies been associated with worse outcome [e.g. 6,20-23].

This study has a number of limitations. First, some of the anxiety symptoms may overlap with traditional symptoms of CHF, such as shortness of breath. However, the assessment of anxiety levels was done by experienced health psychologists, trained by a heart failure nurse in distinguishing pure physical symptoms from anxiety-related complaints. Second, the patients in the current study were asked for participation by a cardiologist or heart failure nurse, which may have led to a selection bias. Third, depressive symptoms were assessed by means of self-report. However, the BDI has been shown to have good sensitivity and specificity compared with the golden standard of a clinical diagnosis of depression [28]. Fourth, anxiety assessment with the HARS was performed by more than one health psychologist and we only administered the interview once per patients; therefore, we have no information on interrater reliability, although previous research on the HARS has shown acceptable interrater reliability [35].

This study also has several strengths. First, the severity of anxiety was not measured by means of self-report, but with a standardised clinical interview. Furthermore, we used a prospective design to examine the relationship between baseline characteristics and psychosocial factors, and severity of anxiety. Third, the response rate in this study was high, with 82%. Finally, we were able to identify those patients who are at high risk of developing psychological distress, such as anxiety. This is in line with the advice of Krumholz and colleagues that there is an urgent need to focus on patient-centred outcomes in cardiovascular disease, including emotional distress and their determinants [7].

Recently, Zerhouni advocated that a personalised approach to medicine is needed, because every individual patient has his or her unique genetic endowment and behaviour [46]. Screening patients for type-D personality fits well into this personalised approach to medicine. Knowing which individuals are at risk for developing psychological distress provides a window of opportunity to intervene at an early stage, thereby preventing the development of psychopathology or emotional problems. More intense coaching on anxiety at an early stage of those patients identified with a type-D personality may be important, as anxiety in some studies has been associated with increased risk of mortality [21,43-45], impaired quality of life [41,42] and more health care consumption [45]. Therefore, in clinical practice, these high-risk patients should be offered psycho-education and some form of counselling.

It may be true that changing personality characteristics is very difficult, but this should not be the primary goal of counselling in the context of type-D. Targets of counselling could be improvement of self-management abilities [47], consolidation of the type-D patient's social network, and improving coping abilities. In a recent

study [47], heart failure patients with a type-D personality were shown to be at increased risk for displaying inadequate self-management behaviour, because they have the tendency not to consult medical services in case of relevant symptoms. Furthermore, type-D patients typically do not share their emotions with others [e.g. 19,20], but this is not to say that they do not feel a need to talk to others about negative emotions; they only avoid sharing their emotions due to fear of rejection and disapproval, which makes social inhibition different from introversion. A supportive, stimulating social network may therefore be of great importance to type-D patients. Finally, counselling should be directly focused on coping styles, as type-Ds cope with negative emotions by not sharing them with others. There is a need to evaluate this ineffective coping style with the patients.

In previous research, it has been shown that type-D patients benefit from behavioural interventions, although to a lesser degree than non type-Ds [20]. However, this does not imply that no efforts of counselling for type-D patients should be made. The reverse is true, in fact, since type-D patients are at high risk for experiencing emotional distress, such as anxiety and depression; hence, they may benefit more from counselling than non type-D patients although they are unlikely to reach the same symptom levels as non type-D patients.

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PART B

TYPE-D PERSONALITY AS A PREDICTOR OF PROGNOSIS IN CHRONIC HEART FAILURE AND MECHANISMS EXPLAINING THE ADVERSE EFFECTS ON HEALTH OUTCOMES

CHAPTER 7

Failure to consult for symptoms of heart failure in patients with a type-D personality

Angélique A. Schiffer[ab], Johan Denollet[a], Jos W. Widdershoven[b], Eric H. Hendriks[b], Otto R.F. Smith[a]

[a]CoRPS – Center of Research on Psychology in Somatic diseases, Tilburg University, Tilburg, the Netherlands
[b]Department of Cardiology, TweeSteden Hospital, Tilburg, the Netherlands

Heart 2007;93:814-818

ABSTRACT

Objective

Self-management and adequate consultation behaviour are essential for successful treatment of chronic heart failure (CHF). Patients with a type-D personality, characterised by high social inhibition and negative affectivity, may delay medical consultation despite elevated symptom levels, and may be at an increased risk for adverse clinical outcomes. We therefore examined whether type-D personality predicts poor self-management and failure to consult for evident cardiac symptoms in CHF.

Design/methods/patients

178 CHF outpatients (age≤80) completed the DS14 (Type-D Scale) at baseline, and the Health Complaints Scale (symptoms) and European Heart Failure Self-care Behaviour Scale (self-management) at 2-month follow-up. Medical information was obtained from the patients' medical records.

Results

At follow-up, type-D patients experienced more cardiac symptoms (OR=6.4;95% CI:2.5-16.3,$p<.001$) and more often appraised these symptoms as worrisome (OR=2.9;95%CI:1.3-6.6,$p<.01$) as compared to non type-D patients. Paradoxically, type-D patients were less likely to report these symptoms to their cardiologist/nurse, as indicated by an increased risk for inadequate consultation behaviour (OR=2.7;95%CI:1.2-6.0,$p<.05$), adjusting for demographics, CHF severity/aetiology, time since diagnosis and medication. Accordingly, of 61 CHF patients that failed to consult for evident cardiac symptoms, 43% were type-D (26 patients). Of the remaining CHF patients, only 14% (16 patients) had type-D personality.

Conclusion

In conclusion, CHF patients with a type-D personality display inadequate self-management. Failure to consult for symptom elevation may partially explain the adverse effect of type-D personality on cardiac prognosis.

INTRODUCTION

Because of the ageing population and increasing rate of chronic medical diseases, finding the best management for these conditions is an important goal in health care [1]. Chronic heart failure (CHF) is a serious chronic condition that has been associated with high mortality and hospitalisation rates, limited functional capacity, impaired health status and escalating health costs, despite recent developments in treatment options [2-5].

Poor self-management, or self-care, is associated with an increased risk of adverse clinical outcome in CHF [6]. Self-management is the individual's ability to manage the symptoms, treatment, and life style changes inherent in living with a chronic condition, such as CHF [7]; it is the process whereby individuals act on their own behalf to promote health [8]. One important aspect of self-management is consultation behaviour, i.e., consulting a physician when experiencing cardiac symptoms [9].

Some patients with CHF may delay consulting medical services for relevant symptoms. This patient delay, which refers to the period between the onset of symptoms and the moment of consultation [10], may contribute to adverse clinical outcomes in CHF. The decision to seek help is influenced by the individual's appraisal of the seriousness of the symptoms [11,12]. However, symptom appraisal is a necessary, but not sufficient condition for seeking help. Consultation behaviour is also influenced by attitudes to help seeking behaviour [13], such as concerns about the consequences of disclosing personal feelings and thoughts. For example, myocardial infarction patients who did not talk with someone about their symptoms had longer delays in help seeking [14]. Hence, patients with CHF who are inhibited in disclosing symptoms to their cardiologist or heart failure nurse may also be more likely to delay medical consultation.

Type-D patients tend to inhibit self-expression in social interactions, as indicated by a high score on social inhibition [15,16]. Given their high level of inhibition, type-Ds may be at risk for inadequate self-management in terms of poor consultation behaviour. This failure to consult for cardiac symptoms is paradoxical because, given their tendency to experience negative feelings and to worry [15,16], type-Ds may experience concerns about their health status. Hence, the objective of this predictive study was to examine the role of type-D personality in poor self-management and failure to consult for clinically evident symptoms in patients with CHF.

METHODS

Study population and procedure

The sample included 178 consecutive outpatients with CHF from the TweeSteden teaching hospital in Tilburg, the Netherlands. Inclusion criteria were: (1) systolic heart failure, (2) left ventricular ejection fraction (LVEF) ≤40%, and (3) pharmacologically stable one month preceding inclusion. Patients (1) older than 80 years, (2) with a history of diastolic heart failure, (3) incapable of understanding and reading Dutch, (4) with cognitive impairments and life-threatening co-morbidities, or (5) diagnosed psychiatric disease (except depression and anxiety) were excluded. Patients were treated for CHF by a cardiologist and a specialised heart failure nurse according to the most recent guidelines [3]. The hospital's medical ethics committee approved the study protocol, and the study was carried out according to the Helsinki Declaration. All patients provided written informed consent.

The cardiologist or specialised heart failure nurse selected CHF patients for inclusion in the study on the basis of the above-mentioned criteria. Patients were informed about the study and asked to participate by their treating cardiologist. If patients agreed to participate, they were called the same week to make an appointment for completing a set of psychological questionnaires. Participation was voluntary. During the first visit, patients completed the Type-D Scale (DS14) [16]. During a second visit, two months later, the patients filled out the Health Complaints Scale (HCS;symptoms) [17], and the European Heart Failure Self-care Behaviour Scale (EHFScBS;self-management) [18]. Patients who did not return the questionnaires within two weeks received a reminder telephone call. The response rate in the present study was 94%.

Self-management and consultation behaviour

The EHFScBS is a disease-specific measure of CHF patients' self-management behaviour [18]. The questionnaire consists of 12 items that are answered on a 5-point Likert scale ranging from "I completely agree" (1) to "I don't agree at all" (5). A high total score indicates less self-care behaviour. Cronbach's alpha for the total scale is .81 [18].

Principal component analysis (PCA) with varimax rotation was used to determine the structure of the EHFScBS at 2-month follow-up. Factors with an eigenvalue >1 were retained according to Kaiser-Meyer-Olkin criterion (KMO).
KMO and Bartlett's test of sphericity were used as fit indices. PCA at 2-month follow-up revealed a 4-factor solution (Table 1). KMO (0.75) and Bartlett's test of sphericity

Table 1. Facets of self-management at 2-month follow-up

		Rotated Factor Solution			
	Items of the EHFScBS[A]	*Factor 1*	*Factor 2*	*Factor 3*	*Factor 4*
4.	*If my feet/legs become more swollen than usual, I contact my doctor or nurse.*	**0.87**	0.04	0.09	0.04
3.	*If my shortness of breath increases, I contact my doctor or nurse.*	**0.85**	0.07	-0.03	-0.01
8.	*If I experience increased fatigue, I contact my doctor or nurse.*	**0.84**	0.26	0.07	0.01
5.	*If I gain 2 kg in 1 week, I contact my doctor or nurse.*	**0.73**	0.15	0.19	-0.03
12.	*I exercise regularly.*	0.07	**0.70**	-0.28	-0.01
9.	*I eat a low salt diet.*	0.15	**0.63**	0.21	0.10
6.	*I limit the amount of fluids I drink (not more than 1.5-2 l/day).*	0.30	**0.52**	0.22	0.07
2.	*If I get short of breath, I take it easy.*	0.19	-0.11	**0.77**	-0.13
7.	*I take rest during the day.*	0.01	0.28	**0.64**	0.18
10.	*I take my medication as prescribed.*	0.11	0.02	0.30	**0.66**
11.	*I get a flu shot every year.*	-0.05	0.27	-0.09	**0.65**
1[B].	*I weigh myself every day.*	0.05	0.42	0.23	-0.56

[A]*The European Heart Failure Self-care Behaviour Scale*
[B]*Item 1 could not be assigned to any of the factors because of ambiguous factor loadings*
Factor loadings are presented in bold face

($X^2(66, n=178)=483.5$, $p<.001$) indicated that PCA was adequate for this data. Only one specific facet of self-management was found, i.e., consultation behaviour (e.g. "If my feet/legs become more swollen than usual, I contact my doctor or nurse"). Cronbach's alpha for this factor was .86, and .46, .37, .28 for the three other factors, respectively (Table 1). Therefore, we constructed a 4-item "consultation behaviour" subscale as a specific component of self-management that should be studied in its own right, in addition to the EHFScBS total scale (Table 1, factor 1; items 3,4,5,8). The mean score of the consultation behaviour subscale was 9.8 (SD=4.9), and the scores were normally distributed. A relative lack of consultation behaviour was defined as a score above median split of this 4-item subscale.

Type-D personality

The DS14 was used to assess type-D personality [16]. The DS14 consists of two 7-item subscales, i.e., negative affectivity and social inhibition [16]. The 14 items are answered on a 5-point Likert scale ranging from "false" (0) to "true" (4). A standardised cut-off of ≥10 on both subscales indicates those with a type-D personality. Both subscales are internally consistent, with a Cronbach's alpha of .88 for the negative affectivity subscale and of .86 for the social inhibition subscale, and have good test-retest reliability with r=.72 and .82, respectively [16]. In the present study, 24% (42/178) of the patients were classified as type-D.

Cardiac symptoms

The HCS contains a 12 item self-report subscale of cardiac symptoms that are frequently experienced by patients with established heart disease [17]. These include cardiopulmonary symptoms (5 items; e.g. "shortness of breath"), fatigue (4 items; e.g. "feelings of exhaustion"), and sleep problems (3 items; e.g. "disturbed sleep"). The HCS contains also a 6-item subscale representing health worry (e.g. "worrying about health", "the idea that you have a serious illness"). Patients indicate how much they suffer from a particular symptom on a 4-point Likert scale ranging from "not at all" (0) to "extremely"(4). All scales have a high internal consistency with Cronbach's alpha ≥.89 and test-retest reliability r≥.69 [17].

Clinical variables

Clinical variables included LVEF, New York Heart Association (NYHA) functional class, aetiology of CHF, medication, and time since diagnosis of CHF. Information on clinical variables was obtained from the patients' medical records and from the

treating cardiologist. Socio-demographic information included sex, age, marital status, and educational level.

Statistical Analyses

Prior to statistical analyses, NYHA class, aetiology of heart failure, educational level and marital status were dichotomised according to: NYHA class III/IV versus NYHA class I/II, ischemic versus non-ischemic aetiology, low versus high educational level, and partner versus no partner, respectively. The EHFScBS, the consultation behaviour subscale, and the HCS were recoded into dichotomous variables using a median split, reflecting respectively good versus poor self-management, good versus poor consultation behaviour, and cardiac versus no cardiac complaints. For comparison between two groups, we used the chi-square test for discrete variables and the *t* test for independent samples for continuous variables.

Logistic regression analyses were used to determine whether type-D was an independent predictor of respectively cardiac symptoms, health worry, self-management, and consultation behaviour, adjusting for gender, age, marital status, educational level, LVEF, NYHA class, aetiology of CHF, medication, and time since diagnosis.

RESULTS

Demographic statistics

Patient characteristics stratified by type-D personality are presented in Table 2. There were significant differences between type-D and non type-D patients only with respect to medication, i.e., diuretics ($X^2(1, n=178)=5.8$, $p<.05$) and calcium antagonists ($X^2(1, n=178)= 3.2$, $p<.01$) were more often prescribed to type-D patients.

Type-D and cardiac symptoms

Type-D personality was an independent predictor of cardiac symptoms at two months (OR=6.4;95%CI:2.5-16.3, $p<.001$), adjusting for socio-demographic variables, LVEF, NYHA class, ischemic aetiology, time since diagnosis, use of diuretics and use of calcium antagonists. Apart from type-D personality, younger age (OR=0.9;95% CI:0.9-1.0, $p<.01$), lower educational level (OR=3.0;95%CI:1.1-8.5, $p<.05$), and NYHA class III/IV (OR=2.2;95%CI:1.1-4.5, $p<.05$) also independently predicted cardiac symptoms at two months.

Table 2. Baseline characteristics stratified by type-D personality

	Total sample	*Type-D (n=42)*	*Non type-D (n=136)*	*p*
Age, mean (SD)	*66.6 (8.4)*	*68.2 (7.8)*	*66.1 (8.6)*	*.16*
Male sex, n (%)	*140 (79)*	*33 (79)*	*107 (79)*	*.98*
Lower educational level, n (%)	*154 (87)*	*39 (93)*	*115 (85)*	*.17*
Having no partner, n (%)	*43 (24)*	*12 (29)*	*31 (23)*	*.45*
LVEF[a] %, mean (SD)	*29.9 (6.7)*	*28.9 (6.6)*	*30.2 (6.7)*	*.32*
NYHA[b] class III and IV, n (%)	*96 (54)*	*28 (67)*	*68 (50)*	*.06*
Ischemic aetiology, n (%)	*100 (56)*	*24 (57)*	*76 (56)*	*.86*
Time since diagnosis, mean (SD)	*3.9 (4.1)*	*3.4 (4.1)*	*4.0 (4.1)*	*.34*
ACE-inhibitor users, n (%)	*142 (80)*	*33 (79)*	*109 (80)*	*.82*
All-antagonist users, n (%)	*30 (17)*	*8 (19)*	*22 (16)*	*.66*
Diuretic users, n (%)	*142 (80)*	*39 (93)*	*103 (76)*	*.02**
Digitalis users, n (%)	*56 (32)*	*15 (36)*	*41 (30)*	*.50*
Beta-blocker users, n (%)	*116 (65)*	*31 (74)*	*85 (63)*	*.18*
Long-acting nitrate users, n (%)	*44 (25)*	*14 (33)*	*30 (22)*	*.14*
Short-acting nitrate users, n (%)	*17 (10)*	*7 (17)*	*10 (7)*	*.07*
Calcium antagonist users, n (%)	*16 (9)*	*8 (19)*	*8 (6)*	*.01**
Anticoagulant users, n (%)	*77 (43)*	*17 (41)*	*60 (44)*	*.68*
Aspirin users, n (%)	*80 (45)*	*19 (45)*	*61 (45)*	*.97*
Statine users, n (%)	*84 (47)*	*20 (48)*	*64 (47)*	*.95*

[a]*LVEF=Left ventricular ejection fraction*
[b]*NYHA=New York Heart Association functional class*
**p<.05*

Type-D patients had a mean score of 17.2 (SD 9.7) on the cardiac symptoms scale of the HCS compared to 9.6 (SD 8.7) for non type-D patients ($p<.001$). Type-Ds scored also significantly higher on cardiopulmonary symptoms ($p=.002$), fatigue ($p<.001$), sleep problems ($p<.001$), and health worry ($p=.001$) as compared to non type-Ds. Finally, type-D personality was an independent predictor of health worry adjusting for all other variables at follow-up. Type-D patients were at a 3-fold increased risk to worry about their cardiac symptoms (OR=2.9;95%CI:1.3-6.6, $p<.01$) compared to non type-D patients.

Type-D, self-management, and consultation behaviour

When the total score of the EHFScBS was used as an outcome measure, socio-demographics, severity of CHF, and type-D personality were not significantly related to overall self-management at 2-month follow-up. Male sex (OR=2.0;95%CI:0.9-4.5, p=.07) and lower educational level (OR=2.4;95%CI:0.9-6.8, p=.07) had a near significant effect.

However, type-D was an independent predictor of displaying little consultation behaviour at follow-up when adjusting for all other variables, including LVEF and NYHA class (OR=2.7:95%CI:1.2-6.0, p<.05) (Table 3). In contrast to their high levels of cardiac symptoms and health worry, type-D patients were at a more than 2-fold increased risk of failing to consult for these symptoms compared with non type-D patients (Table 3). There was also a tendency for patients without partner to be low in consultation behaviour (p=.06).

Table 3. Predictors of displaying little consultation behaviour at 2-month follow-up (multivariable analysis)

	Odds ratio	*95%CI*	*p*
Male sex	*1.34*	*0.61 – 2.95*	*.47*
Age	*0.99*	*0.95 – 1.03*	*.60*
Having no partner	*2.10*	*0.96 – 4.59*	*.06*
Lower educational level	*2.05*	*0.81 – 5.20*	*.13*
NYHA[A] class III and IV	*0.74*	*0.39 – 1.44*	*.38*
LVEF[B]	*1.00*	*0.95 – 1.05*	*.85*
Ischemic aetiology	*0.91*	*0.47 – 1.77*	*.79*
Time since diagnosis	*1.08*	*0.99 – 1.17*	*.07*
Diuretics users	*0.80*	*0.36 – 1.76*	*.59*
Calcium antagonist users	*0.77*	*0.24 – 2.44*	*.66*
Type-D	*2.67*	*1.19 – 6.00*	*.02**

[A]*New York Heart Association functional class*
[B]*Left ventricular ejection fraction*
**p<.05*

Subgroups at risk for inadequate consulting

CHF patients, who experienced clinically evident cardiac symptoms but were less likely to consult for these symptoms, were considered to be at risk for inadequate consulting as a clear indicator of poor self-management. In post-hoc analysis,

patients who reported cardiac symptoms but displayed poor consultation behaviour were compared to all other patients. Multivariable logistic regression analysis revealed that type-D personality was an independent predictor of reporting cardiac symptoms while failing to consult (OR=5.1;95%CI:2.3-11.6,$p<.001$). Hence, of 61 CHF patients that failed to consult for evident cardiac symptoms, 43% were type-D (26 patients). Of the remaining CHF patients, only 14% (16 patients) had a type-D personality (Figure 1). Additionally, there was a significant effect for lower educational level (OR=4.2;95%CI:1.1-16.0,$p<.05$).

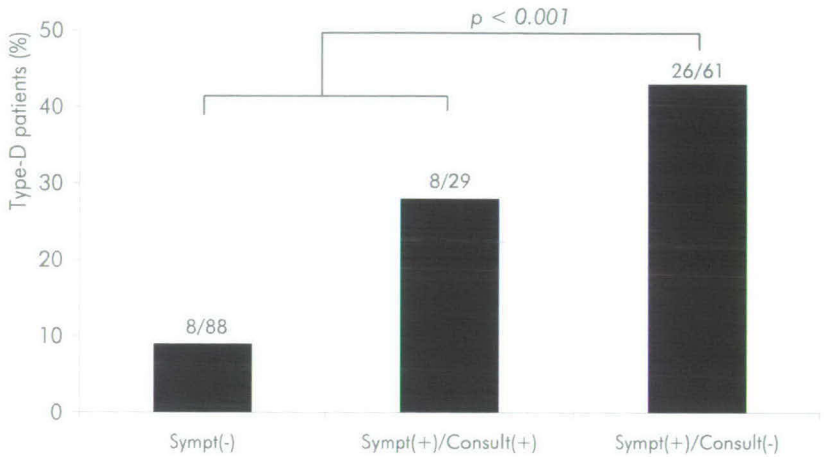

Figure 1. Percentage of CHF patients with a type-D personality, stratified by cardiac symptoms and consultation behaviour

Sympt(-): percentage of type-D patients without relevant cardiac symptoms.
Sympt(+)/Consult(+): percentage of type-D patients with relevant cardiac symptoms who succeed to consult.
Sympt(+)/Consult(-): percentage of type-D patients with relevant cardiac symptoms who fail to consult.

DISCUSSION

To our knowledge, this is the first prospective study to investigate the role of personality, and type-D personality in particular, as a determinant of self-

management behaviour in patients with CHF. The present findings indicated that type-D patients experienced more cardiac symptoms at follow-up as compared to non type-D patients. Type-Ds also reported high levels of health worry, indicating that they appraise these symptoms as serious. Paradoxically however, type-D patients were less likely to contact their doctor or nurse. Hence, type-D patients are at risk for failing to report their elevation of CHF symptoms to health care professionals, in spite of the fact that they appraise them as worrisome.

Previous studies have shown the adverse effect of type-D personality on prognosis in patients surviving myocardial infarction [15,19], in patients with decreased LVEF [20], and patients that were treated with percutaneous coronary intervention [21]. Although there is preliminary evidence that immune-activation [22] or dysfunctional stress-reactivity [23] may comprise links between type-D personality and cardiac events, the underlying mechanisms responsible for the association between type-D and cardiac prognosis are largely unknown. The results of the current study indicate another possible, behavioural, link between type-D personality and prognosis, namely inadequate consultation behaviour.

Type-D patients do not have psychopathology per se, but are characterised as being high on both social inhibition and negative affectivity [15,16]. Social inhibited individuals often report to be socially isolated or to lack a close confidant. Social isolation has been associated with adverse outcome in patients with heart disease, and this association cannot be explained by factors such as disease severity, demographic variables and distress [24,25]. Social inhibition may result in non-adherence to treatment. Dickens and colleagues found that coronary patients without a close confidant were more likely to have further cardiac events, and speculated that these patients may be less likely to seek treatment for heart disease, thereby increasing the risk of adverse clinical outcome [26]. One aspect of social inhibition is feeling insecure and less competent when communicating with others [15,16]. Those socially inhibited patients may fear rejection or a negative reaction from their doctor and may for this reason not go to see a doctor when it is necessary. Furthermore, as Pereira and colleagues stated, there may be a mediating role for passive coping strategies, such as denial, in the relationship between inhibition and poor adherence to treatment [27]. Therefore, type-D patients may have a somewhat more passive and avoidant coping style while dealing with upcoming problems.

Apart from inhibition, negative mood states are related to poor prognosis as well as unhealthy behaviours [28-32]. In a recent study by van der Wal and colleagues for instance, it was found that compliance in CHF was negatively related to depressive symptoms [32]. The results of our study indicate that type-D personality

is a risk factor for the delay to consult a doctor or nurse, despite clinically evident symptoms of CHF and associated high levels of health worry.

This study has a number of limitations. First, there may be a bias in the selection of patients. The cardiologist or heart failure nurse asked patients for participation in the study. So the interaction pattern may influence the selection. Second, the follow-up period is relatively short. It would be interesting to look at the impact of type-D personality on long-term self-management behaviour and to investigate whether self-management, and consultation behaviour in particular, comprises a mechanism linking type-D to adverse prognosis. Third, data on self-management were obtained by means of a self-report questionnaire, and self-report may be prone to socially desirable behaviour. However, as Jaarsma and colleagues indicate, the EHFScBS is a valid and reliable scale to measure the self-management behaviours of CHF patients [18]. Furthermore, strength of the current study is that it is the first to examine the role of personality in consultation behaviour, an aspect of self-management, in CHF patients in a prospective design.

In conclusion, the results of the current study show that CHF patients with a type-D personality are less likely to seek medical assistance in the case of elevated cardiac symptoms in contrast to non type-Ds. Paradoxically, type-Ds do experience more cardiac symptoms and worry more about these symptoms. Because of the still increasing health-care costs associated with chronic illness [33], it is important to identify determinants of high hospital and mortality rates in several patient groups. Improved self-management may help to reduce hospitalisation among patients with CHF [34]. Further research on the role of personality factors in self-management behaviour, health care utilisation and prognosis is warranted. Finally, as Jones mentions, self-management is an essential component of the management of chronic illness and the quality of self-care is important for the quality of life of patients [35]. This means that it is important to know which CHF patients need more intensive interventions, such as more education, to improve self-management abilities. The findings of the present study suggest that type-D patients may be in need of such a behavioural intervention program.

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CHAPTER 8

Type-D personality and chronic kidney disease as predictors of pro- and anti-inflammatory cytokine levels in heart failure

Johan Denollet[a], Angélique A. Schiffer[abc], Martijn Kwaijtaal[a], Herbert Hooijkaas[d], Eric H. Hendriks[b], Jos W. Widdershoven[b], Nina Kupper[a]

[a]CoRPS – Center of Research on Psychology in Somatic diseases, Tilburg University, Tilburg, the Netherlands
[b]Department of Cardiology, TweeSteden Hospital, Tilburg, the Netherlands
[c]Department of Medical Psychology, Twee Steden Hospital, Tilburg, the Netherlands
[d]Department of Immunology, Erasmus Medical Center, Rotterdam, the Netherlands

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ABSTRACT

Background

Interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and soluble TNF-α receptors 1 (sTNFR1) and 2 (sTNFR2) are powerful predictors of mortality in chronic heart failure (CHF). However, little is known about (i) the origins of pro-inflammatory cytokine production and (ii) the determinants of substantial interpatient variability in immune activation. We prospectively examined type-D personality (tendency to experience and inhibit emotional distress) and chronic kidney disease (CKD) as predictors of cytokine production in patients with CHF.

Methods

At baseline, 125 CHF patients were assessed for type-D personality. At 1-year follow-up, we measured serum levels of IL-6, TNF-α, sTNFR1, sTNFR2, and the anti-inflammatory cytokines interleukin-10 (IL-10) and interleukin-1 receptor antagonist (IL-1ra).

Results

At 1-year follow-up, type-D patients had significantly elevated levels of sTNFR1 ($p=0.009$) and sTNFR2 ($p=0.001$), and decreased levels of IL-10 ($p=0.006$) as compared to patients without type-D or CKD. Patients with CKD also had elevated levels of sTNFR1 and sTNFR2 ($p<0.0001$), but their level of IL-10 was not decreased. Type-D personality and CKD predicted increased sTNFR1/IL-10 and sTNFR2/IL-10 ratios (all $ps\leq0.007$); type-D also predicted an increased IL-6/IL-10 ratio ($p=0.013$). Spironolactone and older age were also associated with elevated pro-/anti-inflammatory cytokine ratios. Adjusting for these variables, the odds to have elevated ratios (highest 20%) was still increased in type-D patients (OR=3.92, 19.88 and 3.12, respectively).

Conclusion

Type-D personality and CKD independently predict unfavourable cytokine profiles, and play a role in the interpatient variability in immune activation among patients with CHF.

INTRODUCTION

Chronic heart failure (CHF) is a multi-system disorder that carries a high mortality risk and affects the renal, neuroendocrine and immune systems [1-4]. Tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are pro-inflammatory cytokines involved in CHF progression [3-8], and are major prognostic indicators of atherosclerosis [9], worsening of CHF [10,11], and CHF-related mortality [7,12]. Plasma levels of the soluble TNF-α receptors 1 (sTNFR1) and 2 (sTNFR2) reflect exposure to TNF-α over longer periods of time, and consistently have emerged as important predictors of mortality in patients with CHF [5-8]. Clinical implications of these findings may be enhanced by progress in understanding (i) the balance between pro- and anti-inflammatory cytokines, and (ii) the origins of cytokine production in CHF. Anti-inflammatory cytokines such as interleukin-10 (IL-10) and interleukin-1 receptor antagonist (IL-1ra) dampen the effect of TNF-α, IL-6 and other inflammatory responses in the cardiovascular system [13,14], but their role in CHF is not clear [3]. Little is also known about the determinants of substantial inter-patient variability in immune activation in CHF.

Patients with chronic kidney disease (CKD) are often excluded from cardiovascular research [15]. However, CKD is related to higher IL-6 and TNF-α levels [16-19] and poor clinical outcomes in CHF [20-23], and should therefore be considered in subgroup analyses of inflammation in CHF. Psychological factors may also contribute to poorer CHF outcomes [2,24] and inter-patient variability in inflammation [25], although their relationship with TNF-α and IL-6 levels is unclear [26-29]. Preliminary findings suggest that psychological distress may be related to high levels of TNF-α, sTNFR1 and sTNFR2 in CHF [30-33], and the few studies reporting on IL-10 suggest that psychological distress is also associated with IL-10 levels [32,34]. Given their cross-sectional study design and small sample sizes (ranging from 18 to 42 patients [30,32-34], mean $n=32$), the implications of these reports are uncertain.

A recent study showed that IL-6, TNF-α, sTNFR1/sTNFR2, IL-10 and IL-1ra were all related to increased risk of death and CHF following myocardial infarction [5]. We therefore prospectively examined whether type-D personality and CKD would predict serum levels of these pro- and anti-inflammatory cytokines at 1-year follow-up in patients with CHF, while adjusting for traditional prognostic markers.

METHODS

Study population and procedure

The sample comprised 165 consecutive CHF outpatients (75% male; mean age 65.7±8.9 years) from the TweeSteden teaching hospital in Tilburg, the Netherlands. Patients with a left ventricular ejection fraction (LVEF) ≤40%, ≤80 years, and pharmacologically stable one month preceding inclusion, were included in the study between October 2003 and January 2005. Patients with diastolic CHF, inadequate proficiency of the Dutch language, cognitive impairments, life-threatening co morbidities (such as cancer), clinical signs of acute infections, or use of anti-inflammatory medication were excluded. Of 206 patients, 165 (80%) agreed to participate. Final analyses are based on 125 patients (Figure 1), since patients were lost to follow-up, had missing blood data or constituted outliers, i.e., one sTNFR2 and two IL-6 outliers (defined as >3 standard deviations (SD) of the mean).

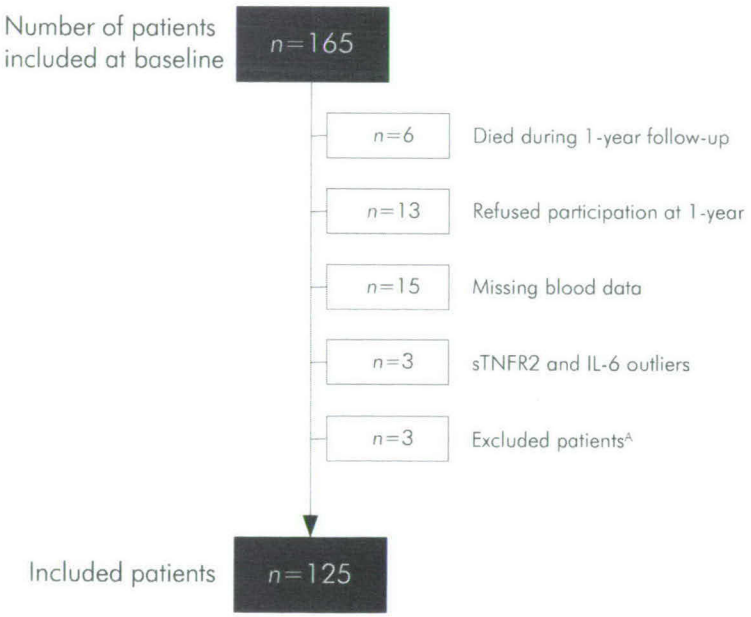

Figure 1. Flow chart of patients included in the study

[A]*These patients were excluded due to medical (e.g. cerebrovascular accident during the study) or logistic reasons (e.g. moving abroad)*

All patients were treated following the most recent guidelines for the treatment of CHF [35,36], and were informed about the study by a cardiologist or a specialised heart failure nurse. All patients provided written informed consent and participation was voluntary. The hospital's medical ethics committee approved the study protocol, and the study was carried out according to the Helsinki Declaration. The study design was prospective. Patients completed a psychological questionnaire assessing type-D and socio-demographic information at baseline. Blood samples were collected at baseline and one year. Patients were asked to complete the questionnaire at home and return it in a self-addressed envelope. All questionnaires were checked for completeness. Patients who had left open several questions were called to obtain the answers or they were mailed a copy of the items and asked to complete them after all. In case the questionnaires were not returned within two weeks, patients received a reminder telephone call or letter.

Assessment of type-D personality

All patients completed the Type-D Scale (DS14) at baseline [37]. This scale consists of 14 items that are divided into two subscales measuring negative affectivity (tendency to experience negative emotions) and social inhibition (tendency to inhibit self-expression in social interaction). The two subscales have good psychometric qualities, with Cronbach's α= .88/.86 and 3-month test-retest reliability r=.72/.82 for the negative affectivity and social inhibition subscale, respectively. According to previously published findings, a standardised cut-off $\geq$10 on both subscales indicates type-D caseness [37].

Diagnosis of CKD

According to the K/DOQI guidelines [38], the MDRD formula was used to determine glomerular filtration rate (GFR). CKD was defined as either kidney damage or having a decreased kidney function, as assessed by a GFR of <60 ml/min per 1.73m^2 at baseline.

Pro-/anti-inflammatory cytokines at follow-up

Blood was allowed to clot at room temperature and centrifuged. Serum samples were stored at –80°C in anticipation of further processing. TNF-α (sensitivity: 0.75 pg/ml), sTNFR1 and sTNFR2 (sensitivity: 0.08 ng/ml), IL-6 (sensitivity: 0.82 pg/ml), IL-10 (sensitivity: 2.30 pg/ml) and IL1ra (sensitivity: 0.0794 ng/ml) were measured using quantitative enzyme-linked immunosorbent assay (ELISA). ELISA-kits were purchased from DiaMed Eurogen (Turnhout, Belgium). All tests were measured in

accordance with the manufacturer's recommendations. The sensitivity of all tests was calculated by the mean of six zero-values + three SDs extrapolated on the standard curve. Values below sensitivity (detection level) were raised to sensitivity value. The intra-assay variation was less than 10%, and the inter-assay variation less than 11%.

Clinical covariates

Demographic variables included sex and age. Smoking status was assessed by means of self-report. Information on clinical variables at baseline and follow-up, including LVEF, NYHA class, aetiology of CHF (ischemic/non-ischemic), risk factors (body mass index, hypertension, diabetes and hyperlipidemia), and medication (beta-blockers, aspirin, spironolactone, diuretics, ACE-inhibitors, statins, digoxin) were obtained from the patients' medical records or the treating cardiologist.

Statistical analyses

Linear regression analyses, adjusting for sex and age, were used to analyse differences in mean continuous measures of pro- and anti-inflammatory cytokines at 1-year follow-up in (i) type-D patients and (ii) patients with co morbid CKD, as compared to reference group of patients without type-D or CKD. Fourteen type-D patients also had CKD; these patients were included in both the type-D and CKD groups. Pearson's correlations and principal components analysis (varimax rotation) were used to examine the relationships among pro- and anti-inflammatory markers. In order to estimate the influence of type-D and CKD on the balance between pro- and anti-inflammatory activity, three ratios of pro versus anti-inflammatory cytokine levels (sTNFR1/IL-10, sTNFR2/IL-10, and IL-6/IL-10) were calculated. Logistic regression analysis was used to estimate the risk for an elevated pro-/anti-inflammatory cytokine ratio (defined by the 20% of CHF patients with the highest ratios) in type-D patients, after adjustment for relevant clinical covariates. All tests were two-tailed, and all analyses were performed using *SPSS 12.0* for Windows.

RESULTS

Baseline characteristics of type-D and CKD patients

At baseline, type-D CHF patients did not differ from non type-D patients on clinical or demographic characteristics, except for NYHA class and diuretics, with type-D patients more likely to be classified in NYHA-III/IV (Table 1). However, type-D and non type-D patients did not differ in mean LVEF ($p=.46$) or ratio of LVEF<25% ($p=.45$). As expected, CKD patients were more likely to be treated with diuretics

(p=.02) and were somewhat older (p=.05), but did not differ from non-CKD patients on any other baseline characteristic.

Table 1. Baseline characteristics stratified by type-D and chronic kidney disease

	Type-D-/CKD- (n=52)	*Type-D+ (n=32)*	*p value*	*CKD+ (n=55)*	*p value*
Demographics					
Male sex	*79% (41)*	*75% (24)*	*0.68*	*69% (38)*	*0.25*
Age ≥70 yrs	*29% (15)*	*41% (13)*	*0.27*	*47% (26)*	***0.05***
CHF characteristics					
Ischemic aetiology	*50% (26)*	*50% (16)*	*1.00*	*64% (35)*	*0.15*
History of MI	*42% (22)*	*50% (16)*	*0.49*	*53% (29)*	*0.28*
LVEF (%;M±SD)	*30 ± 7%*	*29 ± 7%*	*0.46*	*31 ± 6%*	*0.81*
LVEF<25%	*33% (17)*	*25% (8)*	*0.45*	*24% (13)*	*0.30*
NYHA class III/IV	*42% (22)*	*72% (23)*	***0.008***	*58% (32)*	*0.10*
Risk Factors					
BMI ≥30	*23% (12)*	*31% (10)*	*0.41*	*24% (13)*	*0.95*
Smoking	*25% (13)*	*19% (6)*	*0.51*	*18% (10)*	*0.39*
Hypertension	*37% (19)*	*31% (10)*	*0.62*	*36% (20)*	*0.98*
Hyperlipidemia	*52% (27)*	*53% (17)*	*0.92*	*53% (29)*	*0.93*
Diabetes	*19% (10)*	*28% (9)*	*0.34*	*27% (15)*	*0.33*
Medication					
Beta-blocker	*62% (32)*	*72% (23)*	*0.33*	*71% (39)*	*0.31*
Aspirin	*46% (24)*	*50% (16)*	*0.73*	*38% (21)*	*0.40*
Spironolactone	*17% (9)*	*19% (6)*	*0.87*	*26% (14)*	*0.31*
Diuretics	*67% (35)*	*91% (29)*	***0.02***	*86% (47)*	***0.02***
ACE-inhibitor	*77% (40)*	*78% (25)*	*0.90*	*78% (43)*	*0.88*
Statins	*48% (25)*	*47% (15)*	*0.92*	*49% (27)*	*0.92*
Digoxin	*31% (16)*	*38% (12)*	*0.53*	*33% (18)*	*0.83*

Type-D-/CKD-:patients with a non type-D personality and no chronic kidney disease;Type-D+:patients with a type-D personality;CKD+:patients with chronic kidney disease. MI: myocardial infarction;LVEF:left ventricular ejection fraction;NYHA:New York Heart Association; BMI: body mass index.

Cytokine levels at 1-year follow-up

At 1-year follow-up, type-D patients had significantly elevated levels of sTNFR1 (p=.009) and sTNFR2 (p=.001), and decreased levels of IL-10 (p=.006) as compared to the reference group of patients without type-D or CKD (Table 2). CKD patients had elevated levels of sTNFR1 (p=.0001) and sTNFR2 (p=.0001), but they

did not have decreased levels of IL-10 ($p=.31$) as compared to the reference group. There were no statistical differences with reference to TNF-α, IL-6 and IL1ra as a function of personality or CKD.

Table 2. Pro- and anti-inflammatory cytokine levels at 1-year follow-up

	Type-D-/CKD- (n=52)	*Type-D+ (n=32)*		*CKD+ (n=55)*	
	Mean±SD	*Mean±SD*	*p-value*	*Mean±SD*	*p-value*
Pro-Inflammatory					
sTNFR1 (pg/ml)	3598 ±1495	4988 ±2627	**.009**	5159 ±2271	**.0001**
sTNFR2 (pg/ml)	2064 ± 972	3356 ±1849	**.001**	3234 ±1871	**.0001**
TNF-α (pg/ml)	6.22 ±4.73	6.72 ±4.37	.62	7.35 ±4.52	.21
IL-6 (pg/ml)	2.02 ±1.82	2.59 ±2.05	.20	2.20 ±1.70	.62
Anti-Inflammatory					
IL-10 (pg/ml)	4.02 ±3.06	2.72 ±1.00	**.006**	3.47 ±2.38	.31
IL-1ra (pg/ml)	289 ±232	220 ±175	.12	328 ±312	.46

Type-D-/CKD- patients with a non type-D personality and no chronic kidney disease;Type-D+: patients with a type-D personality;CKD+:patients with chronic kidney disease.

Relationships among cytokine markers

sTNFR1 and sTNFR2 correlated positively with TNF-α and IL-6, and the correlation among TNF-α receptors was r=.61 (Table 3, left). These markers shared 5%-37% of variance, indicating that they were related, but not identical. IL-1ra correlated positively both with TNF-α and IL-10. IL-10 was unrelated to any of the other cytokine measures. IL1ra and IL10 shared only a small part of the variance (6%). Principal components analysis confirmed that sTNFR1, sTNFR2 and IL-6 reflect the dimension of pro-inflammatory activity (Table 3, right), as indicated by factor loadings between .63 and .87. IL-10, and IL-1ra reflected the anti-inflammatory dimension, with factor loadings of respectively .80 and .70. TNF-α had similar loadings on both factors and was not a pure marker of one domain.

Table 3. Relationship among pro- and anti-inflammatory cytokine markers at 1-year follow-up in patient with CHF (n=125)

	Correlations					Factors	
	sTNFR1	sTNFR2	IL-6	TNF-α	IL-10	Factor 1	Factor 2
sTNFR1	-					**.87**	-.07
sTNFR2	.61*	-				**.78**	.14
IL-6	.37*	.27*	-			**.63**	.11
TNF-α	.28*	.22*	.27*	-		.44	.46
IL-10	-.08	.06	.04	.14	-	-.17	**.80**
IL-1ra	.14	.29*	.15	.27*	.24*	.25	**.70**

Cytokine levels with a factor loading >.60 are presented in boldface.
*$p<.05$.

Pro-/anti-inflammatory cytokine ratios

The results from the factor analysis were used to compose three ratios of pro- versus anti-inflammatory activity (sTNFR1/IL-10, sTNFR2/IL-10 and IL-6/IL-10) to estimate the influence of type-D and CKD on the balance in pro-/anti-inflammatory activity (Table 4). CKD was associated with increased sTNFR1/IL-10 ($p=0.004$) and sTNFR2/IL-10 ($p=0.007$) ratios, but not with IL-6/IL-10 ratio ($p=0.39$). Type-D personality predicted increased sTNFR1/IL-10 ($p=0.003$), sTNFR2/IL-10 ($p=0.0001$) as well as IL-6/IL-10 ($p=0.013$) ratios at 1-year follow-up, adjusting for clinical variables (Table 4). Spironolactone was independently associated with the sTNFR1/IL-10 ratio, and beta-blockers with the sTNFR2/IL-10 ratio.

Type-D, CKD and cytokine imbalance

Next, the highest 20% of proportions of CHF patients with an elevated pro-/anti-inflammatory cytokine ratio, stratified by type-D personality or CKD, were contrasted with a "low risk" reference group, consisting of all other non type-D, non-CKD patients. Type-D personality predicted a significantly increased risk of elevated sTNFR1/IL-10 ($p=0.04$), sTNFR2/IL-10 ($p=0.001$), and IL-6/IL-10 ratios ($p=0.05$), adjusting for clinical and demographic variables (Figure 2). CKD also predicted elevated sTNFR1/IL-10 ($p=0.012$) and sTNFR2/IL-10 ($p=0.002$) ratios, but not IL-6/IL-10 ratios ($p=0.16$).

Table 4. Multivariable prediction models of pro-/anti-inflammatory cytokine ratios

Cytokine Ratio		Multivariable Analyses	
	Mean±SD (pg/ml)	Variables	p-value
sTNFR1/IL-10			
Reference group*	1224 ±708		
CKD	1850 ±987	**CKD**	**.004**
Type-D	1971 ±1132	**Type-D**	**.003**
		Male sex	.42
		Age ≥70 y	.58
		LVEF<25%	.69
		NYHA-III/IV	.09
		BMI ≥30	.55
		Smoking	.06
		Beta-blocker	.33
		Aspirin	.44
		Spironolactone	**.001**
sTNFR2/IL-10			
Reference group*	674 ±389		
CKD	1127 ±725	**CKD**	**.007**
Type-D	1330 ±794	**Type-D**	**.0001**
		Male sex	.98
		Age ≥70 y	.08
		LVEF<25%	.36
		NYHA III/IV	.52
		BMI ≥30	.06
		Smoking	.24
		Beta-blocker	**.043**
		Aspirin	.41
		Spironolactone	.13
sTNFR2/IL-10			
Reference group*	0.64 ±0.64		
CKD	0.78 ±0.67	**CKD**	.39
Type-D	1.04 ±0.88	**Type-D**	**.013**
		Male sex	.46
		Age ≥70 y	.93
		LVEF<25%	.94
		NYHA-III/IV	.21
		BMI ≥30	.40
		Smoking	.34
		Beta-blocker	.26
		Aspirin	.11
		Spironolactone	.83

*Reference group consists of patients without Type-D and without CKD.
CKD: chronic kidney disease;Type-D: type-D personality;LVEF: left ventricular ejection fraction; NYHA:New York Heart Association;BMI:body mass index.

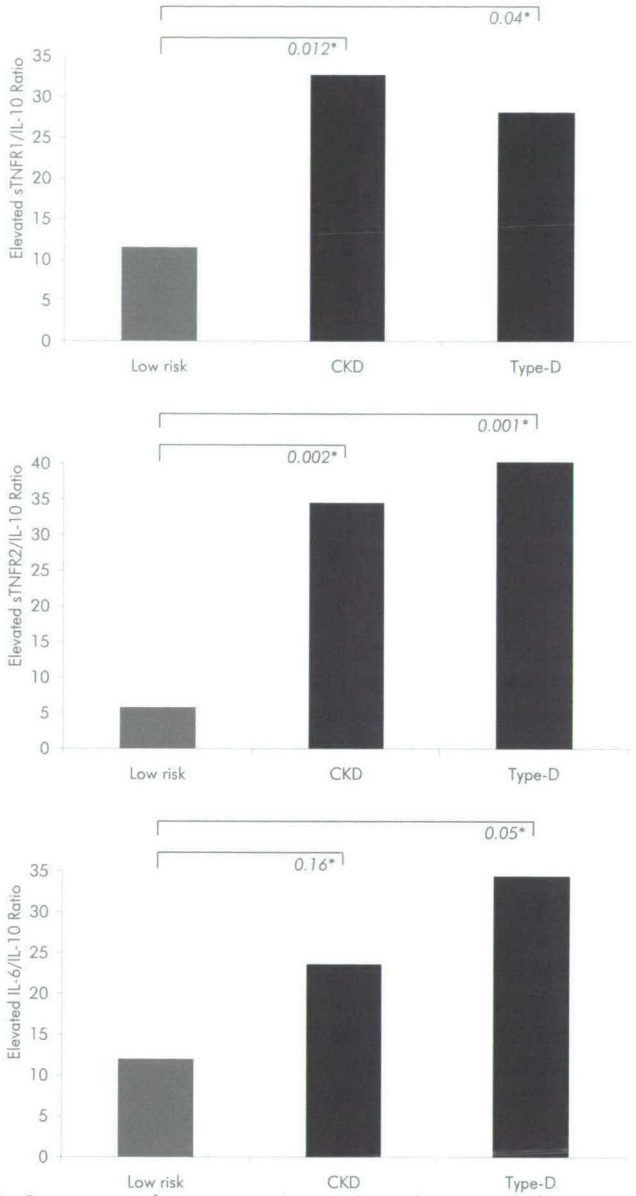

Figure 2. Percentage of patients with an elevated pro-/anti-inflammatory cytokine ratio, stratified by type-D personality and CKD

CKD: chronic kidney disease.
Low risk refers to the reference group of patients without type-D and without CKD.
**Type-D patients and CKD patients versus low risk patients, adjusting for demographic and clinical variables.*

In a final multivariate prediction model, including older age, spironolactone and beta-blockers, type-D personality was associated with a more than three-fold increased risk of elevated sTNFR1/IL-10 (OR=3.92) and IL-6/IL-10 (OR=3.12) ratios at follow-up (Table 5, top). Type-D personality independently predicted an even greater increased risk of elevated sTNFR2/IL-10 ratios (OR=18.88). CKD was significantly associated with elevated sTNFR1/IL-10 (OR=4.23) and sTNFR2/IL-10 (OR=7.75) ratios (Table 5, bottom). Older age, spironolactone and beta-blockers were also related to elevated sTNFR1/IL-10 and sTNFR2/IL-10 ratios (Table 5).

Table 5. Type-D personality (A) and chronic kidney disease (B) as predictors of a pro-/anti-inflammatory cytokine imbalance

Elevated Ratio (Highest 20%)	*(A) Type-D personality*	*Odds Ratio [95%CI]*	*p-value*
sTNFR1/IL-10	*Type-D*	*3.92 [1.11-13.87]*	**.034**
	Age ≥70 y	*0.65 [0.17-2.54]*	.54
	Spironolactone	*5.68 [1.45-22.34]*	**.013**
	Beta-blocker	*0.37 [0.10-1.36]*	.13
sTNFR2/IL-10	*Type-D*	*18.88 [3.61-98.85]*	**.001**
	Age ≥70 y	*7.94 [1.79-35.27]*	**.006**
	Spironolactone	*2.77 [0.53-14.42]*	.23
	Beta-blocker	*0.19 [0.04-0.89]*	**.036**
IL-6/IL-10	*Type-D*	*3.12 [1.03-9.39]*	**.044**
	Age ≥70 y	*2.22 [0.73-6.78]*	.16
	Spironolactone	*1.44 [0.37-5.59]*	.59
	Beta-blocker	*1.13 [0.34-3.81]*	.84
Elevated Ratio (Highest 20%)	*(B) Chronic kidney disease*	*Odds Ratio [95%CI]*	*p-value*
sTNFR1/IL-10	*CKD*	*4.23 [1.44-12.45]*	**.009**
	Age ≥70 y	*0.70 [0.26-1.94]*	.49
	Spironolactone	*2.24 [0.76-6.58]*	.14
	Beta-blocker	*0.48 [0.17-1.31]*	.15
sTNFR2/IL-10	*CKD*	*7.75 [2.05-29.30]*	**.003**
	Age ≥70 y	*4.04 [1.39-11.78]*	**.01**
	Spironolactone	*0.94 [0.27-3.32]*	.93
	Beta-blocker	*0.73 [0.24-2.26]*	.60
IL-6/IL-10	*CKD*	*1.79 [0.63-5.06]*	.28
	Age ≥70 y	*2.09 [0.77-5.73]*	.15
	Spironolactone	*0.84 [0.24-2.89]*	.78
	Beta-blocker	*0.90 [0.31-2.57]*	.84

Type-D: type-D personality; CKD: chronic kidney disease.

DISCUSSION

The present study is the first to examine prospectively the relationship between type-D personality and cytokine levels in CHF. In addition, the present study reports novel results on the predictive qualities of CKD in the determination of cytokine levels. Both type-D personality and CKD were associated with pro- and anti-inflammatory cytokine imbalance after 1-year follow-up in CHF patients. Moreover, type-D personality and CKD were found to be equally significant, independent predictors of cytokine imbalance after adjustment for major confounding baseline clinical characteristics, such as LVEF.

There is increasing evidence that cytokines (and thereby immune activation) play an important role in the pathogenesis of heart failure [4,39,40]. In response to cardiac stress, due to e.g. left ventricular pressure or volume overload, cells within the myocardium synthesise and release TNF-α. TNF receptors 1 and 2 are present on the cell surfaces of human myocardial cells. The release of TNF-α triggers these surface receptors to release their extra cellular domain into the circulation, which then become the soluble receptors sTNFR1 and sTNFR2. These bind to circulating TNF-α, serving as a "slow-release reservoir". Other pro-inflammatory cytokines, such as IL-1 and IL-6, also play a role in the progression of CHF [6,40], and predict mortality in CHF patients. sTNFR1 and sTNFR2 have shown to be strong, long-term predictors of death and heart failure in cardiac patients [5-8]. Univariate results of the present study showed that levels of both soluble TNF-α receptors, but not of TNF-α, differed significantly between CHF patients with and without type-D personality, and between CHF patients with and without CKD. Because the soluble TNF receptors are shed in response to TNF-α release, increased levels of these receptors in CHF patients with a type-D personality may represent increased activation of TNF-α at a local level. Concurrently, serum TNF-α levels were equivalent in type-D and non type-D patients, potentially reflecting the down-regulation of TNF-α activity by the increased levels of soluble TNF receptors in type-D CHF patients.

IL-10 is an immunomodulator that down-regulates the production of TNF-α [41], IL-1 [41], and IL-6 [42], and enhances the shedding of soluble TNF receptors [43]. The current results show that IL-10 is decreased in type-D CHF patients and unchanged in CHF patients with CKD. Combined, this reflects an imbalance in the cytokine profile, i.e., too much pro-inflammatory cytokines (reflected by increased sTNFR1, sTNFR2 and IL-6 levels) as compared to the levels of anti-inflammatory cytokines (that either were decreased or invariant (i.e., IL-10, IL1ra)) at 1-year follow-up. These results indicate the plausibility that the observed cytokine imbalance may

explain the link between type-D personality or CKD on the one hand, and cardiac morbidity and mortality on the other hand.

In two previous cross-sectional studies was found that type-D personality was associated with increased circulating levels of TNF-α and TNF-α receptors [30,31]. The findings of the current study build on these and other previous findings that emotional distress such as psychological stress [44] and vital exhaustion [28] is associated with increments in cytokine levels in both cardiac patients and healthy volunteers. For depression however, results have been inconsistent. Although there are multiple studies testifying to a significant relationship between depression and cytokine levels in cardiac patients [25,32-34,45], other studies did not [29,46,47]. In a study of 37 cardiac patients for example, no association was found between IL-1β levels and depressive symptom severity or depression diagnosis [46]. In addition, depression was not related to IL-6 in patients two months after hospitalisation for an acute coronary syndrome [29]. In a cross-sectional study of women with coronary heart disease, depressive symptoms did not correlate significantly with IL-6 or IL1ra [47].

Recent evidence suggests that hypothalamus-pituitary-adrenal (HPA) dysfunction and associated increased cortisol levels may contribute to the pro-inflammatory state of cardiac patients with a type-D personality [48]. Although cortisol is universally considered to have anti-inflammatory effects, it actually may have anti-inflammatory as well as rather unexpected pro-inflammatory properties that can co-exist at the same time [49]. Prior exposure to stress or cortisol may have a priming effect on the subsequent inflammatory response to an immune challenge [50,51]. Animal research shows that acute stress increases plasma levels of IL-6 and TNF-α [50], and that treatment with glucocorticoids 12 hours prior to immune challenge increases IL-6 and TNF-α production [52]. Finally, while glucocorticoids may reduce the expression of pro-inflammatory cytokines under certain conditions, they often simultaneously increase the expression of the corresponding cytokine receptor [49].

CHF often is complicated by the additional diagnosis of CKD [17,23,53], since the kidney is the main organ affected when cardiac function is compromised [54]. It was recently shown that inflammation, as assessed by higher levels of sTNFR1 and 2, may mediate this association [17]. However, to date, a temporal relationship between renal impairment and worsening heart failure has not been established [23]. The present study is the first to report that presence of CKD in CHF patients at baseline is a strong, independent predictor of an unfavourable cytokine profile (too much pro-inflammatory cytokines (reflected by increased sTNFR1, sTNFR2),

compared to the levels of anti-inflammatory cytokines that were invariant (i.e., IL-10, IL1ra)) one year later. Since pro-inflammatory cytokines are significant predictors of poor outcome in heart failure [7,55], the findings indeed suggest that there is a temporal relation between kidney impairment and prognosis in heart failure, and that this relationship is partly mediated by inflammation.

Although our findings are promising, they should be interpreted sensibly in the light of some limitations of the study design. Although no significant differences were found between males and females, the fact that only 25% of the sample was female, may have precluded finding sex differences. A further limitation to this study is that only a limited amount of patients had both type-D personality and CKD. It would be interesting to find out whether the effects of type-D personality and CKD are additive, since this would specify those CHF patients at high risk even further. The majority of the studies in CHF that have found associations between psychological distress and cytokine levels have been cross-sectional and based on small sample sizes [30-34]. Our study differs from these reports, as we used a prospective design and had a relatively larger sample.

Concluding, both type-D personality and CKD independently predict unfavourable cytokine profiles in CHF patients. Such alterations in immune processes may be one mechanism explaining the adverse relationship between these risk factors and prognosis in heart failure. Whether these type-D and CKD related alterations in immune balance actually explain adverse prognosis and mortality in CHF patients is subject for further study.

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CHAPTER 9

Type-D personality and mortality in patients with chronic heart failure

Angélique A. Schiffer[abc], Otto R.F. Smith[ab], Susanne S. Pedersen[a], Jos W. Widdershoven[b], Johan Denollet[a]

[a]CoRPS – Center of Research on Psychology in Somatic diseases, Tilburg University, Tilburg, the Netherlands
[b]Department of Cardiology, TweeSteden Hospital, Tilburg, the Netherlands
[c]Department of Medical Psychology, TweeSteden Hospital, Tilburg, the Netherlands

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ABSTRACT

Background

Clinical predictors of mortality in chronic heart failure (CHF) are established, but less is known about chronic psychological predictors. Therefore, we examined the prognostic value of type-D personality (i.e., the tendency to experience negative feelings and inhibit self-expression) in CHF patients.

Methods

Consecutive systolic CHF patients (n=232) filled in the Type-D Scale (DS14) at baseline. Socio-demographic and clinical data were obtained from the patients' medical records or treating cardiologist/CHF nurse. The primary endpoint was cardiac mortality after a follow-up of 30.7 months (SD=11.1). Early (≤6 months) versus late (>6 months) cardiac mortality were secondary endpoints.

Results

Type-D patients had a higher incidence of cardiac mortality (15/48=31.3%) as compared to non type-D patients (32/184=17.4%), OR=2.16;95%CI:1.05-4.43, p=.04. Type-D was a near significant independent predictor of total cardiac mortality (OR=1.40;95%CI:0.93-4.29,p=.08). Type-D did not predict early cardiac mortality (p=.83), but was a significant independent predictor of late cardiac mortality, adjusting for sex, age and left ventricular ejection fraction (OR=2.34;95%CI: 1.05-5.26,p=.04).

Conclusions

Type-D personality was an independent predictor of late cardiac mortality, adjusting for socio-demographics and disease-severity, but not of early cardiac mortality. These findings suggest that chronic psychological factors may play less of a role in short-term CHF prognosis, but are of importance in long-term prognosis. Future studies are warranted to replicate these findings.

INTRODUCTION

Worldwide high prevalence and incidence rates of chronic heart failure (CHF) have been reported; up to 2% of the total population has CHF [1-3]. Despite impressive advances in therapy, CHF still has a poor prognosis [1,2,4]. Clinical predictors of CHF prognosis are established [5-10], and episodic psychological risk factors such as depression and to a lesser extent anxiety, have also been studied [8,9,11-16]. However, the role of chronic psychological factors, such as personality, in relation to CHF mortality has largely been overlooked.

Type-D personality, i.e., the tendency to experience negative emotions combined with the tendency to inhibit self-expression, has been shown to predict worse prognosis in patients with coronary artery disease (CAD) [17-21]. Preliminary evidence also shows that type-D personality predicts mortality in post-myocardial infarction (MI) patients with a decreased left ventricular ejection fraction (LVEF) [18], and in heart transplantation recipients [22]. The prognostic value of type-D personality in patients with established CHF has not yet been explicitly examined, but recent research has shown that type-D personality is associated with increased levels of depressive symptoms and anxiety in CHF patients [23,24]. Given the chronicity of type-D, and that CHF patients with this personality disposition have an increased risk for the convergence of psychosocial risk factors, may increase the risk of worse prognosis [17,25-29].

The objectives of this study were to (1) investigate whether type-D personality predicts adverse cardiac prognosis in patients with CHF, and (2) examine the role of type-D personality in early (≤6months) and late (>6 months) cardiac mortality as secondary endpoints.

METHODS

Patient population

Between October 2003 and March 2006, consecutive CHF patients from the cardiology unit of the TweeSteden teaching hospital in Tilburg, the Netherlands, were included in the current study. Of 305 eligible patients, 232 agreed to participate (response rate of 76%). No patients were lost to follow-up, but four patients were excluded from analyses because they died from other than cardiac causes.

Patients were eligible for the current study if they had a diagnosis of systolic CHF with a LVEF≤40%, were ≤80 years of age, and stable on medication for at least one month prior to inclusion. Patients with a diagnosis of diastolic heart failure,

who were unable to read, write or understand Dutch, who had life-threatening co morbidities (e.g. cancer or MI one month prior to inclusion), or severe cognitive impairments, were excluded. All patients were treated following the most recent guidelines for CHF [3,30-32]. The study was approved by the hospital medical ethics committee and carried out according to policies to protect human subjects as formulated by the Word Medical Association, described in the Helsinki Declaration (2004).

The treating cardiologist or CHF nurse informed patients about the study and asked them to participate. If they agreed, the investigator called them in the same week to make an appointment for assessment. During this visit, patients were given additional information about the study; they provided written informed consent and were asked to complete a questionnaire at home. All questionnaires were returned in a self-addressed envelope and were checked for completeness. Patients who had left open several items were asked to answer those questions. In case the questionnaire was not returned within two weeks, patients received a reminder telephone call or letter.

Clinical endpoints

The primary endpoint in this study was cardiac mortality. Information on mortality (date and cause of death) was collected by checking the hospital's electronic system/the patients' medical records or by contacting the general practitioner. Secondary endpoints were early ($\leq$6 months) versus late (>6 months) cardiac mortality. In previous studies in coronary patients, also in patients with an impaired pump function, was shown that the cardio-toxic effect of type-D personality was more prominent on the long term [18,20]. Furthermore, in previous research in cardiac patients, the endpoint of major cardiac events has been split up into early versus late events, with a cut-off at six months [33].

Type-D personality

At baseline, the Type-D Scale (DS14) was used to assess type-D personality [34]. The DS14 comprises two subscales of seven items each, measuring negative affectivity (e.g. "I am often irritated"; "I often find myself worrying about something") and social inhibition (e.g. "I am a closed kind of person; "I would rather keep other people at a distance"), respectively. Items are answered on a 5-point Likert Scale from "false" (0) to "true" (4). Type-D caseness is defined as a score of $\geq$10 on both DS14 subscales, which has been shown to be the most optimal cut-off [34,35]. It is the interaction of negative affectivity and social inhibition that predicts poor clinical outcome in

coronary patients and not the single traits, with social inhibition moderating the effect of negative affectivity on prognosis [36]. The DS14 is internally consistent (Cronbach's α=.88/.86 for the negative affectivity and social inhibition subscale, respectively) and stable over time [34,37]. Recent studies in post-MI patients showed that type-D personality is not confounded by disease severity [37,38].

Clinical characteristics

Information on sex, age, disease characteristics (LVEF, New York Heart Association (NYHA) functional class and aetiology), co morbidities (previous cardiac history and diabetes) and medication (diuretics, aspirin, beta-blockers, ACE-inhibitors and statins) was obtained from the patients' medical records and the treating cardiologist/CHF nurse at the time of inclusion into the study.

Statistical analyses

Prior to statistical analyses, NYHA-class, aetiology and cardiac history were recoded into dichotomous variables. For comparison between two groups, we used the chi-square test for discrete variables and the *t* test for independent samples for continuous variables. Logistic regression analyses were used to assess the relationships between type-D personality and cardiac mortality. In order to obtain reliable estimates in multivariable analyses, we selected a maximum of three additional predictors a priori, i.e., sex, age and LVEF. All analyses were performed using *SPSS 14.0.* for Windows.

RESULTS

Baseline characteristics

Of all eligible patients, 73 refused participation. Participants and non-participants differed systematically on some baseline characteristics, with non-participants being older (69.6 versus 65.5;p=.002), more likely to be female (47.9% versus 25.4%;p<.001), to have non-ischemic CHF (59.7% versus 45.7%;p=.04), and to use aspirin (66.7% versus 40.1%;p<.001), but less likely to use ACE-inhibitors (63.9% versus 76.3%;p=.04), compared to participants.

Of the total sample, 48 patients (20.7%) were classified as type-D. Type-D patients did not differ from non type-D patients on demographic and clinical variables, although a trend was found for increased use of diuretics among patients with a type-D personality (p=.06;Table 1).

Table 1. Baseline characteristics stratified by type-D personality

	Total sample	*Type-D (n=48)*	*Non type-D (n=184)*	*p-value*
Male sex	*75 (173)*	*79 (38)*	*73 (135)*	*.41*
Age, mean (SD)	*65.5 (9.9)*	*66.5 (10.6)*	*65.2 (9.8)*	*.44*
LVEF[A], mean (SD)	*30.5 (6.9)*	*30.1 (7.4)*	*30.6 (6.7)*	*.64*
NYHA[B] class III/IV	*48 (112)*	*56 (27)*	*46 (85)*	*.21*
Ischemic aetiology	*54 (126)*	*52 (25)*	*55 (101)*	*.73*
Cardiac history‡	*57 (133)*	*56 (27)*	*58 (106)*	*.87*
Diabetes	*27 (63)*	*25 (12)*	*28 (51)*	*.71*
Diuretics	*77 (179)*	*88 (42)*	*75 (137)*	*.06*
Aspirin	*40 (93)*	*46 (22)*	*39 (71)*	*.36*
Beta-blockers	*66 (154)*	*69 (33)*	*66 (121)*	*.70*
ACE-inhibitors	*76 (177)*	*79 (38)*	*76 (139)*	*.60*
Statins	*49 (113)*	*50 (24)*	*48 (89)*	*.84*

Data are presented as % (n), unless otherwise indicated
‡ Previous myocardial infarction, coronary artery bypass surgery, and/or percutaneous coronary intervention
[A]Left ventricular ejection fraction
[B]New York Heart Association

Type-D personality and cardiac mortality

The mean follow-up period was 30.7 months (SD=11.1). During this period, 47 patients (20.3%) had died due to cardiac causes. An additional four patients had died due to other causes (i.e. cancer and chronic obstructive pulmonary disease), and were excluded from further analyses.

Logistic univariable regression analysis revealed that type-D personality was a significant predictor of cardiac mortality (OR=2.16;95%CI:1.05-4.43, p=.04). Furthermore, higher age (OR=1.05;95%CI:1.01-1.09, p=.01) and lower LVEF (OR=0.92;95%CI: 0.87-0.96, p<.001) predicted cardiac mortality in univariable analyses. A trend towards significance was found for male sex (OR=2.23;95%CI: 0.94-5.30, p=.07). In Figure 1 (left), the incidence of cardiac mortality for patients with a type-D personality (15/48=31.3%) as compared to patients without type-D (32/184=17.4%) is provided (p=.04).

In multivariable analysis, we entered type-D, sex, age, and LVEF. Lower LVEF (OR=0.93;95%CI:0.88-0.98, p=.003) and higher age (OR=1.04;95% CI:1.00-1.08, p=.049) were independently associated with cardiac mortality, whereas there was also a trend for type-D personality (OR=1.40;95%CI:0.93-4.29, p=.08).

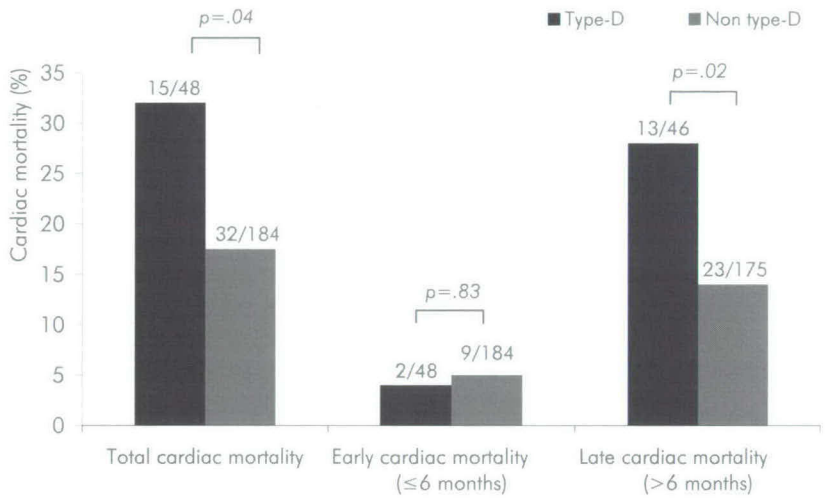

Figure 1. Effect of type-D personality on cardiac mortality

Type-D personality and early versus late cardiac mortality

As a secondary endpoint, we divided cardiac mortality into early (≤6 months) versus late (>6 months) cardiac events. There were 11 early events (4.7%) and 36 late events (15.5%).

Univariable logistic regression revealed that type-D was not associated with early cardiac mortality (OR=0.85;95%CI:0.18-4.05, p=.83), but it was related to late cardiac mortality (OR=2.54;95%CI: 1.17-5.52, p=.02). In Figure 1 (centre), the incidence of early cardiac mortality for CHF patients with a type-D personality (2/48=4.2%) as compared to CHF patients without type-D (9/184=4.9%) is provided (p=.83). Furthermore, Figure 1 (right) also shows the incidence of late cardiac mortality for type-D CHF patients (13/46=28.3%) as compared to non type-D CHF patients (23/175=13.1%, p=.02).

In multivariable analysis, type-D remained a significant independent predictor of late cardiac mortality (OR=2.34;95%CI:1.05-5.26, p=.04), adjusting for sex, age and LVEF. In addition, LVEF predicted late cardiac mortality (OR=0.95 ;95%CI:0.89-1.00, p=.04), but not as strongly as it predicted total cardiac mortality. This suggests that CHF patients who died within the first six months are characterised by a more impaired LVEF. This was confirmed in post-hoc analysis, comparing the LVEF of patients who died early to those who died late (mean $LVEF_{early}$=23.7;mean $LVEF_{late}$=28.4;t=2.01;df=45, p=.05).

In Table 2, the results for the multivariable analyses for early and late cardiac mortality are provided.

Table 2. Predictors of early and late cardiac mortality (multivariable analyses)

	Odds ratio	*95%CI*	*p-value*
Early cardiac mortality			
Age	*1.04*	*0.96 – 1.13*	*.30*
Male sex	*2.45*	*0.29 – 20.56*	*.41*
LVEF[A]	*0.87*	*0.79 – 0.96*	*.006*
Type-D personality	*0.61*	*0.12 – 3.21*	*.56*
Late cardiac mortality			
Age	*1.04*	*1.00 – 1.09*	*.09*
Male sex	*1.61*	*0.62 – 4.21*	*.33*
LVEF[A]	*0.95*	*0.89 – 1.00*	*.04*
Type-D personality	*2.34*	*1.05 – 5.26*	*.04*

[A]*Left ventricular ejection fraction*

DISCUSSION

We found that type-D CHF patients had a significantly higher incidence of cardiac mortality as compared to non type-D CHF patients. Type-D personality was a significant predictor of cardiac mortality in univariable analysis. After adjusting for sex, age and CHF severity, the relationship was no longer significant, although there was a trend. When dividing total cardiac mortality into early (≤6 months) versus late (>6 months) mortality, we found type-D personality to be significantly associated with late cardiac mortality, also when adjusting for the mentioned confounders, but not with early cardiac mortality.

Several episodic psychological and psychosocial variables, such as depression, anxiety, social isolation and avoidant coping have been identified as important predictors of mortality in CHF [8,9,11-16,39,40]. However, few studies have examined the prognostic value of personality in patients with diagnosed CHF, although one study found that neuroticism independently predicted cardiac death [41], and two studies reported that type-D personality was related to adverse prognosis in post-MI patients with an impaired pump function [18] and in heart transplantation recipients [22]. To our knowledge, this is the first study investigating the predictive value of type-D personality on cardiac prognosis in patients with established CHF.

In the current study, type-D patients did not differ from non type-D patients on disease severity as assessed by means of LVEF. This result is in line with those of a recent sub study from the Myocardial Infarction and Depression-Intervention (MIND-IT) trial, comparing the extent to which type-D personality and depression were confounded by measures of somatic health [38]. De Jonge and colleagues found that depression, but not type-D personality, was related to impaired LVEF and co morbidities [38].

In previous studies of patients with CAD, type-D personality has been shown to predict mortality and re-infarction, with the associated risk being around 4-fold [17,19-21,36]. In addition, type-D personality also independently predicted cardiac death over 6-10 years in MI survivors with an impaired pump function [18], and impaired prognosis in heart transplantation recipients [22]. In this study, we found a significant independent association between type-D and late cardiac mortality, but not between type-D personality and early cardiac mortality. Thus, it seems that, at least in CHF, personality is especially important in long-term prognosis. Our results are in line with those of the study in coronary patients with an impaired pump function (but no diagnosed CHF) [18]. In the latter study, the

influence of type-D personality on cardiac events was more prominent the longer the follow-up period [18]. Given that in the current study, patients who died in the first six months after inclusion had a significantly more impaired LVEF compared to patients who died later, we may assume that these patients had worse heart failure. It is unlikely that psychological variables, such as type-D personality, are relevant for prognosis in this very ill subgroup of CHF patients. Next to the already mentioned study in coronary patients with an impaired pump function [18], results of another study in post-percutaneous cardiac intervention patients also showed that personality becomes especially cardio-toxic in the long run [20]. It might also be that personality factors are less cardio-toxic in terms of predicting mortality in CHF patients compared to CAD patients, as CHF patients tend to have a long history of heart disease and have often survived several cardiac events. However, this needs to be confirmed in a larger study with a longer follow-up period.

Mechanisms relating type-D personality to adverse prognosis may be of physiological and/or behavioural nature. Previously, type-D personality has been associated with increased cytokine levels in CHF patients [42,43], and cytokines are related to increased risk of death and CHF in post-MI patients [44]. Of behavioural mechanisms, compliance and self-care behaviour, such as consultation behaviour, may be important. A recent study showed that type-D patients with CHF are less likely to consult their cardiologist or CHF nurse, despite experiencing relevant cardiac symptoms and worrying about them [45]. Furthermore, physically healthy type-D persons also seem to engage in significantly fewer health behaviours as compared to non type-D persons [46]. For clinical practice, this means that efforts should be concentrated on improving type-D patients' self-care abilities and health behaviours, as this may help to reduce the cardio-toxic effects of type-D on the long-term.

Limitations and strengths

The sample size of the current study is relatively small and it has a relatively short follow-up period. Furthermore, the sample could be biased by mobility and younger age, because participating patients were required to visit the outpatient clinic. There were also several differences on baseline characteristics between participants and non-participants. Finally, the sample used in this study was quite heterogeneous, as end stage CHF patients as well as newly diagnosed CHF patients were included. However, this is also a strength, as it reflects "the real world" of CHF patients seen in daily clinical practise. Other strengths of the study include that patients comprised consecutive, unselected outpatients, that the response rate was quite high, and that

this is the very first study to examine the prognostic value of type-D personality in patients with established CHF.

Conclusions

In this study, type-D personality was associated with cardiac mortality in CHF. Type-D personality was an independent predictor of late cardiac mortality, but not of early cardiac mortality. These findings warrant replication in studies with a larger sample size and longer follow-up periods.

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CHAPTER 10

General discussion and summary

This thesis described a longitudinal follow-up study in outpatients with chronic heart failure (CHF). The aim of the thesis was to examine the associations between type-D personality and health outcomes in CHF outpatients. Possible behavioural and physiological mechanisms in explaining the adverse impact of type-D personality on patient-centred outcomes and prognosis were also investigated. In the present chapter, the main findings of this thesis are summarised, implications for clinical practice are described, and methodological reflections are presented.

TYPE-D PERSONALITY AS A PREDICTOR OF PATIENT-CENTRED OUTCOMES IN CHF

Previous research has examined the associations between type-D personality (tendency to experience a broad range of negative feelings while not sharing them in social interaction) and health status, quality of life and psychological distress in patients with coronary artery disease (CAD) [e.g. 1-9]. Until now, no studies reported on the influence of type-D personality on these patient-centred outcomes in CHF. Therefore, the first part of the present thesis (Part A) focused on the impact of type-D personality on patient-centred outcomes in patients with CHF.

After a general introduction (Chapter 1) and an introduction on the type-D personality construct (Chapter 2), the aim of Chapter 3 was to examine whether type-D personality was associated with impaired health and mood status, and increased depressive symptoms in CHF, independent of disease characteristics. Results showed that CHF patients with a type-D personality were more likely to experience impairment in health and mood status, and increased depressive symptoms as compared to non type-D patients. Type-D personality was still associated with impaired health status, increased depressive symptoms and impaired mood status (i.e. more negative and less positive affect) when adjusting for severity and aetiology of CHF, and socio-demographic characteristics.

The aim of the study reported in Chapter 4 was to replicate the above-mentioned findings in a larger sample of CHF patients, while using a more broad measure of health status and a prospective design. More specific, this study investigated whether type-D personality would exert a stable, independent effect on disease-specific and generic health status in CHF over 12 months, when adjusting for depressive symptoms, disease characteristics, socio-demographic variables, relevant medication, and baseline health status. Results showed that there was a general improvement in disease-specific and mental generic health status over time. However, type-D patients reported significantly lower disease-specific as well as

mental health status as compared to non type-Ds. Furthermore, depressed patients also reported significantly lower health status as compared to the non-depressed. The negative impact of type-D personality and depressive symptoms on health status was stable over time and could not be attributed to the severity of CHF. The results elaborate on findings from previous studies on determinants of health status in CHF in that is shown that type-D personality is predictive of impaired health status above and beyond depressive symptoms. In this study, no association between type-D personality and physical health status was found. An explanation for this may be that the patients in this study were chronically ill with hardly any options left concerning invasive interventions; generic physical health status may be largely a function of CHF severity.

Chapter 5 focused on CHF patients treated with cardiac resynchronisation therapy (CRT). Although clinical trials have shown that CRT exerts positive effects on mortality, morbidity, quality of life, functional status and exercise capacity in CHF, a subgroup of patients still report significant symptoms and high levels of disability following CRT [e.g. 10-14]. The study presented in Chapter 5 was the first to examine the associations between negative affectivity, social inhibition and type-D personality, and patient-centred outcomes such as health status and symptom levels, in patients treated with CRT. Results showed general improvements in patient-centred outcomes over time. However, high negative affectivity patients reported significantly lower disease-specific health status and more cardiac symptoms and perceived disability as compared to low negative affectivity patients. When adjusting for disease-severity, sex and age, high negative affectivity patients still reported lower disease-specific health status and significantly more perceived disability. The main conclusion therefore was that CHF patients treated with CRT improved over a 2-month period in patient-centred outcomes, but also that negative affectivity exerted a stable, negative effect on these outcomes. In this exploratory study, type-D personality was not associated with more impaired health status or symptoms, probably because of the small sample size with only eight patients being identified as type-D, and the relatively short follow-up period. Hence, replication of these findings in a larger data set is warranted.

A paucity of studies has focused on anxiety and its determinants in CHF. Therefore, Chapter 6 examined whether type-D personality and depressive symptoms would predict clinically significant anxiety at 1-year follow-up. Hypertension, type-D personality and anxiety sensitivity, but not depressive symptoms, were significant predictors in univariable analyses. When adjusting for depressive symptoms, anxiety sensitivity, socio-demographic and clinical variables, type-D personality remained a

significant independent predictor of clinically significant anxiety at 12 months. Furthermore, when using a hierarchical logistic regression model comprising standard and psychological risk factors, type-D personality enhanced the level of prediction of clinically significant anxiety substantially.

Taken together, the results of the first part of this thesis showed that type-D personality and its subcomponent negative affectivity were important predictors of patient-centred outcomes, such as health status, mood status, depressive symptomatology, anxiety, cardiopulmonary symptoms and perceived disability in CHF. Knowledge about determinants of such patient-centred outcomes may help to identify patients at high risk for adverse prognosis, as impaired health status, and anxiety and depression have been related to increased mortality in heart patients [e.g. 15-22].

TYPE-D PERSONALITY AS A PREDICTOR OF PROGNOSIS IN CHF AND MECHANISMS EXPLAINING THE ADVERSE EFFECTS ON HEALTH OUTCOMES

Type-D personality has been shown to predict worse prognosis in patients with CAD [e.g. 23-27]. Although one study examined type-D personality in relation to prognosis in coronary patients with an impaired pump function [23], and another focused on type-D and prognosis in heart transplantation recipients [28], no study has focused on the prognostic value of type-D personality in patients diagnosed with CHF per se. Furthermore, although there are two cross-sectional studies describing associations between type-D personality and cytokines in CHF patients [29,30], no studies have reported on the relationship between type-D personality and cytokines prospectively. A very recent cross-sectional study evaluated the association between type-D personality and health-related behaviours in physically healthy persons [31], but, again, no prospective studies have investigated the behavioural mechanisms that may explain associations between type-D personality and health outcomes. Therefore, the second part of the present thesis (Part B) focused on possible physiological and behavioural mechanisms underlying the relationship between type-D personality and health outcomes in CHF.

Because poor self-management, or self-care, is associated with an increased risk of adverse clinical outcome in CHF [32], Chapter 7 examined whether type-D personality would predict poor self-management and failure to consult for clinically evident symptoms in CHF patients. Results indicated that type-D patients experienced more cardiac symptoms and more often appraised these symptoms as

worrisome as compared to non type-D patients. Paradoxically, however, type-Ds were less likely to report these symptoms to their cardiologist/nurse, as indicated by an increased risk for inadequate consultation behaviour, adjusting for socio-demographics, severity/aetiology of CHF, time since diagnosis and medication. Thus, patients with a type-D personality were at an increased risk for inadequate consultation behaviour as a specific facet of self-management behaviour. Impaired self-management behaviour could therefore be a possible behavioural mechanism explaining adverse effects of type-D personality on health outcomes.

A possible mechanism in the relationship between type-D personality and prognosis is of pathophysiological nature. Previous cross-sectional studies have shown associations between type-D personality and the cytokines TNF-α and its soluble receptors sTNFR1 and sTNFR2 [29,30]. It has also been shown that the pro-inflammatory cytokines IL-6, TNF-α, sTNFR1/sTNFR2, IL-10 and IL-1ra were related to increased risk of death and CHF following myocardial infarction [33]. Chapter 8 therefore prospectively examined whether type-D personality predicted serum levels of these pro- and anti-inflammatory cytokines at 1-year follow-up in CHF patients while adjusting for traditional prognostic markers, such as left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) functional class. Furthermore, the latter study also examined the association between chronic kidney disease (CKD) and pro- and anti-inflammatory cytokine imbalance, because patients with kidney disease are often excluded from cardiovascular research, although CKD is related to higher IL-6 and TNF-α levels and poor clinical outcomes in CHF [34]. In the study presented in Chapter 8, type-D personality and CKD were both associated with pro- and anti-inflammatory cytokine imbalance after 1-year follow-up, exerting an independent effect of similar magnitude. This prospective study presented therefore evidence for a pathophysiological pathway in the associations between type-D personality and prognosis.

The study presented in Chapter 9 is the first to report on the relationship between type-D personality and cardiac prognosis in the context of CHF. Type-D CHF patients had higher incidence of cardiac mortality as compared to the non type-Ds. Furthermore, after adjusting for LVEF, sex and age, type-D personality predicted total cardiac mortality near significant, but was a significant predictor of late cardiac mortality. There was no effect of type-D personality on early cardiac mortality in this study. The relatively small sample size and the short follow-up period may be reasons for not finding significant associations between type-D personality and total cardiac mortality. Replication of the findings in studies with larger samples and longer follow-

up periods is therefore warranted. However, the results indicated that type-D personality is of importance in, at least, late cardiac mortality in CHF.

Overall, the results of the studies presented in the second part of the present thesis elaborated on results from previous studies on the relationship between type-D personality and prognosis in patients with CAD, and on studies providing preliminary evidence that immune-activation and health-related behaviours may comprise a link between type-D personality and health outcomes.

IMPLICATIONS FOR CLINICAL RESEARCH AND PRACTICE

Interventions aimed at behavioural and physiological mechanisms

The present thesis represents a step towards more attention for patient-centred outcomes and their determinants in CHF, as strongly recommended by Krumholz and colleagues [35]. Furthermore, the thesis aimed to initiate prospective research on possible physiological and behavioural mechanisms explaining adverse effects of type-D personality on health outcomes. Apart from self-management and cytokine levels, there is also some evidence that the type-D traits are associated with decreased heart rate variability, increased blood pressure reactivity and increased cortisol production [36-38]. As type-D personality has been associated with increased cortisol and a greater cortisol awakening response, a role for the hypothalamic-pituitary-adrenal (HPA) axis has been proposed [36-38]. Furthermore, a recent study indicated that it is important to give attention to the type-D patient's marital status, as lack of a partner further exacerbated the risk on emotional distress in type-D patients [39].

Further research on this topic of physiological and behavioural mechanisms is recommended, because of its importance for clinical practice. In particular, knowing which mechanisms are at play will provide opportunities for (psychological) intervention in the near future, thereby enhancing secondary prevention in patients with CHF [40]. For instance, in previous research it has been shown that disease management programmes (DMPs) for patients with CHF have beneficial effects on hospital readmission and mortality [41,42]. One crucial component of DMPs is self-management [41,43]. Furthermore, there is also evidence that self-management programmes for CHF patients decrease overall hospital readmissions and readmission for CHF [44]. As pointed out by van der Wal and colleagues, patient-related factors are of importance in compliance, an important aspect of self-management [45]. These authors also state that results of intervention studies on self-

care behaviour are rather inconsistent, probably because of the heterogeneity in content, the difference in disciplines involved and the duration of the intervention [45]. However, it may also be that different patients need different interventions, in other words, that a more personalised approached to the intervention on self-care behaviours is needed. It might be that patients with a type-D personality need another type of intervention than non type-D patients.

Apart from interventions aimed at behavioural mechanisms, attention should also be paid to potential physiological mechanisms. Several studies have focused on effects of psychosocial interventions on immunologic parameters in both healthy and physically ill persons. These studies have yielded inconsistent results. It has been shown that immunologic markers can be influenced by psychological interventions, such as relaxation and mindfulness training [e.g. 46-49]. In one recent study, the effect of a home-based cognitive behavioural intervention on immunologic markers was evaluated in female patients treated with coronary artery bypass (CABG) surgery. It was found that, among depressed post-CABG women, cognitive behavioural intervention positively affected immunological parameters [49]. However, there are also studies indicating no beneficial effect of relaxation training or other psychological interventions on immunologic parameters [e.g. 50,51]. Thus, results on the effect of psychological interventions on immunological functioning are rather inconsistent, although some studies show promising results. Further research is therefore warranted, in particular in the context of type-D personality and immune parameters.

Interventions aimed at type-D personality

Until now, no intervention study has targeted type-D personality and we can only speculate about interventions that may reduce the toxic effects of type-D. However, it is important to emphasise that the fact that type-D refers to a personality construct, does not imply that type-D patients do not benefit from psychological interventions. It may be true that changing personality characteristics is very difficult, but this should not be the primary goal of counselling in the context of type-D; rather health care professionals should be working with type-D patients on changing behaviours and enhancing emotional well-being [52]. In our opinion, efforts should be directed towards high-risk patients such as type-Ds, because this subgroup has a substantial risk of a wide variety of emotional problems and may therefore benefit the most from counselling. Sher has proposed a series of possible interventions for type-D patients, including cognitive behavioural therapy, social skills training, interpersonal

psychotherapy, biofeedback and pharmacological therapy [37]. In our opinion, efforts should especially be concentrated on:

a. Improvement of self-management and self-care abilities.
b. Consolidation of the social network. A supportive, stimulating, social network is of great importance for the socially inhibited type-D patients, because these patients tend to perceive the social world as threatening and stressful. For example, type-D patients fear rejection or disapproval while interacting with other people, although they feel a need for sharing feelings in interpersonal contact.
c. Counselling in order to improve emotional coping and to expand on coping strategies. Type-D patients typically deal with negative emotions by not sharing them with others. Counselling efforts should be directed towards teaching type-D patients other ways to deal with their negative feelings and seek to alter their gloomy view of self and the world.

Specific cognitive behavioural techniques to identify negative and unrealistic thoughts might be very useful. Another promising treatment option for patients with a type-D personality is interpersonal psychotherapy (IPT). IPT is a manualised, time-limited form of psychotherapy, originally designed to treat depression, but nowadays used to treat various forms of psychological distress [53,54]. IPT is a practical, present-oriented treatment with a focus on interpersonal distress, social factors and interpersonal problems. The intervention is tailored to current interpersonal relations and seeks to modify patterns of social dysfunction [53,54]. Empirical data support the efficacy of IPT in the treatment of depression [54,55]. A recent study in elderly depressed patients, for example, showed that IPT was more effective than general practitioners' care [56]. However, another study failed to document a benefit of IPT in comparison with clinical management of depression in patients with CAD [57]. The latter study compared IPT with an intervention of clinical management given by an IPT-focused therapist [57].

Patients with a type-D personality are very much in need for supportive and stimulating interpersonal contacts, because they feel a need to share their negative feelings, emotions and thoughts with others, but refrain from doing it, because they fear disapproval or rejection. Furthermore, this treatment approach might be especially effective in type-D patients with CHF, because, apart from having difficulties in establishing valuable interpersonal relationships because of being a type-D person, the condition of CHF itself may have adverse effects on interpersonal contacts. For example, the disease may go together with changes in social roles

because of physical limitations. In particular, for type-D patients this may be very difficult to manage, leading to increased psychological distress and poor quality of life.

Next to emphasising possible treatment options for patients with a type-D personality, the importance of screening for type-D personality in CHF has also to be stressed. Results from studies such as presented in the present thesis indicate that type-D personality is associated with a broad range of negative health outcomes in patients with CHF. Knowing which individuals are at increased risk for impaired health status, for developing psychological distress and for worse prognosis provides a window of opportunity to intervene at an early stage. Screening patients for type-D personality fits well into the personalised approach to medicine that has recently been advocated [58]. The use of the Type-D Scale as a screening instrument for the influence of psychological and psychosocial factors in clinical practice has also been advocated by others [59].

LIMITATIONS AND STRENGTHS OF THE PRESENT WORK

The work presented in this thesis has some limitations. First, all data were collected at the same hospital, which makes generalisation of the results difficult. Second, not all eligible patients have participated in the studies. Furthermore, study participants were required to visit the outpatient clinic to be included in the study, and hence the sample could be biased by mobility and younger age. Fourth, there were several differences on clinical variables between patients who agreed to participate in the study versus those who declined (see Chapters 4 and 9). Fifth, in some studies, the number of patients was relatively small, which limits the number of variables that could be controlled for in statistical analyses and the generalisation of the results. Next, there is an overlap between symptoms of CHF and some forms of psychological distress, such as symptoms of anxiety. However, we used a clinical interview to measure anxiety and the assessment of anxiety levels was done by experienced health psychologists. Seventh, we had no control group, which is of especial concern in the study presented in Chapter 5.

Despite these limitations, the work presented in this thesis also has a number of strengths. This thesis reported on longitudinal follow-up research, focusing on type-D personality as a determinant of health outcomes in CHF. Most chapters in this thesis were the first in the (psycho) somatic literature on CHF to report on these issues. Furthermore, participants were consecutive unselected outpatients with CHF

and response rates were in general high. Finally, this work also comprised research on mechanisms that may explain the relationship between type-D personality and health outcomes in CHF.

CONCLUDING REMARKS

Apart from focusing on acute and episodic risk factors in heart disease in general, and in CHF in particular, it now seems timely to expand our focus to include also more chronic psychological risk factors. Personality, and more specifically type-D personality, is a potentially important chronic psychological risk factor that may explain substantial individual differences in health outcomes in CAD and CHF. Hence, when studying health outcomes and its determinants in cardiovascular disease (CVD), future research should not only focus on acute and episodic determinants of these outcomes, but also on the role of chronic psychological risk factors.

A challenging task for the near future is designing an intervention for type-D personality. As with many other psychological risk factors, such as depression, it is very unlikely that one specific intervention, or monotherapy, is the solution or the treatment. By analogy, is it very unlikely that type-D personality is the psychosocial risk factor in CVD or CHF. However, type-D personality can be seen as an umbrella, capturing several psychological risk factors in heart disease, thereby increasing the risk on negative health outcomes. Thus, focusing on personality as a determinant of health outcomes entails focusing on (1) chronic emotional distress in addition to episodic distress, and on (2) clustering of risk factors instead of focusing on single risk factors [60-62]. The findings presented in this thesis indicate that type-D personality is of special interest in the context of CHF.

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CHAPTER 11

Nederlandse samenvatting (summary in Dutch)

DE EPIDEMIE VAN CHRONISCH HARTFALEN

Hart- en vaatziekten zijn een belangrijke doodsoorzaak, niet alleen in Nederland, maar wereldwijd. Chronisch hartfalen (CHF), het best te omschrijven als een klinisch syndroom dat bestaat uit een combinatie van klachten die het gevolg zijn van een tekortschietende pompfunctie van het hart, is het eindstadium van verschillende vormen van hart- en vaatziekten en gaat gepaard met een hoge mortaliteit. In 2004 overleden in Nederland 5,624 patiënten aan CHF, wat neerkomt op 12% van de totale mortaliteit voor hart- en vaatziekten in Nederland in dat jaar. In het Verenigd Koninkrijk waren de mortaliteitscijfers voor 2,445 patiënten opgenomen met CHF in 2000, 37.3%, 52.9% en 78.5%, respectievelijk 1, 2 en 5 jaar na ontslag uit het ziekenhuis. In de Verenigde Staten nam de mortaliteit voor CHF tussen 1994 en 2004 toe met 28%. De ziekenhuisopnames voor CHF stegen in diezelfde periode met 175%.

Omdat er sprake is van vergrijzing, mensen vaker een hartinfarct overleven en hoge bloeddruk vaker voorkomt, neemt de incidentie en prevalentie van CHF toe. Daardoor is er inmiddels sprake van een wereldwijde hartfalenepidemie. Een grote Nederlandse studie uit 2004 rapporteerde prevalentiecijfers van 6.4% (1997), 6.7% (1998) en 7.0% (1999). Dezelfde studie vermeldde een incidentie van 14.4/1000 personen-jaar. De Nederlandse Hartstichting vermeldde een prevalentie van 163,800-176,400 en een incidentie van 37,400-43,400 in Nederland in het jaar 2000. Naast een slechte prognose, gaat CHF ook gepaard met een verminderde levenskwaliteit en gezondheidstoestand.

PSYCHOLOGISCHE RISICOFACTOREN EN TYPE-D PERSOONLIJKHEID

Inmiddels is er in wetenschappelijk onderzoek meer aandacht voor de rol van psychologische en psychosociale factoren bij hart- en vaatziekten in het algemeen. Echter, dit onderzoek richt zich, ook bij CHF, vooral op depressie als risicofactor voor bijvoorbeeld een verminderde prognose of levenskwaliteit, waardoor andere belangrijke psychologische variabelen over het hoofd kunnen worden gezien. Psychologische risicofactoren kunnen ingedeeld worden in (1) acute, (2) episodische en (3) chronische risicofactoren. Depressie is een voorbeeld van een episodische risicofactor, die gedurende een periode van een aantal maanden tot maximaal twee jaar invloed uitoefent. Een chronische risicofactor echter heeft een impact van langer

dan twee jaar. Persoonlijkheid, het geheel van stabiele gedragingen en affecten van een persoon, is een voorbeeld van een chronische risicofactor.

Onderzoek naar de relatie tussen persoonlijkheid en negatieve gezondheidsuitkomsten, zoals een verminderde levenskwaliteit en gezondheidstoestand, psychologische problematiek (zoals angst en depressie) en verhoogde mortaliteit heeft de laatste jaren in toenemende mate aandacht gekregen bij patiënten met coronair hartlijden. Echter, bij patiënten met CHF is bovengenoemde relatie tussen een chronische psychologische risicofactor en gezondheidsuitkomsten nog nauwelijks onderzocht. Onderzoek naar patiëntgerichte ("patient-centred") uitkomsten, zoals gezondheidstoestand, en de determinanten wordt door een aantal auteurs echter sterk aanbevolen.

In dit proefschrift is de relatie tussen de type-D, ofwel de distressed, persoonlijkheid en gezondheidsuitkomsten, zoals een aangetaste gezondheidstoestand, angst, depressie, maar ook een verslechterde prognose, bij patiënten met CHF onderzocht. Het type-D persoonlijkheidsconstruct bestaat uit twee stabiele en niet-psychopathologische persoonlijkheidstrekken, namelijk negatieve affectiviteit en sociale inhibitie. Mensen met een type-D persoonlijkheid hebben de neiging om een keur aan negatieve gevoelens te ervaren en een negatieve kijk op de wereld, anderen en zichzelf te hebben (negatieve affectiviteit). Tegelijkertijd zijn ze geneigd om deze negatieve gevoelens niet te delen met anderen, terwijl ze dit wel zouden willen, uit angst voor afkeuring of kritiek (sociale inhibitie). Onderzoek bij patiënten met coronair hartlijden heeft uitgewezen dat patiënten met een type-D persoonlijkheid een hoger risico hebben om vroegtijdig te overlijden, en een verminderde levenskwaliteit en meer psychologische problematiek te ervaren.

Zoals al vermeld, is er nog tot heden geen studie gepubliceerd die zich richt op de relatie tussen type-D persoonlijkheid en gezondheidsuitkomsten bij patiënten met CHF. Ook over mogelijke mechanismen die negatieve effecten van type-D persoonlijkheid op gezondheidsuitkomsten zouden kunnen verklaren is weinig bekend. Dit proefschrift had derhalve tot doel om de impact van type-D persoonlijkheid op patiëntgerichte uitkomsten bij patiënten met CHF na te gaan. Een tweede focus lag op het exploreren van mechanismen die mogelijke negatieve effecten van type-D persoonlijkheid op gezondheidsuitkomsten zouden kunnen verklaren en op de relatie tussen type-D persoonlijkheid en mortaliteit bij CHF.

SAMENVATTING VAN DE BELANGRIJKSTE RESULTATEN VAN DIT PROEFSCHRIFT

DEEL A

Type-D persoonlijkheid als voorspeller van patiëntgerichte uitkomsten bij CHF

In dit proefschrift is, met uitzondering van Hoofdstuk 3, een longitudinale follow-up studie bij patiënten met CHF beschreven. Alle patiënten die aan deze studie deelnamen, zijn afkomstig van de polikliniek cardiologie van het TweeSteden ziekenhuis in Tilburg. Nadat eerst een algemene inleiding is gegeven op het proefschrift (Hoofdstuk 1), is dieper ingegaan op de kenmerken van type-D persoonlijkheid en welke onderzoeksresultaten er zijn (Hoofdstuk 2). Vervolgens richtte het eerste deel van dit proefschrift (deel A) zich op de relatie tussen type-D persoonlijkheid en gezondheidstoestand, klachtenniveau, stemmingstoestand en angst hij patiënten met CHF (Hoofdstuk 3-6).

In Hoofdstuk 3 is ingegaan op de relatie tussen type-D persoonlijkheid enerzijds, en gezondheidstoestand, depressieve symptomen en stemmingstoestand anderzijds. Deze cross-sectionele studie bij 84 patiënten liet een significante relatie zien tussen type-D persoonlijkheid en de genoemde uitkomstmaten. Wanneer er in de analyses gecorrigeerd werd voor belangrijke ziektekenmerken (zoals pompfunctie van het hart), etiologie van het hartfalen, leeftijd en geslacht, bleef type-D persoonlijkheid geassocieerd met een verminderde gezondheids- en stemmingstoestand, en toegenomen depressieve symptomen.

In Hoofdstuk 4 is bovengenoemde studie gerepliceerd in een grotere steekproef en in een longitudinale studieopzet. Bij 166 hartfalenpatiënten werd zowel ziektespecifieke als generieke gezondheidstoestand gemeten bij inclusie en 12 maanden later. Hoewel de ziektespecifieke en mentale gezondheidstoestand over de tijd heen verbeterde, rapporteerden type-D patiënten een verminderde ziektespecifieke en mentale gezondheidstoestand in vergelijking tot niet type-Ds. Ook patiënten die verhoogd scoorden op depressieve gevoelens rapporteerden een lagere gezondheidstoestand dan patiënten die niet verhoogd scoorden op depressie. Type-D persoonlijkheid bleek in deze studie een significante en onafhankelijke voorspeller van verminderde ziektespecifieke en mentale gezondheidstoestand, ook wanneer gecontroleerd werd voor depressieve gevoelens, baseline gezondheidstoestand, medicatie en belangrijke ziektekenmerken. Ook depressieve

gevoelens bleek een onafhankelijke voorspeller van verminderde gezondheidstoestand te zijn. In deze studie was type-D persoonlijkheid echter geen significante voorspeller voor fysieke gezondheidstoestand, waarschijnlijk omdat de fysieke gezondheidstoestand vooral door de ernst van het hartfalen werd bepaald.

In Hoofdstuk 5 is nagegaan of 31 CHF patiënten die behandeld werden met een biventriculaire pacemaker (resynchronisatie therapie) verbeterden in gezondheidstoestand, klachtenniveau, waargenomen onvermogen en functionele capaciteit over een periode van twee maanden. In het algemeen was er een verbetering over de tijd op de genoemde uitkomstmaten. Echter, patiënten die verhoogd scoorden op negatieve affectiviteit, een van de persoonlijkheidstrekken waaruit het type-D construct bestaat, bleken een lagere gezondheidstoestand en meer symptomen en waargenomen onvermogen te rapporteren dan patiënten die laag scoorden op negatieve affectiviteit, zowel voor als na implantatie van de pacemaker.

In het laatste hoofdstuk van het eerste deel van dit proefschrift, Hoofdstuk 6, is de relatie tussen type-D persoonlijkheid en klinisch relevante angst (gemeten met een interview) nagegaan. CHF patiënten ($n=149$) vulden de DS14 (Type-D Schaal) in op baseline. Een jaar later werd bij deze patiënten een klinisch interview afgenomen om het angstniveau vast te stellen. Type-D persoonlijkheid bleek klinisch relevante angst significant te voorspellen, ook wanneer er werd gecontroleerd voor depressieve gevoelens, angstgevoeligheid ("anxiety sensitivity"), socio-demografische kenmerken en kenmerken van het hartfalen, zoals de pompfunctie van het hart.

DEEL B

Type-D persoonlijkheid als voorspeller van prognose in CHF en mechanismen in de gevonden relaties tussen type-D en gezondheidsuitkomsten

Het tweede deel van dit proefschrift (deel B) richtte zich op de relatie tussen type-D persoonlijkheid en mortaliteit, en mogelijke mechanismen die de gevonden negatieve verbanden tussen type-D persoonlijkheid en gezondheidsuitkomsten zouden kunnen verklaren.

In Hoofdstuk 7 is de relatie tussen type-D persoonlijkheid en zelfzorgvaardigheden bij 178 patiënten met CHF beschreven. Specifiek werd aandacht besteed aan consultatiegedrag als een afzonderlijke aspect van zelfzorg. De studie liet zien dat patiënten met een type-D persoonlijkheid geneigd zijn hun arts of

verpleegkundige minder vaak te consulteren dan niet type-D patiënten, terwijl ze wel meer gezondheidsklachten rapporteerden en zich daar ook zorgen over maakten. Type-D patiënten hadden dus een grotere kans op het ervaren van relevante klachten, het zich daarover zorgen maken, maar tegelijkertijd niet de arts of verpleegkundige raadplegen. Deze studie was de eerste studie die aangeeft dat verminderde zelfzorg, en dan meer specifiek verminderd consultatiegedrag, een gedragsmatig mechanisme zou kunnen zijn in de relatie tussen type-D persoonlijkheid en negatieve gezondheidsuitkomsten.

Hoofdstuk 8 exploreerde de relatie tussen type-D persoonlijkheid en chronische nierziekte enerzijds, en cytokines anderzijds bij 125 patiënten met CHF. Cytokines zijn proteïnen, zogenaamde "boodschapperstoffen" van het immuunsysteem, vergelijkbaar met hormonen, die een rol spelen in de immuunafweer. Uit de prospectieve studie beschreven in Hoofdstuk 8 bleek dat type-D persoonlijkheid en chronische nierziekten voorspellend waren voor toegenomen pro-inflammatoire cytokinewaarden en afgenomen anti-inflammatoire cytokinewaarden. De effecten van type-D persoonlijkheid waren vergelijkbaar met de effecten die chronische nierziekte had. Deze studie was de eerste prospectieve studie naar de relatie tussen type-D persoonlijkheid en chronische nierziekten enerzijds, en verstoorde balans tussen pro- en anti-inflammatoire cytokines anderzijds. Cytokines zouden dan ook een fysiologisch mechanisme kunnen zijn in de gevonden relaties tussen type-D persoonlijkheid en mortaliteit.

In Hoofdstuk 9 worden de resultaten gerapporteerd van een eerste studie naar de relatie tussen type-D persoonlijkheid en cardiale prognose bij CHF patiënten. Type-D persoonlijkheid bleek een significante voorspeller voor late cardiale mortaliteit (6 maanden of langer na inclusie) bij CHF, ook wanneer er gecontroleerd werd voor pompfunctie van het hart, leeftijd en geslacht, maar niet voor vroege cardiale mortaliteit (binnen 6 maanden na inclusie). De relatie tussen type-D persoonlijkheid en totale cardiale mortaliteit was rand-significant na controle voor de eerder genoemde variabelen. Omdat de steekproef in deze studie relatief klein was en de follow-up periode relatief kort, worden studies naar de replicatie van deze bevindingen aanbevolen.

Hoofdstuk 10 van dit proefschrift omvat een algemene discussie en samenvatting, waarin de belangrijkste bevindingen van dit proefschrift zijn geïntegreerd. Implicaties voor toekomstig wetenschappelijk onderzoek en voor de klinische praktijk zijn beschreven en de sterke en zwakke punten van de studies worden genoemd.

In de Appendix tenslotte, is een Nederlandstalig artikel over de kenmerken van en het onderzoek naar type-D persoonlijkheid opgenomen.

AFSLUITENDE OPMERKINGEN EN CONCLUSIES

Concluderend kan gesteld worden dat uit de studies beschreven in dit proefschrift is gebleken dat type-D persoonlijkheid een belangrijke chronische psychologische risicofactor is, die voorspellend is voor negatieve gezondheidsuitkomsten bij CHF. In navolging van eerder onderzoek verricht bij patiënten met coronair hartlijden, bleek het type-D persoonlijkheidsconstruct, dan wel negatieve affectiviteit als belangrijke component van het type-D persoonlijkheidstype, voorspellend voor een verminderde generieke en ziektespecifieke gezondheidstoestand, verhoogde niveaus van psychologische problematiek, verhoogde klachtenniveaus, meer ervaren onvermogen en een verminderde cardiale (lange termijn) prognose bij patiënten met CHF. Tevens bleek type-D persoonlijkheid geassocieerd met verminderde zelfzorg, meer specifiek met verminderd consultatiegedrag, en verstoringen in de balans tussen pro- en anti-inflammatoire cytokines. Verminderde zelfzorg en een verstoorde cytokinebalans zouden mogelijke verklarende mechanismen kunnen zijn in de gevonden negatieve relaties tussen type-D en gezondheidsuitkomsten.

Dit proefschrift is een eerste aanzet tot meer aandacht voor (1) patiëntgerichte uitkomsten bij CHF, (2) chronische psychologische risicofactoren als belangrijke determinanten van gezondheidsuitkomsten en (3) verder onderzoek naar mechanismen die de gevonden negatieve relaties tussen type-D persoonlijkheid en gezondheidsuitkomsten zouden kunnen verklaren. Het gegeven dat type-D persoonlijkheid dus niet alleen een belangrijke psychologische risicofactor is bij coronair lijden, maar ook bij CHF, vaak een laatste fase in het proces van een hartziekte, is indicatief voor de stabiliteit van het construct.

In de klinische praktijk is het van belang om patiënten die een verhoogd risico lopen op negatieve gezondheidsuitkomsten vroeg te identificeren. Deze patiënten verdienen, naast optimale farmacologische behandeling, extra aandacht in de vorm van psychosociale begeleiding of behandeling. Tot nu toe is er nog geen interventiestudie verricht naar type-D persoonlijkheid. Het ontwikkelen van interventies gericht op type-D persoonlijkheid is dan ook een belangrijke volgende stap.

APPENDIX

Type-D gaat je aan het hart

Angélique A. Schiffer[ab], Aline J. Pelle[b] en Ankie. M. Tobben[a]

[a]Afdeling Cardiologie/Psychologie TweeSteden Ziekenhuis, Tilburg, Nederland
[b]CoRPS – Center of Research on Psychology in Somatic diseases, Universiteit van Tilburg, Tilburg, Nederland

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De laatste jaren wordt in wetenschappelijk onderzoek steeds meer aandacht besteed aan psychosociale factoren bij hartaandoeningen. Meer en meer blijkt dat zij een belangrijke rol spelen. Echter, de rol van persoonlijkheid is, na inconsistentie in onderzoeksresultaten rondom Type A "persoonlijkheid", in de vergeethoek geraakt. Type-D persoonlijkheid heeft onderzoek naar de relatie tussen persoonlijkheidstrekken en hart- en vaatziekten een nieuwe impuls gegeven.

Nog steeds gelden hart- en vaatziekten, met 45.000 gevallen van overlijden per jaar, als doodsoorzaak nummer één in Nederland [1]. Maar niet alleen de prognose is slecht, ook is bij hart- en vaatziekten sprake van een verminderde kwaliteit van leven [o.a. 2]. Psychologische factoren worden geassocieerd met zowel een slechtere prognose als met verminderde levenskwaliteit bij hart- en vaatziekten [3,4]. De nadruk in wetenschappelijk onderzoek op dit terrein ligt veelal op het verband tussen depressiviteit enerzijds en prognose en levenskwaliteit anderzijds [5]. Daardoor kunnen andere psychologische factoren, zoals persoonlijkheid, over het hoofd worden gezien. Dit artikel geeft een overzicht van wetenschappelijk onderzoek verricht naar de rol van de "distressed", ofwel type-D persoonlijkheid, op het gebied van hart- en vaatziekten.

DEFINITIE EN ASSESSMENT

Type-D persoonlijkheid bestaat uit twee stabiele en niet-psychopathologische persoonlijkheidstrekken, namelijk negatieve affectiviteit en sociale inhibitie [6-8]. Negatieve affectiviteit is de neiging om in verschillende situaties negatieve emoties te ervaren, terwijl sociale inhibitie de neiging reflecteert om deze negatieve emoties te onderdrukken en niet te uiten in sociale interacties uit angst voor kritiek of afwijzing door anderen [6]. Kortom, type-Ds maken zich veel zorgen, hebben een negatieve kijk op het leven, voelen zich vaak neerslachtig en gespannen, zijn verhoogd geïrriteerd en ervaren minder vaak positieve gemoedstoestanden. Deze negatieve gevoelens worden niet snel geuit in aanwezigheid van anderen, uit angst voor sociale afkeuring of kritiek.

Type-D persoonlijkheid komt relatief veel voor. In West-Europa ligt de prevalentie tussen de 13% en 32.5% in de algemene populatie [6,9-11]. De prevalentie type-D bij patiënten met hart- en vaatziekten ligt tussen de 26% en 53% [6,7,12].

De oorsprong van Type-D ligt in de klinische setting. Bij evaluatie van een hartrevalidatieprogramma viel op dat niet alle deelnemers evenveel baat hadden bij

de interventie. Deze impressie werd onderbouwd met het gegeven dat emotionele distress bijdraagt aan de progressie van hart- en vaatziekten [o.a. 13] én de notie dat emotionele distress veelal ontstaat vanuit persoonlijkheidskenmerken [14,15]. Vanuit gevestigde persoonlijkheidstheorieën werden specifieke kenmerken geselecteerd [16] en de prognostische waarde van type-D persoonlijkheid werd empirisch aangetoond voor patiënten met coronair lijden [14,17].

Persoonlijkheid is een product van zowel omgevings- als erfelijkheidsfactoren. Tweelingenonderzoek naar persoonlijkheidstrekken, zoals neuroticisme, toonde aan dat deze karaktertrek voor ongeveer 50% erfelijk bepaald is [18]. De overige 50% van persoonlijkheidstrekken kan worden toegeschreven aan omgevingsfactoren, zoals opvoeding. Ook type-D persoonlijkheid bevat, conform andere persoonlijkheidstrekken, een belangrijke erfelijkheidscomponent (52%) [19].

Type-D persoonlijkheid is goed te onderscheiden van depressiviteit. Op de eerste plaats omvat het type-D construct een coping-aspect: met negatieve gevoelens wordt omgegaan door deze op te kroppen [20]. Op de tweede plaats is negatieve affectiviteit (zoals verhoogde irritatie, piekeren) kenmerkend voor type-D, terwijl bij depressie neerslachtigheid of depressief affect het kenmerkende symptoom is. Op de derde plaats geldt type-D persoonlijkheid als een stabiel, niet-psychopathologisch persoonlijkheidsconstruct en is het geen toestandsbeeld, zoals depressie dat wel is [6,21].

De aanwezigheid van type-D persoonlijkheid kan eenvoudig vastgesteld worden. Denollet ontwikkelde hiervoor een korte, voor de patiënt gemakkelijk en snel (3 tot 5 minuten) in te vullen vragenlijst, de DS14 (Type-D Schaal) [6]. De lijst omvat twee maal zeven vragen, die respectievelijk de persoonlijkheidstrekken negatieve affectiviteit en sociale inhibitie meten, en op een 5-punts antwoordschaal beantwoord worden [6]. Voorbeelden van items zijn: "ik maak me dikwijls zorgen" (negatieve affectiviteit) en "ik ben een gesloten persoon" (sociale inhibitie). Patiënten die op beide schalen tien of meer punten scoren, worden geclassificeerd als type-D. De DS14 heeft uitstekende psychometrische kwaliteiten (Cronbach's α =0.88/0.86; test-hertest betrouwbaarheid =0.72/0.82, voor respectievelijk de negatieve affectiviteit en sociale inhibitie schaal) [6].

TYPE A, TYPE-D.....IS ER EEN VERSCHIL?

Eén van de mogelijke redenen waarom persoonlijkheid relatief weinig onderzocht is in relatie tot hart- en vaatziekten is de inconsistentie in onderzoeksbevindingen rondom de Type A "persoonlijkheid" [21]. Friedman en Rosenman herleidden Type A van klinische observaties en indrukken, en definieerden het construct als "an action-emotion complex that can be observed in any person who is aggressively involved in a chronic, incessant struggle to achieve more and more in less and less time, and if required to do so, against the opposite efforts of other things and other persons" [22]. Mensen die Type A gedrag vertonen zijn competitief, zeer nauw betrokken bij hun werk, ongeduldig, agressief, vijandig en hebben een continu gevoel van gehaastheid en tijdsdruk [4,23]. Over het verband tussen Type A gedrag en het risico op hart- en vaatziekten zijn inconsistente onderzoeksbevindingen gepubliceerd. Werden er eerst verbanden aangetoond, in latere studies werden deze niet gerepliceerd [24,25]. Een mogelijke verklaring voor deze inconsistentie ligt wellicht in zogenaamde "derde variabelen", zoals sociale steun [4]. Tevens leidden de inconsistente bevindingen tot de veronderstelling dat niet het complete Type A gedragspatroon, maar specifieke componenten hieruit, met name vijandigheid (hostiliteit), een negatieve invloed hebben op het ontstaan van hart- en vaatziekten [26].

De term "Type A persoonlijkheid" is in feite incorrect, aangezien het hier niet gaat om de beschrijving van een persoonlijkheidsconstruct, maar om een beschrijving van een gedragspatroon [27]. Er dient daarom gesproken te worden van het Type A gedragspatroon en we kunnen concluderen dat bepaalde gedragscomponenten uit het Type A gedragspatroon samen lijken te hangen met het risico op het ontwikkelen van hart- en vaatziekten. Het type-D construct daarentegen is, zoals eerder beschreven, niet ontwikkeld als gedragspatroon, maar als persoonlijkheidsconstruct met fundering in bestaande persoonlijkheidstheorieën [14,17]. Het verschil met het Type A gedragspatroon is dat type-D een afgebakende groep mensen definieert, namelijk de mensen die veel negatieve gevoelens ervaren en deze niet uiten wanneer ze in gezelschap zijn, terwijl Type A, een verzamelnaam voor verscheidene gedragingen, een meer heterogeen construct is [21].

TYPE-D PERSOONLIJKHEID EN HARTZIEKTEN

De laatste jaren zijn onderzoeksbevindingen gepubliceerd waaruit blijkt dat type-D persoonlijkheid samenhangt met verschillende negatieve uitkomsten bij patiënten met

een hartaandoening. Verschillende groepen hartpatiënten zijn onderzocht. In deze paragraaf wordt een overzicht gegeven van de voornaamste onderzoeksbevindingen. In Tabel 1 wordt, in chronologische volgorde van verschijningsdatum van de studies, aangegeven welke studies besproken worden.

Type-D persoonlijkheid is verschillende malen in verband gebracht met een verhoogd risico op mortaliteit bij hartziekten. Zo werd in een studie uit 1996 aangetoond dat coronair patiënten met een type-D persoonlijkheid een beduidend groter risico op overlijden hadden dan niet type-Ds, na statistische controle voor biomedische risicofactoren [8]. Zoals weergegeven in Figuur 1, was type-D persoonlijkheid een voorspeller van mortaliteit, onafhankelijk van ejectiefractie (pompfunctie van het hart) en vernauwingen in meerdere kransslagaders.

Voorts bleek type-D persoonlijkheid mortaliteit of een niet-fataal myocard infarct over 6 tot 10 jaar te voorspellen [28]. In een studie uit 2000 bij 319 coronair patiënten toonden Denollet en collega's aan dat type-D persoonlijkheid, samen met jongere leeftijd en een verminderde pompfunctie van het hart, een onafhankelijke voorspeller voor prognose over 5 jaar was [7]. In een recente studie werd aangetoond dat type-D een onafhankelijke voorspeller was van het gecombineerde eindpunt "mortaliteit, non-fataal hartinfarct en bypassoperatie/dotterprocedure" [29]. Type-D patiënten uit een hartrevalidatieprogramma bleken, bezien over een periode van 5 jaar, een bijna driemaal zo groot risico te lopen op het genoemde eindpunt dan niet type-Ds. Type-D persoonlijkheid bleek voorts ook bij patiënten die gedotterd waren gerelateerd aan een vijfmaal groter risico op overlijden of het optreden van een hartinfarct wanneer statistisch gecontroleerd werd voor geslacht, leeftijd, eerdere bypassoperatie, stent[1]-type, en de interactie persoonlijkheid * stent-type [30]. Denollet en collega's [31] bekeken in een volgende studie in dezelfde patiëntengroep specifiek de rol van de sociale inhibitie component. Uit de studie bleek dat het interactie-effect negatieve affectiviteit * sociale inhibitie (type-D) negatief gerelateerd was aan prognose. Te concluderen valt dan ook dat niet enkel negatieve affectiviteit het negatieve effect op mortaliteit verklaart, maar dat juist het gecombineerde effect met sociale inhibitie van cruciaal belang is [31].

Naast de genoemde verbanden tussen type-D en "harde" uitkomsten als mortaliteit, zijn er ook studies in verschillende groepen hartpatiënten, die verbanden

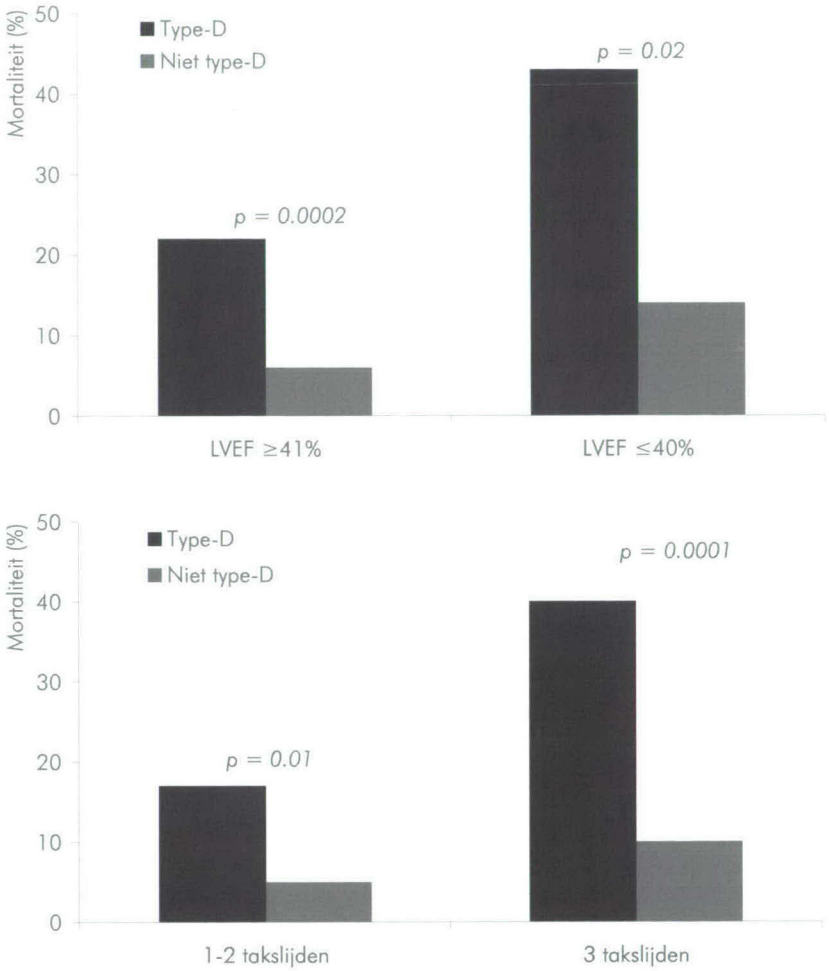
[1] *een stent is een metalen veertje dat ingebracht wordt in een slagder bij een dotteringreep en tot doel heeft de plaque, die door de dotteringreep opzij is geduwd, op zijn plaats te houden.*

Tabel 1: Type-D persoonlijkheid en negatieve uitkomsten bij hart- en vaatziektenpatiënten

Auteur	*Steekproef*	*Studie design*	*Eindpunt*	*Risico*
Denollet et al. (1996)	*303 coronair patiënten*	*prospectief*	*mortaliteit*	*OR= 4.1*
Denollet & Brutsaert (1998)	*87 coronair patiënten*	*prospectief*	*cardiale mortaliteit hartinfarct*	*RR= 4.7*
Denollet et al. (2000)	*319 coronair patiënten*	*prospectief*	*cardiale mortaliteit hartinfarct*	*OR= 8.9*
Denollet et al. (2000)	*104 coronair patiënten*	*prospectief*	*KvL*	*OR= 2.2*
Pedersen & Middel (2001)	*171 coronair patiënten*	*interventiestudie*	*vitale uitputting*	*OR= 4.7-6.4*
Pedersen et al. (2004)	*875 PCI patiënten*	*prospectief*	*mortaliteit hartinfarct*	*OR= 5.3*
Pedersen et al. (2004)	*182 ICD patiënten 144 partners*	*cross-sectioneel*	*angst/depressie*	*OR= 4.4-8.7*
Al-Ruzzeh et al. (2005)	*437 CABG patiënten*	*cross-sectioneel*	*KvL*	*OR= 2.3-5.5*
Schiffer et al. (2005)	*84 CHF patiënten*	*cross-sectioneel*	*KvL/depressie*	*OR= 3.3-7.1*
Denollet et al. (2006)	*337 coronair patiënten*	*prospectief*	*cardiaal incident**	*OR= 2.9*
Denollet et al. (2006)	*875 PCI patiënten*	*prospectief*	*cardiale mortaliteit hartinfarct*	*HR= 1.9*
Pedersen et al. (2006)	*542 PCI patiënten zonder depressie*	*prospectief*	*depressie*	*OR= 3.0*

KvL=Kwaliteit van leven; PCI=Percutaneous coronary intervention; ICD=Implantable cardioverter defibrillator; CABG=Coronary artery bypass graft surgery; CHF=Chronisch hartfalen; OR=Odds ratio; RR=Relative risk; HR=Hazard ratio.

**cardiale mortaliteit, myocard infract, PCI, CABG*



Figuur 1. Mortaliteit opgesplitst naar pompfunctie en type-D persoonlijkheid (boven), en kransslagaderlijden en type-D persoonlijkheid (onder)

aantonen tussen type-D persoonlijkheid en kwaliteit van leven of andere psychologische uitkomstmaten. Zo werd er een verband tussen type-D en verminderde kwaliteit van leven bij coronair patiënten aangetoond [7]. Type-D persoonlijkheid bleek binnen de groep coronair lijders ook gerelateerd aan vitale

uitputting. Type-Ds rapporteerden meer symptomen van vitale uitputting (dat wil zeggen uitgesproken vermoeidheid, verhoogde geïrriteerdheid en een gevoel van demoralisatie) dan niet type-D patiënten [32,33]. Bij patiënten die een bypassoperatie hadden ondergaan, bleek type-D een jaar na de ingreep gerelateerd aan een verminderde fysieke en mentale kwaliteit van leven [34]. In een groep van patiënten met chronisch hartfalen was type-D geassocieerd met een verminderde kwaliteit van leven en met toegenomen depressieve symptomen [12]. Ook uit een studie bij patiënten bij wie een defibrillator (ICD) geïmplanteerd was en hun partners, bleek dat type-D persoonlijkheid een belangrijke verklarende factor was voor het optreden van angstige en depressieve gevoelens bij zowel de patiënt als bij de partner [35]. In een recente studie uitgevoerd bij patiënten die een dotterprocedure hadden ondergaan, bleek type-D persoonlijkheid, samen met diabetes mellitus, een risicofactor voor het ontwikkelen van depressieve symptomen een jaar na de interventie [36].

Binnen de hart- en vaatziektenpopulatie is type-D persoonlijkheid dus herhaaldelijk in verband gebracht met een verhoogd risico op mortaliteit, een verminderde kwaliteit van leven en emotionele problemen.

TYPE-D PERSOONLIJKHEID IN ANDERE PATIËNTENGROEPEN

Hoewel het type-D construct voornamelijk onderzocht is bij patiënten met hartziekten, is eveneens onderzoek gedaan in andere patiëntenpopulaties. In een case-control studie van Aquarius en collega's [9] is nagegaan of type-D persoonlijkheid invloed had op de kwaliteit van leven van patiënten met perifeer vaatlijden, en of deze invloed los stond van de ernst van de ziekte. Uit de studie bleek dat de ernst van het perifeer vaatlijden niet samenhing met kwaliteit van leven, maar in de steekproef van patiënten met perifeer vaatlijden werd wel een minder goede kwaliteit van leven gerapporteerd dan in de gezonde controlegroep. Daarnaast werd er door type-Ds een minder goede kwaliteit van leven gerapporteerd dan door niet type-Ds, zowel in de "zieke" groep als in de gezonde controle groep. Na statistische controle voor de aanwezigheid of afwezigheid van perifeer vaatlijden, bleef type-D persoonlijkheid geassocieerd met een verminderde kwaliteit van leven, waarbij type-Ds een meer dan zevenmaal verhoogd risico hadden op een aangetaste levenskwaliteit dan niet-type-Ds (OR=7.4) [9].

Denollet [6] vond een hoge prevalentie (53%) type-D bij patiënten met hypertensie. In een andere studie werd gevonden dat type-Ds in vergelijking met niet

type-Ds een sterkere bloeddrukreactiviteit hadden [37], maar verder onderzoek naar type-D en hypertensie is nog niet verricht.

Onderzoek naar type-D persoonlijkheid binnen andere patiëntenpopulaties zal in de toekomst verdere aandacht krijgen.

VERKLARENDE MECHANISMEN

Het onderzoek naar type-D persoonlijkheid begint zich meer en meer te richten op "verklaringen". Hoe kunnen de aangetoonde verbanden tussen type-D en allerlei negatieve gezondheidsuitkomsten verklaard worden? Meer duidelijkheid over onderliggende fysiologische en gedragsmatige mechanismen is een belangrijke stap op weg naar mogelijke behandeling van type-D persoonlijkheid.

Op de eerste plaats wordt een rol voor de hypothalamic-pituitary-adrenal-(HPA)as verondersteld [38]. De hypothalamus stimuleert de hypofyse bij confrontatie met stress. De hypofyse scheidt adrenocorticotroop hormoon (ACTH) uit en prikkelt hiermee de bijnierschors om cortisol af te scheiden. Bij langdurige stress worden er aldus grote hoeveelheden van het hormoon cortisol uitgescheiden, waardoor allerlei negatieve gevoelens in de hand worden gewerkt [39]. De beide persoonlijkheidstrekken waaruit type-D bestaat, negatieve affectiviteit en sociale inhibitie, bleken in een studie uit 2003 geassocieerd met verhoogde cortisolspiegels [37].

Ten tweede geeft onderzoek aanwijzingen voor een mogelijk verband tussen type-D en cytokines [40,41]. Cytokines zijn boodschapperstoffen van het immuunsysteem, vergelijkbaar met hormonen. Een cytokine is een proteïne, die een rol speelt in de immuunafweer. Er bestaan verschillende soorten cytokines, die door verschillende soorten lichaamscellen worden geproduceerd en ook werken op verschillende lichaamscellen. Bij patiënten met chronisch hartfalen worden verhoogde cytokinewaarden geassocieerd met een verslechterde prognose [42]. Vanuit deze onderzoeksbevinding formuleerden Denollet en collega's [41] en Conraads en collega's [40] de hypothese dat de verhoogde cytokinewaarden bij chronisch hartfalenpatiënten samenhingen met type-D [40,41]. Uit de genoemde studies bleek inderdaad dat type-D persoonlijkheid onafhankelijk geassocieerd was met de cytokinesoort TNF-α en diens receptoren [40,41].

Op de derde plaats zijn er aanwijzingen voor een verband tussen respectievelijk negatieve affectiviteit en sociale inhibitie, en afgenomen variabiliteit in de hartslag bij gezonde mannen [37].

Tenslotte wordt er een relatie verondersteld met gedragsfactoren. Hoewel nog geen onderzoek hiernaar verricht is, is het denkbaar dat type-D persoonlijkheden minder trouw zijn aan medicatievoorschriften, bezoeken aan de medisch specialist en dergelijke. Bovendien zou type-D persoonlijkheid kunnen samenhangen met ongezonde leefgewoonten als roken en weinig bewegen. Uit eerder onderzoek is bekend dat verschillende psychologische en psychosociale risicofactoren geassocieerd zijn met inadequaat gebruik van medische middelen, zoals bijvoorbeeld vertraagd hulp zoeken voor serieuze symptomen en slechte opkomst bij hartrevalidatieprogramma's [43,44]. Dergelijke risicofactoren kunnen een belemmering vormen voor het aannemen van een gezonde leefstijl en het vasthouden hiervan [45]. De veronderstelling is dat dit ook voor type-D persoonlijkheid geldt. Overigens toont een recente studie aan dat chronisch hartfalenpatiënten met een type-D persoonlijkheid de neiging hebben hun klachten, waarover ze zich wel grote zorgen maken, niet te melden aan hun arts of hartfalenverpleegkundige. Deze slechte zelfzorg zou ook een mechanisme kunnen zijn dat de relatie tussen type-D, en verslechterde prognose en verhoogde morbiditeit mede verklaard [46].

Concluderend kan gesteld worden dat er nog weinig bekend is over de fysiologische en gedragsmatige mechanismen die de in onderzoek aangetoonde verbanden tussen type-D en negatieve uitkomsten verklaren. Onderzoek in de nabije toekomst zal zich dan ook hierop dienen te richten.

DE KLINISCHE PRAKTIJK

Voor de klinische praktijk zijn de behandelingsmogelijkheden van type-D patiënten met hart- en vaatziekte van belang. Verschillende psychologische en psychosociale factoren kunnen de ontwikkeling en het beloop van coronaire hartziekten negatief beïnvloeden [4,43,44,47-49]. Aangezien uit onderzoek is gebleken dat type-D persoonlijkheid een belangrijke risicofactor is voor verhoogde mortaliteit en morbiditeit, aangetaste kwaliteit van leven en verhoogde kans op emotionele problemen, is het een psychologische risicofactor waarmee rekening gehouden dient te worden. Vroegtijdig opsporen van die patiënten met een type-D persoonlijkheid en het bieden van extra aandacht, steun en begeleiding is van belang. De gedachte dat iemands persoonlijkheid toch niet te veranderen is en dat behandeling van patiënten met een type-D persoonlijkheid dan dus zinloos is, moeten we verlaten. Een dergelijke hoge risicogroep verdient juist extra aandacht in de klinische praktijk. Bij de behandeling van type-D patiënten moet het doel echter niet het veranderen van

het persoonlijkheidstype zijn, maar veel eerder het veranderen van het gedrag dat voortkomt uit de persoonlijkheid, waardoor negatieve effecten op uitkomstmaten, zoals bijvoorbeeld de genoemde aangetaste kwaliteit van leven of emotionele problemen, verminderd kunnen worden. Overigens is uit een studie van Denollet & Brutsaert [50] gebleken dat een interventie, ook bij type-D patiënten, wel degelijk zin heeft. Een uitvoerig revalidatieprogramma, bestaande uit een combinatie van beweging, een psychosociale interventie en indien nodig individuele psychologische begeleiding, leidde tot vermindering van emotionele "distress" (op korte termijn) en een betere prognose (op lange termijn) bij patiënten met coronaire hartziekten. De studie maakte duidelijk dat uitvoerige fysieke en psychische revalidatie het emotionele welbevinden en de overleving van coronaire hartpatiënten, óók patiënten met een type-D persoonlijkheid, gunstig kan beïnvloeden [7,50].

Naar onze mening zijn een drietal aspecten van belang in de behandeling en begeleiding van type-D patiënten. Op de eerste plaats lijkt, zoals eerder in dit artikel aangehaald, het verbeteren van zelfzorgvaardigheden belangrijk. Uit een recente studie verricht bij patiënten met chronisch hartfalen bleek dat patiënten met een type-D persoonlijkheid een vergroot risico hadden op verminderde zelfzorg, omdat zij de neiging hadden geen contact met hun arts of verpleegkundige te zoeken wanneer zij relevante cardiale symptomen bemerkten, waarover ze ook bezorgd waren [46]. Op de tweede plaats is het belangrijk om de type-D patiënt te helpen in het verstevigen en uitbreiden van het sociale netwerk. Aangezien type-D patiënten niet geneigd zijn hun moeilijkheden en vervelende gevoelens spontaan te delen met anderen, is het van belang de patiënt te begeleiden in het creëren van een stimulerend, begripvol en steunend sociaal netwerk. Type-D patiënten willen namelijk wel hun vervelende gevoelens delen met anderen (in tegenstelling tot sociaal introverte patiënten die hieraan geen behoefte hebben), maar durven dit niet uit angst voor afwijzing of kritiek van hun gesprekspartners. Een derde aangrijppunt voor behandeling en begeleiding van de type-D patiënt is de copingstrategie die gehanteerd wordt. Deze patiënten gaan met vervelende gevoelens om door deze op te kroppen en niet te delen met anderen. In de behandeling zou aandacht besteed moeten worden aan het aanleren van andere copingstrategieën en het veranderen van hun negatieve kijk op de wereld. Uit voorgaande studies is overigens ook gebleken dat lichaamsbeweging kan bijdragen aan een verbetering van de kwaliteit van leven bij hartpatiënten [51,52]. Onbekend is echter of dit effect ook gevonden wordt voor type-D patiënten. Mocht dit het geval zijn, dan zou stimulatie tot meer beweging een aanvullende interventie op gedragsniveau kunnen zijn. De effecten van de genoemde interventies of combinaties van interventies bij type-D

persoonlijkheid zijn nog niet onderzocht. Onderzoek naar verschillende interventiemogelijkheden bij type-D persoonlijkheden wordt daarom aanbevolen.

Naast interveniëren is de stap daarvoor, vroegtijdige herkenning van type-D persoonlijkheid, zoals al eerder aangegeven, zeker ook van belang. Screening van patiënten kan op een eenvoudige, voor de patiënt niet belastende, manier door gebruik te maken van de DS14 [6]. Wanneer type-D patiënten sneller geïdentificeerd worden, behoort preventief ingrijpen nog tot de mogelijkheden. Voorkomen is immers beter dan genezen!

Concluderend kunnen we stellen dat uit verschillende studies in de afgelopen jaren gebleken is dat type-D persoonlijkheid samenhangt met een verslechterde prognose, meer morbiditeit, een verminderde kwaliteit van leven en een verhoogde mate van depressieve gevoelens, angst en vitale uitputting bij patiënten met hart- en vaatziekten. Onderzoek richt zich nu met name op de mechanismen die het verband tussen type-D en de genoemde negatieve uitkomsten zouden kunnen verklaren. Hoewel er nog geen onderzoek verricht is naar interventiemogelijkheden, is het vroegtijdig herkennen van type-D patiënten in de klinische praktijk van belang.

SUMMARY IN ENGLISH

Cardiovascular disease, the leading cause of death in the Netherlands, is associated with high mortality and morbidity rates, as well as impaired quality of life. The importance of psychosocial variables in heart disease is nowadays recognised. However, the role of personality in cardiovascular disease has been overlooked. Recently, there is some research focusing on the distressed, or type-D, personality. Patients who score high on two stable personality traits, negative affectivity and social inhibition, are defined as type-D. It has been shown that type-D is related to mortality, morbidity, quality of life, and psychological distress in cardiovascular patients. In the near future, research should focus on possible physiological and behavioural mechanisms that link type-D to negative outcome. In clinical practice, type-D can be used to identify high-risk patients.

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PUBLICATIONS

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ABOUT THE AUTHOR

Angélique Schiffer was born on May 18, 1981 in Heerlen, the Netherlands. In 1999 she graduated at Sophianum College in Gulpen. From 1999 to 2003, she studied psychology at Tilburg University. Her research internship focused on determinants of health status in patients with chronic heart failure. In October 2003, she started working full-time on her dissertation. In April 2004, she accepted a position as a psychologist in the TweeSteden hospital, thereby also starting education to become a health psychologist ("GZ-psycholoog"). She finished the training to become a health psychologist in August 2007 and her dissertation in November 2007. Currently, she is working as a health psychologist in the TweeSteden hospital and as a researcher at Tilburg University.

Angélique Schiffer is op 18 mei 1981 in Heerlen geboren. In 1999 behaalde zij haar VWO diploma aan het Sophianum in Gulpen. Van 1999 tot 2003 studeerde ze psychologie aan de Universiteit van Tilburg. Haar afstudeerproject concentreerde zich op determinanten van gezondheidstoestand bij hartfalenpatiënten. In 2003 startte zij met haar promotieonderzoek en in april 2004 met de post-doctorale opleiding tot gezondheidszorgpsycholoog. In augustus 2007 rondde ze deze opleiding af, in november van hetzelfde jaar haar proefschrift. Momenteel werkt ze als gezondheidszorgpsycholoog in het TweeSteden ziekenhuis en is ze als onderzoeker gedetacheerd naar de Universiteit van Tilburg.

nodig ik u uit voor het bijwonen van de openbare verdediging van mijn proefschrift, getiteld:

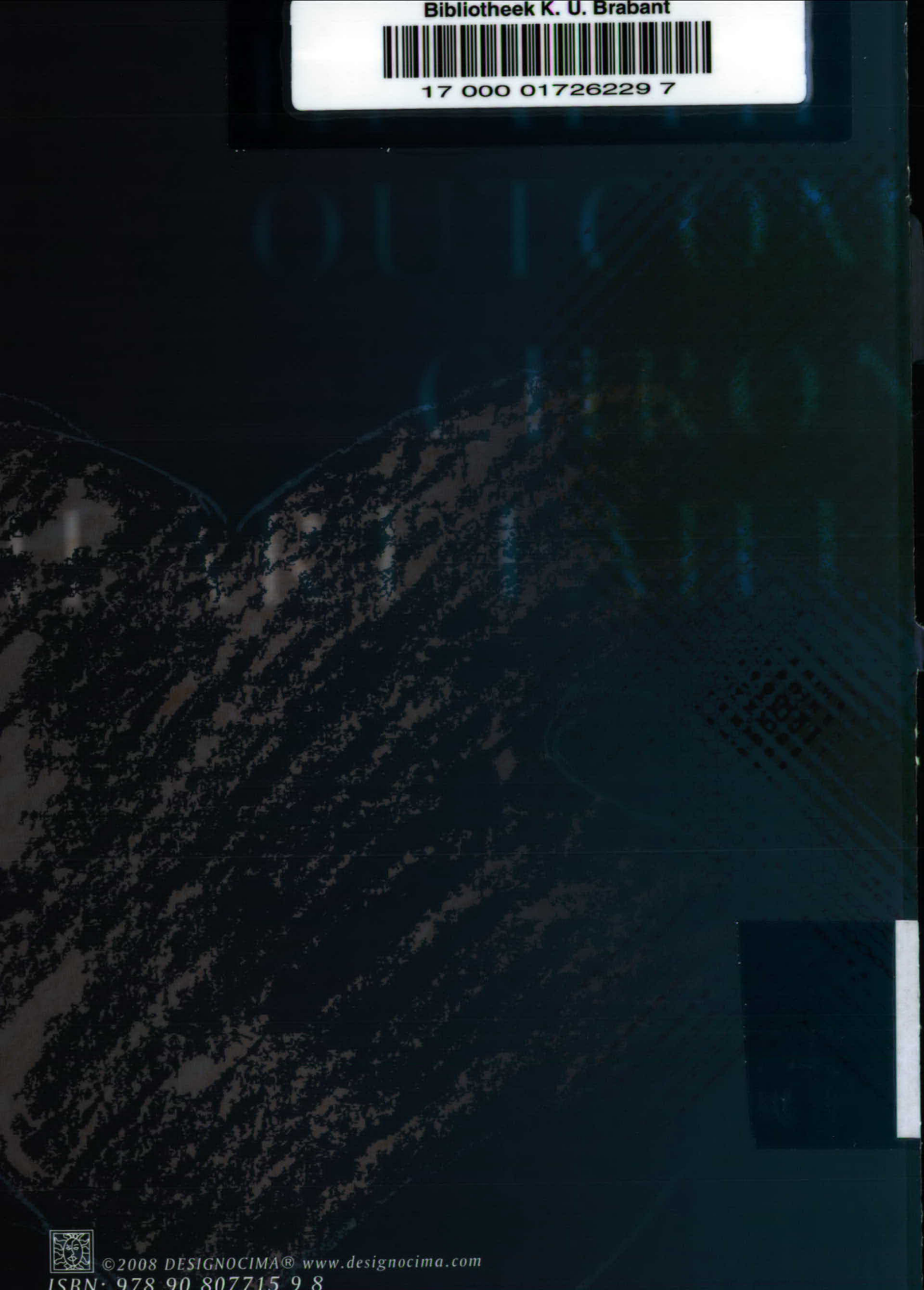
HEALTH OUTCOMES in CHRONIC HEART FAILURE

the role of type-D personality

jdag 25 april 2008 in de aula van de Universiteit van Tilburg, Warandelaan 2, Tilburg. De tieplechtigheid begint om 14.15 uur en wordt vooraf gegaan door een korte presentatie van het chrift om 14.00 uur. Na afloop is er een receptie ter plaatse.

que Schiffer
an 427, 5011 SK Tilburg, telefoon: 013-4562204

Paranimfen:
Aline Pelle (a.j.m.pelle@uvt.nl)
Charlotte Stupers (cstupers@gmail.com)
Manon Voskamp (manonvoskamp@gmail.com



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