

# Anxiety in implantable defibrillator treatment

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*Publication date:*
2008

# Anxiety in Implantable Defibrillator Treatment: Vulnerability Factors and Clinical Consequences

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# Anxiety in Implantable Defibrillator Treatment:

# *Vulnerability Factors and Clinical Consequences*

**Proefschrift**

ter verkrijging van de graad van doctor aan de Universiteit van Tilburg, op gezag van de rector magnificus, prof.dr. F.A. van der Duyn Schouten, in het openbaar te verdedigen ten overstaan van een door het college voor promoties aangewezen commissie in de aula van de Universiteit op vrijdag 19 september 2008 om 14.15 uur

door

**Christina Catharina Louisa Theresia van den Broek,**
geboren op 17 april 1978 te Zundert.

| | |
|---|---|
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Printed by Ridderprint Offsetdrukkerij B.V., Ridderkerk
Cover: Elfentaal, www.elfentaal.nl

ISBN/EAN: 978-90-5335-159-8

Financial support by the Netherlands Heart Foundation and Stichting Vrienden van het Hart Zuidoost-Brabant for the publication of this thesis is gratefully acknowledged.

# TABLE OF CONTENTS

*Chapter 1*

# General Introduction

## IMPLANTABLE DEFIBRILLATOR TREATMENT

Sudden cardiac death accounts for approximately 50% of mortality from cardiovascular disease[1] and about 85% of these deaths are attributable to ventricular arrhythmias[2]. Ventricular tachycardia refers to an abnormal rapid heart rhythm that originates in the ventricles and may progress to ventricular fibrillation during which the ventricles quiver. As a consequence, effective pumping of blood is ceased, with brain and heart damage within minutes.

The implantable cardioverter defibrillator (ICD) was first implanted in 1980[3] and has now become the treatment of choice in patients who have experienced ventricular arrhythmias (secondary prevention), but also in patients at increased risk for these arrhythmias, due to coronary artery disease and left ventricular dysfunction (primary prevention)[4, 5]. Both secondary as well as primary prevention trials have shown that the ICD is significantly more effective in reducing the risk for sudden cardiac death as compared to antiarrhythmic drugs[5]. As a consequence, the number of implantations has increased substantially[6]. However, it is important to note that sudden cardiac death may still occur in a small proportion of ICD patients[7].

The ICD is a sophisticated device with three therapy options to terminate ventricular arrhythmias[8]. Ventricular fibrillation requires *immediate defibrillation* by high-energy shocks. Ventricular tachycardia is treated with *antitachycardia pacing* (ATP), which involves short bursts of pacing impulses at faster rates than the tachycardia, or *low energy shocks (cardioversion)*[8]. Due to the complex features of the ICD, its reliability has been questioned[9]. According to a report by Maisel et al.[9], ICD replacement due to malfunctioning of devices has increased markedly by number and rate between 1996 and 2002, with a peak in the years 2000-2002 when 26.8 per 1000 ICD implants had to be replaced. Most cases of ICD malfunctioning relate to hardware abnormalities, like battery problems or electrical issues[9].

## PSYCHOLOGICAL DISTRESS FOLLOWING ICD IMPLANTATION

Many patients adjust well to their implanted defibrillator, but a subgroup of patients experiences psychological problems following ICD implantation, including anxiety, depression, impaired quality of life, and avoidance behaviors[10-18]. A review by Sears et

al.[13] indicates that diagnosable levels of anxiety and depression may be experienced by respectively 13%-38% and 10%-15% of ICD patients, which suggests that anxiety may be particularly common in this population. Levels of anxiety and depressive symptoms in ICD patients may decrease within 6[19] or 12[15] months after ICD implantation, although other studies suggest stability of these levels over various periods within 1 month and 5 years post-implantation[14, 18, 20, 21].

Adaptation problems in ICD patients may be caused by several stressful experiences, including the experience of resuscitation, diagnosis of a life-threatening disease, unpredictable reoccurrence of ventricular arrhythmias, and restricted physical capabilities, but also by the ICD implantation itself, which involves medical examinations and induction and termination of ventricular fibrillation[22]. ICD indication (primary versus secondary prevention) does not seem to influence adjustment[12, 23]. In contrast, shocks may lead to increased psychological distress, although results are not conclusive[24]. A number of studies suggest that shocked patients experience more anxiety[12, 14, 25], depression[15, 25], and impaired quality of life[16, 26] as compared to non-shocked patients, although other studies report no significant psychological differences between shocked and non-shocked patients[10, 17, 18]. Another device-related factor that may be associated with maladjustment is ICD recall[27], which refers to a notification of ICD manufacturers that some of their devices may malfunction.

Several studies have also focused on non-device related risk factors for anxiety in ICD patients. These factors include younger age (< 50 years)[13], female gender[13, 25], and history of psychological difficulties[13]. Only a few studies have focused on personality as a risk factor, including Type D personality[12, 28] (tendency to experience increased negative emotions paired with social inhibition[29]) and anxiety sensitivity[21, 30] (fears of anxiety-related sensations based on beliefs that these sensations have harmful consequences, such as illness, embarrassment, or additional anxiety[31, 32]).

## PSYCHOLOGICAL FACTORS AND RISK OF VENTRICULAR ARRHYTHMIAS IN ICD PATIENTS

ICDs do not prevent ventricular arrhythmias. Given the increase in the number of ICD patients[6] paired with possible negative psychological consequences of ICD shocks[12, 14-16]

and the notion that ICDs are not completely protective against sudden cardiac death[7], knowledge of precipitating factors of ventricular arrhythmias is essential for the identification of high-risk patients. Clinical factors that increase the risk for ventricular arrhythmias include New York Heart Association Class (i.e., functional class) III[33] or IV[34], vigorous exercise[1, 35], atrial fibrillation, and low left ventricular ejection fraction[36]. Despite preliminary evidence that psychological factors may play a role in the onset of ventricular arrhythmias[37], only a few studies have investigated this issue in ICD patients[38-41]. These patients provide a good opportunity to study psychological precipitants of ventricular arrhythmias due to the ICD's capacity to store arrhythmia episodes. Whang et al.[41] reported that depression triggered arrhythmias, whereas Dunbar et al.[38] found that anxiety was a trigger, but not depression or anger. Finally, Lampert et al.[39] reported that anger may precipitate ventricular arrhythmias, but anxiety, worry, sadness, happiness, challenge, feeling in control, or interest may not. In addition to the role of mood states, personality factors may also play a role, as Burg et al.[40] found that ICD patients with trait anger or trait anxiety were at increased risk to experience anger- or anxiety-triggered appropriate shocks, respectively. Taken together, depression, anxiety, and anger were precipitants of ventricular arrhythmias in some, but not all studies.

As psychological factors may precipitate ventricular arrhythmias in patients, it is important to identify these patients and offer them adequate support. However, only a few studies have examined interventions for anxiety and depression in ICD patients. These studies focused on comprehensive cardiac rehabilitation[42, 43], cognitive behavioral therapy[44, 45], support groups[46-48], or telephone support[49], with some[42-45, 49, 50] but not all[46-48] studies demonstrating an effect of the intervention on distress.

## THE ROLE OF PARTNERS IN ICD TREATMENT

Partner status may also be associated with emotional distress in ICD patients. Generally, lack of social support may be related to increased emotional distress[51], impaired quality of life[26], and mortality[52]. Therefore, not having a partner may also be associated with adverse outcomes, especially in Type D patients who already have fewer social ties and experience less social support as compared to non-Type D patients[53].

Partners of ICD patients themselves may also experience emotional distress, but only a few studies investigated this issue, even though anxiety levels in partners have been reported to be as high as levels in ICD patients[54, 55] or even higher[15, 28]. Initially, partners may feel insecure and uncertain about the effectiveness of the ICD, but later on they may adjust thereby diminishing their protective behavior[56].

## AIMS OF THIS THESIS

The main focus of this thesis is on anxiety, as anxiety may be more prevalent in ICD patients as compared to depression[13]. The importance of anxiety in ICD patients may stem from a number of specific ICD treatment characteristics, including the experience of resuscitation, the diagnosis of a life-threatening disease, and the unpredictability of ventricular arrhythmias and ICD shocks[22]. Moreover, anxiety has been related to adverse outcomes across cardiovascular disease[38, 57]. In this thesis, anxiety predominantly refers to general symptoms of state anxiety, which refers to a transient emotional status, characterized by feelings of apprehension (i.e., worries and concerns) and tension as well as increased activity of the autonomic nervous system[58]. However, interviewer-rated levels of clinical anxiety as well as disease-specific anxiety are also discussed in some papers.

The present thesis reports the findings of ongoing prospective research in ICD patients and their partners. A theoretical model of research concerning ICD patients only is shown in Figure 1a and an explorative model of research involving partners of patients is shown in Figure 1b. Following the importance of anxiety in ICD patients, the aims of this thesis were to i) examine vulnerability factors for anxiety in ICD patients, ii) examine the precipitating role of anxiety for adverse psychological and clinical outcomes, including ventricular arrhythmias, and iii) examine anxiety in partners of ICD patients. Figure 2 shows a schematic presentation of the aims and outline of this thesis.

***Figure 1a.*** *Theoretical model for research on ICD patients described in this thesis*

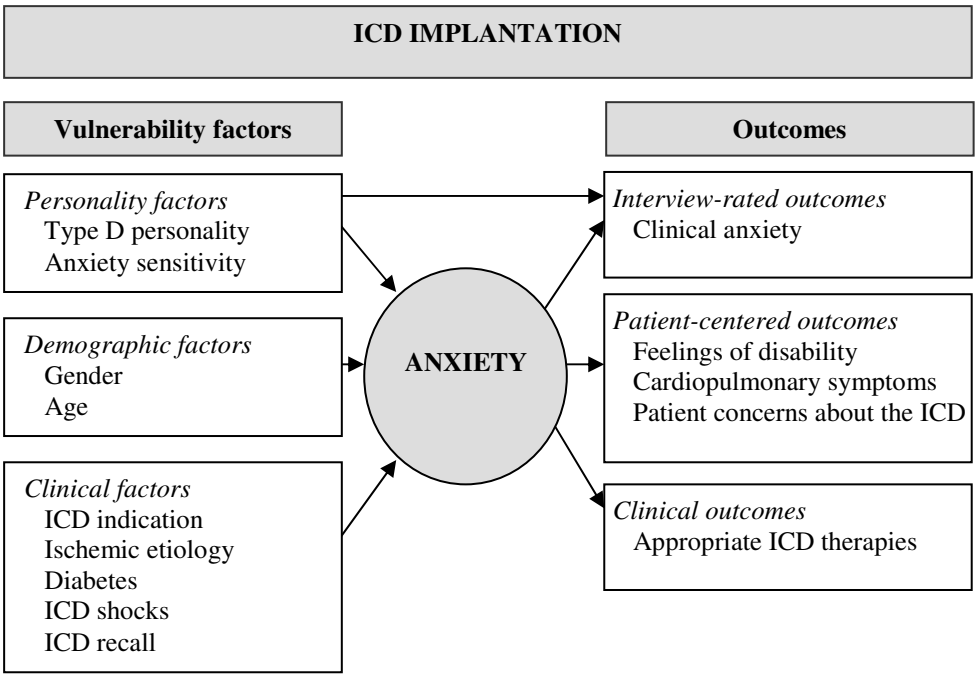
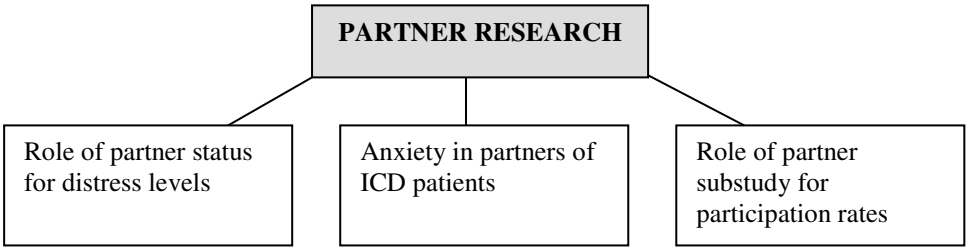



***Figure 1b.*** *Explorative model for research involving partners described in this thesis*




Patients were recruited from two Dutch referral hospitals: the Catharina Hospital in Eindhoven (since May 2003), and the Amphia Hospital in Breda (since June 2005). Patients were approached during their hospitalization for ICD implantation and were asked to voluntarily participate in a longitudinal study on psychological reaction to ICD implantation. The study includes four time points, that is, baseline and 2, 12, and 18 months post-implantation. Patients were excluded in case of significant cognitive

impairments (e.g., dementia), severe life-threatening comorbidities (e.g., cancer), or inability to read and understand Dutch. In September 2005, a substudy involving partners of ICD patients was started in both hospitals. Partners could only participate in this substudy when they were living together with the patient and the patient had already agreed to participate in the study. No further criteria were formulated for the partners. The study was approved by the Medical Ethic Committees of the participating hospitals. The study was conducted in accordance with the Helsinki Declaration, and all subjects provided written informed consent. Four of the papers in this thesis concern additional data from other studies. *Chapter 3* includes the results of an extra measurement of anxiety after device recall. *Chapters 4* and *7* are partially based on data from the "*Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter Defibrillator: A prospective Study* (MIDAS)", which is conducted in the Erasmus Medical Center in Rotterdam. Finally, the results in *Chapter 10* are based on merged data, including this ICD population as well as a myocardial infarction population.

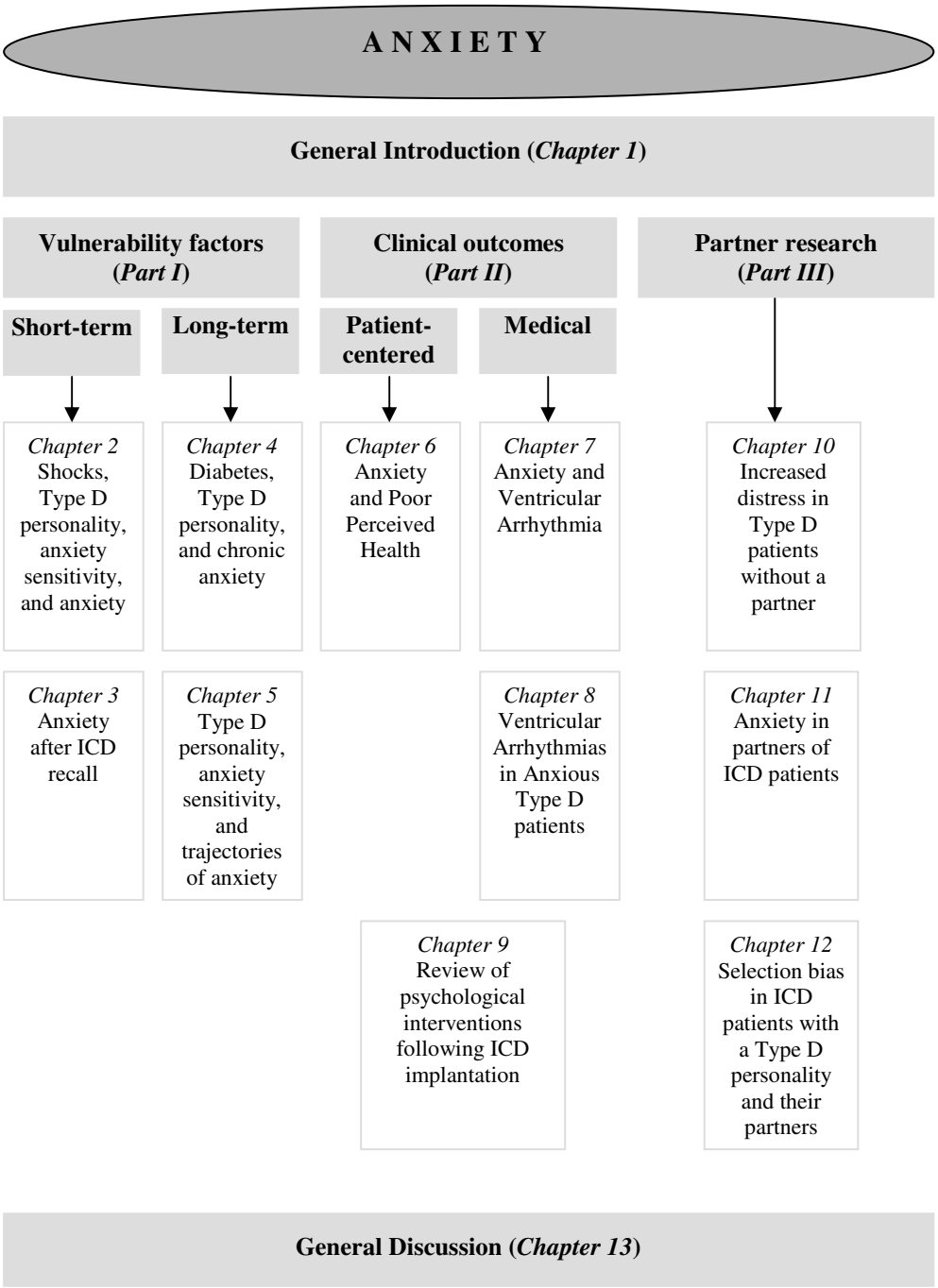
## OUTLINE OF THIS THESIS

### *Part I* Vulnerability factors for anxiety in ICD treatment

ICD patients frequently show increased anxiety, but little is known about the determinants of anxiety in these patients. It is important to identify patients with increased anxiety, because studies on general cardiovascular patients have shown that anxiety may have a negative effect on quality of life and prognosis. More specifically in ICD patients, anxiety may be associated with an increased risk for ventricular arrhythmias. The first part of this thesis describes vulnerability factors for anxiety in order to identify high-risk patients.

*Chapter 2* describes the role of shocks, Type D personality, anxiety sensitivity, and demographic and clinical variables for anxiety in 308 ICD patients. Previous studies have found that shocks may lead to increased anxiety, although other studies did not find this association. In addition, little is known about the role of personality dispositions for anxiety in ICD patients. Hence, this short-term follow-up study investigated vulnerability factors, including shocks and personality, for self-reported as well as interviewer-rated anxiety at 2 months post-implantation.

***Figure 2.*** *Outline of thesis*



*Chapter 3* investigates the extent to which ICD recalls may lead to increased anxiety. Following Medtronic's notification in 2005 on potential malfunctioning of certain ICDs, all patients with these ICDs had an extra device evaluation. After this evaluation, 33 patients completed a questionnaire on anxiety because we hypothesized that ICD recall may lead to increased anxiety in these patients. The aim of this additional study was to determine whether the proportion of ICD patients with high levels of anxiety would increase after the extra device evaluation.

In *Chapter 4*, the determinants of chronic anxiety were examined. Previous studies have focused on anxiety, but little is known about patients who experience chronic levels of anxiety. We hypothesized that these patients may differ from patients who are only anxious at the time of implantation. This long-term follow-up study only included the 222 patients of the current study in combination with those of the MIDAS with increased anxiety at the time of implantation. Demographic, clinical, and psychological predictors were examined of patients who were still anxious at 12 months post-implantation versus patients whose anxiety had resolved at 12 months.

*Chapter 5* describes trajectories of anxiety and depressive symptoms over a 12-month period as well as determinants of these trajectories in 312 ICD patients. Only a few studies have examined the course of anxiety and depressive symptoms in ICD patients. However, all of these studies examined overall mean scores, which does not allow for the identification of trajectories of subgroups of patients with different levels of symptoms.

***Part II* The role of anxiety in the outcome of ICD treatment**

While part I of this thesis focused on the effect of ICD implantation on anxiety, part II focuses on the role of anxiety for clinical outcomes in ICD patients.

The focus of *Chapter 6* is on the predictive value of general anxiety versus disease-specific anxiety for poor perceived health at 2 months post-implantation in 205 ICD patients. Most of the studies on anxiety in ICD patients have focused on general anxiety, but attention may also be directed towards specific disease-related anxiety as this type of anxiety may be differentially related to outcomes as compared to general anxiety. The outcomes in this study comprise self-reported feelings of disability, cardio-pulmonary symptoms, and concerns about the ICD, but also interviewer-rated clinical anxiety. The

psychometric characteristics of the disease-specific anxiety measure we used (Cardiac Anxiety Questionnaire), are also examined.

*Chapter 7* reports the results of a large prospective study in 565 ICD patients from the current study as well as the MIDAS that investigated the role of anxiety as predictor of appropriate ICD therapies (ATPs and shocks) within 12 months following ICD implantation. Two previous studies by others also investigated the role of anxiety as a trigger of ventricular arrhythmias, but as one study found a significant relationship whereas the other study did not, more research is warranted on this topic.

*Chapter 8* also focuses on psychological precipitants of ventricular arrhythmias within 12 months post-implantation, but this study ($N$ = 324) included anxiety as well as depressive symptoms, Type D personality, and their interaction terms. Until now, Type D personality has not been investigated in relation to ventricular arrhythmias and more research is needed to examine the relative importance of anxiety, depression, and personality as potential predictors of ventricular arrhythmias.

*Chapter 9* reports a review of studies on psychological interventions in ICD patients. As stated before, a subgroup of patients experiences psychological problems, which may be decreased by means of psychological treatment. Several studies have addressed possible interventions for these patients and our aim was to give an overview of these studies and to evaluate their efficacy. Another aim was to provide recommendations for future research.

***Part III*** **The role of partners in ICD treatment**

Partners may also play a role in psychological well-being of ICD patients. Moreover, anxiety in partners of ICD patients may be as high as in patients themselves. However, little is known about these issues. Therefore, the last part of this thesis focuses on research involving partners of ICD patients.

*Chapter 10* reports the results of a short-term follow-up study on the influence of not having a partner in combination with a Type D personality for emotional distress. Type D personality is associated with morbidity and mortality, but not all Type D patients are at risk. We hypothesized that not having a partner may enhance the detrimental effects

of Type D personality on anxiety and depressive symptoms. The results of this study are based on ICD patients as well as MI patients ($N = 554$).

*Chapter 11* presents the findings of a short-term prospective study on anxiety and posttraumatic stress in 182 partners of ICD patients. Prospective studies investigating anxiety in partners of ICD patients are sparse, even more so for determinants of anxiety in partners. Therefore, the aims of this study were to examine the prevalence of anxiety and posttraumatic stress in partners, as well as to determine the influence of i) Type D personality, anxiety sensitivity, gender, and age of the partner and ii) the patient variables ICD indication and shocks.

*Chapter 12* describes the influence of adding a partner substudy on participation rates of patients, especially Type D patients ($N = 507$). We also examined partner nonparticipation rates among Type D patients ($N = 276$). Generally, study participants may systematically differ from non-participants. However, nonparticipation may also be influenced by the addition of a substudy on partners. As mentioned before, the partner study started only in September 2005. Therefore, we were able to examine characteristics of participants before and after the start of the substudy on partners, more specifically we examined whether addition of a partner substudy was associated with participation rates of patients with a Type D personality. A secondary aim was to examine whether Type D personality of patients was associated with participation rates of partners. A potential selection bias may influence the results of studies involving partners, thereby threatening the generalizability of findings.

**General discussion and summary**

The thesis will be closed with a general discussion and summary (*Chapter 13*). The main findings of this thesis will be summarized and integrated. Next, clinical implications, limitations, and directions for future research will be discussed.

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*PART I*

# Vulnerability Factors for Anxiety in ICD Treatment

*Chapter 2*

# Shocks, Personality, and Anxiety in Patients with an Implantable Defibrillator

**Van den Broek KC, Nyklíček I, Van der Voort PH, Alings M, Denollet J. Shocks, personality, and anxiety in patients with an implantable defibrillator. Pacing Clin Electrophysiol, *in press*.**

**ABSTRACT**

**Background** Studies have examined the relationship between shocks and anxiety, but little is known about the role of personality. Our aim was to examine the determinants of self-reported and interviewer-rated anxiety following implantable cardioverter defibrillator (ICD) implantation.

**Methods** At baseline, that is, 0-3 weeks following ICD implantation, 308 ICD patients (82% men, mean age = 62.6 years) completed the DS14 (Type D personality) and ASI (anxiety sensitivity). The STAI (self-reported symptoms of state-anxiety) was assessed at baseline and follow-up, which was 2 months following ICD implantation. At this follow-up, the HAM-A interview (interviewer-rated anxiety) was assessed in a subsample (57%); the occurrence of ICD shocks was deduced from medical records.

**Results** ANCOVA for repeated measures showed a significant interaction effect between time and shocks ($F$ = 9.27, $p$ = .003), with patients who had experienced a shock experiencing higher levels of self-reported anxiety at follow-up. The main effects of Type D personality ($F$ = 33.42, $p$ < .0001) and anxiety sensitivity ($F$ = 66.31, $p$ < .0001) were significant, indicating that these patients scored higher on self-reported anxiety across time points. Multivariable linear regression analyses yielded Type D personality ($\beta$ = .18, $p$ = .021) and anxiety sensitivity ($\beta$ = .19, $p$ = .016), but not shocks, as independent predictors of interviewer-rated anxiety. Covariates included gender, marital status, education, age, ICD indication, cardiac history, and comorbidity.

**Conclusions** Type D personality and anxiety sensitivity were independent predictors of both self-reported and interviewer-rated anxiety outcomes while ICD shocks were related to an increase in levels of self-reported anxiety only. Identification and support of ICD patients with Type D personality, increased anxiety sensitivity, or shocks is important.

## INTRODUCTION

Despite the medical benefits of the implantable cardioverter defibrillator (ICD), several psychological problems following ICD implantation have been described, including anxiety, with the prevalence of clinically relevant levels ranging from 13% to 38% in ICD patients[1]. Symptoms of anxiety refer to a variety of worries and fears as well as physiological arousal. ICD discharges may enhance the levels of anxiety, although studies report inconsistent results, with some studies finding a significant association between shocks and anxiety[2, 3], but other studies not[4, 5]. These inconsistencies may be due to differences in measurements and time points, but also due to the low power to detect differences, because of small samples or a low prevalence of shocks. In this context, the role of personality may be important, since personality may mediate the relationship between discharges and anxiety. Furthermore, some studies have found that anxiety may also precipitate ventricular arrhythmias[6, 7]. Due to this untoward effect of anxiety in ICD patients, it is important to identify patients who are at risk for experiencing anxiety.

Although studies have examined the relationship between shocks and anxiety, little is known about the role of personality in ICD patients. Personality traits, including Type D personality and anxiety sensitivity, may play a central role in the identification of ICD patients at risk for experiencing increased levels of anxiety. Type D personality refers to the combination of two personality traits; that is, negative affectivity (the tendency to experience negative emotions across time and situations) and social inhibition (the tendency to inhibit the expression of emotions due to fears of how others will react)[8]. Type D patients tend to experience increased negative emotions (e.g., they tend to worry and have a gloomy view of life), and they tend to inhibit the expression of these emotions[8]. The prevalence of Type D personality varies from 23% to 27% in ICD patients[5, 9, 10] to 53% in hypertensive patients[11]. Type D personality has been associated with an increased risk for morbidity and mortality in patients with coronary heart disease[11], as well as increased feelings of anxiety[5, 11]. The relationship between Type D personality and anxiety in ICD patients has been evaluated in two studies[5, 12], with the cross-sectional study reporting an independent association between Type D personality and anxiety[5] and the prospective study reporting a large effect of Type D personality on anxiety levels 6 months following ICD implantation[12].

Anxiety sensitivity is a personality trait that refers to the fears of anxiety-related sensations based on beliefs that these sensations have harmful consequences, such as illness, embarrassment, or additional anxiety[13, 14]. For example, persons with high anxiety sensitivity may believe that heart palpitations indicate a heart attack, whereas those with low anxiety sensitivity experience these sensations as unpleasant but nonthreatening. This misinterpretation of sensations may lead to a vicious cycle, where higher levels of anxiety may cause further anxiety-related sensations that may be misinterpreted again, and so on. Hence, the experience of shocks as well as personality traits may play an important role in anxiety in ICD patients.

The aim of the current study was to examine whether shocks, Type D personality, and anxiety sensitivity were predictors of self-reported symptoms of anxiety as well as interviewer-ratings of anxiety, independent of each others' effects and of those of possible confounders, such as indication for ICD implantation.

## METHODS

### Patient population and design

Patients who had an ICD implanted in two large Dutch referral hospitals between May 2003 and January 2007 were included. Inclusion criteria were implantation with an ICD and age between 18 and 80 years. Patients were excluded when they were unable to read or understand Dutch.

The study was approved by the Medical Ethics Committees of the participating hospitals. The study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent.

### Clinical characteristics

Demographic variables included sex, age, marital status, and low educational level (less than 13 years of education, that is, secondary education or less). Clinical variables included shocks (no shocks versus ≥ 1 shock), ICD indication (primary versus secondary prevention), comorbidity (lung disease, renal disease, rheumatic disease, or diabetes mellitus), and ischemic heart disease (previous myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery).

**Personality: Type D and anxiety sensitivity**

At baseline, which was between 0 and 3 weeks after ICD implantation, patients completed self-report measures on Type D personality and anxiety sensitivity. Table 1 provides an overview of the study measurements.

***Table 1.*** *Description of measures*

| Measures | Construct | Description construct | Self-report vs. interview |
|---|---|---|---|
| **Personality dispositions** | | | |
| Type D scale (**DS14**) | Type D personality | Tendency to experience negative emotions and to inhibit self-expression | Self-report questionnaire |
| Anxiety Sensitivity Index (**ASI**) | Anxiety sensitivity | Tendency to be sensitive to, and afraid of, anxiety symptoms | Self-report questionnaire |
| **Anxiety outcomes** | | | |
| State-Trait Anxiety Inventory (**STAI-state**) | General symptoms of state anxiety | Feelings of apprehension and tension; increased activity of the autonomic nervous system | Self-report questionnaire |
| Hamilton Anxiety Rating Scale (**HAM-A**) | Psychiatric standard for anxiety severity | Anxious mood, tension, insomnia, and several somatic symptoms | Semi-structured interview |

*Type D personality*.

The 14-item Type D personality Scale (DS14) was used to assess Type D personality[8]. The DS14 consists of the 7-item subscales negative affectivity (e.g., "I often feel unhappy") and social inhibition (e.g., "I am a 'closed' person"). Items are answered on a five-point Likert scale ranging from *0-false* to *4-true*. Total scores on both subscales range from 0 to 28. Patients scoring high on both subscales, that is, equal to or above 10, are classified as Type D. Internal consistency is high with Cronbach's α values of 0.88 for negative affectivity and 0.86 for social inhibition[8]. The temporal stability of Type D personality has been confirmed by means of test-retest correlations, which were 0.72 and 0.82 for negative affectivity and social inhibition, respectively[8].

*Anxiety sensitivity*.

Anxiety sensitivity was measured using the 16-item Anxiety Sensitivity Index (ASI), designed to assess sensitivity and fear of anxiety symptoms[14]. Items are rated on a five-point Likert scale from *0-very little* to *4-very much*. Total scores are obtained by summing the scores on the 16 items, that is, total scores range from 0 to 64, with higher scores reflecting greater sensitivity and fear of anxiety symptoms. Examples of items are: 'It scares me when I feel faint' and 'When I am nervous, I worry that I might be mentally ill'. In our study, the reliability of the ASI was good, with Cronbach's $\alpha = 0.88$. Since there is no standardized cut-off for the ASI, we used the upper quartile score (i.e., ASI $\geq$ 19) to dichotomize ASI scores. As a final point, it is important to distinguish anxiety sensitivity; that is, the beliefs that anxiety symptoms have negative effects, from anxiety; that is, the frequency of occurrence of anxiety symptoms[14].

**Outcome: symptoms and ratings of anxiety**

The anxiety outcomes comprise both self-reported and interviewer-ratings of anxiety. Self-reported anxiety refers to subjective feelings of anxiety as experienced and reported by the patient, whereas interviewer-ratings denote the interviewer's assessment of the severity of anxiety, which may be rated as a psychiatric diagnosis. At baseline, self-reported symptoms of anxiety were assessed. Two months following implantation, assessment of self-reported symptoms of anxiety as well as interviewer-ratings of anxiety was realized. Interviews were administered in the hospital and the questionnaires were subsequently completed at home and returned via mail. This procedure was applied till August 2006 (interview group; $n = 199$). Due to logistic reasons, interviews could not be administered after August 2006. Patients who had their 2 month follow-up time point after this date, received the questionnaires via mail (mail only group; $n = 169$).

*Self-reported symptoms of anxiety*.

The state version of the State-Trait Anxiety Inventory (form Dutch Y-1; STAI) is a 20-item self-report measure. The STAI was used to assess the current presence of general symptoms of state anxiety[15]. This form of anxiety refers to a transient emotional status, characterized by feelings of apprehension (i.e., worries and concerns) and tension as well

as increased activity of the autonomic nervous system[15]. Items are scored on a 4-point Likert scale from *1-not at all* to *4-very much so*. Scores range from 20, that is, low level of state-anxiety to 80, that is, high level of state-anxiety. The STAI has been demonstrated to have adequate validity and reliability, with Cronbach's α ranging from 0.87 to 0.92[15]. To indicate clinically elevated levels of general anxiety, a cut-off ≥ 40 was used. This cut-off was previously used in studies on ICD[16] and myocardial infarction patients[17].

*Interviewer ratings of anxiety*.

The Hamilton Rating Scale for Anxiety (HAM-A) is a 14-item semi-structured interview and is a psychiatric standard for the assessment of current severity of anxiety[18]. The items comprise the symptoms of anxiety, including anxious mood, tension, insomnia, and several somatic symptoms. The severity of the symptoms is rated by the interviewer on a scale from *0-not present* to *4-very severe/incapacitating*. Scores range from 0 to 56, with a score above 17 indicating clinically elevated anxiety[18]. The validity and reliability are good, with Cronbach's α ranging from 0.82 to 0.92, and interrater reliability (i.e., intraclass coefficient) ranging from 0.74 to 0.98[18-20]. The HAM-A has been used as an outcome measure of clinical anxiety in previous studies on ICD patients[4, 21].

**Statistical analysis**

Patients with and without complete data were compared regarding baseline demographic and clinical variables, using a Chi-square test for nominal variables and Student's *t*-test for continuous data. To investigate differences between baseline and follow-up levels of anxiety and the proportion of patients with clinically relevant anxiety, a paired *t*-test and the McNemar test were used, respectively. A *t*-test for independent samples was performed to determine the association between Type D personality and anxiety sensitivity. Next, a biserial correlation coefficient was calculated to examine the plausibility of multicollinearity between these personality characteristics. To examine the influence of shocks and personality for self-reported anxiety at baseline and 2 months follow-up, and for changes in anxiety, an ANCOVA for repeated measures was performed. To examine whether interviewer-rated anxiety at follow-up differed as a function of shocks, Type D, or increased anxiety sensitivity a number of *t*-tests for

independent samples were applied. Next, a series of linear regression analyses were performed to determine the predictive value of personality and shocks for interviewer-ratings of anxiety. In ANCOVA for repeated measures and linear regression analyses, we adjusted for the effects of the other predictors, including sex, marital status, age, education, indication for ICD, comorbidity, and history of cardiac disease. A $p$-value < 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS 14.0 for Windows.

## RESULTS

### Patient characteristics

Of the initial 368 patients who were included at baseline, 308 (84%) patients completed the study at 2 months follow-up (mean = 64.07±15.82 days, range 29-139 days). Reasons for not completing the study were death ($n$ = 6), loss to follow-up and refusal to further participate ($n$ = 27), and missing data on self-report measures or medical data ($n$ = 27). Patients without complete data were more likely to be Type D (36% versus 20%, $p$ = .008) and to be without a partner (23% versus 11%, $p$ = .007). Furthermore, these patients had higher levels of anxiety sensitivity ($p$ = .001) and general anxiety ($p$ = .001) at baseline compared to included patients.

The interview group (who also received questionnaires) eventually comprised 176 (57%) patients and the mail only group comprised 132 (43%) patients. These groups were compared on all variables included in this study, except for HAM-A scores. Results only showed differences regarding shocks (2.8% versus 8.3%, $p$ = .032) and primary prevention (46.6% versus 64.4%, $p$ = .002). The results regarding shocks must be interpreted with caution because of reduced power. The higher percentage of primary prevention patients in the mail only group was expected, since indications for ICD implantation have been expanded in recent years, with nowadays relatively more primary prevention reasons being applied. Table 2 shows the demographic, clinical, and personality characteristics of the 308 study participants, as well as the mean scores and prevalences of clinically elevated levels of both self-reported and interviewer-rated anxiety. A total number of 57 appropriate as well as inappropriate shocks were experienced by 16 patients (5%), including 1 patient who had experienced an electrical

storm of 33 shocks. The prevalences of Type D personality and anxiety sensitivity were consistent with previous literature[5, 9, 22]. Levels of self-reported anxiety diminished significantly from baseline to follow-up ($p < .0001$). Similarly, the proportion of patients with clinically elevated scores of self-reported anxiety decreased significantly from baseline to follow-up ($p < .002$).

***Table 2.*** *Patient characteristics (N = 308)*

| | **% (*N*)** | **Mean (SD)** | **Range** |
|---|---|---|---|
| **Demographics** | | | |
| Female | 18 (54) | | |
| No partner | 11 (33) | | |
| Low education* | 48 (147) | | |
| Age | | 62.6 (10.1) | 24-79 |
| **Clinical variables** | | | |
| Secondary prevention | 46 (141) | | |
| ≥ 1 shock since implantation | 5 (16) | | |
| Ischemic heart disease† | 71 (220) | | |
| Comorbidity‡ | 36 (112) | | |
| **Personality** | | | |
| Type D personality | 20 (61) | | |
| Anxiety sensitivity score | | 13.5 (9.2) | 0-47 |
| Anxiety sensitivity ≥ 19 | 26 (79) | | |
| **Mean anxiety levels** | | | |
| Self-reported anxiety score at baseline | | 38.6 (11.4) | 20-76 |
| Self-reported anxiety score at follow-up | | 36.3 (10.8) | 20-69 |
| Interviewer-rated anxiety at follow-up§ | | 4.7 (5.5) | 0-24 |
| **Clinically elevated anxiety (≥ cut-off)** | | | |
| Self-reported anxiety at baseline ≥ 40 | 46 (140) | | |
| Self-reported anxiety at follow-up ≥ 40 | 36 (110) | | |
| Interviewer-rated anxiety at follow-up ≥ 17§ | 13 (24) | | |

Measures: Type D personality: *Type D Scale (DS14)*, Anxiety sensitivity: *Anxiety Sensitivity Index (ASI),* Self-reported symptoms of anxiety: *State-Trait Anxiety Inventory (STAI),* Interviewer-ratings of anxiety: *Hamilton Anxiety Rating Scale (HAM-A).*

* Secondary education or less; † Previous myocardial infarction, percutaneous coronary intervention, and/or coronary artery bypass graft; ‡ Lung, renal, and/or rheumatic disease, and/or diabetes; § $n = 176$

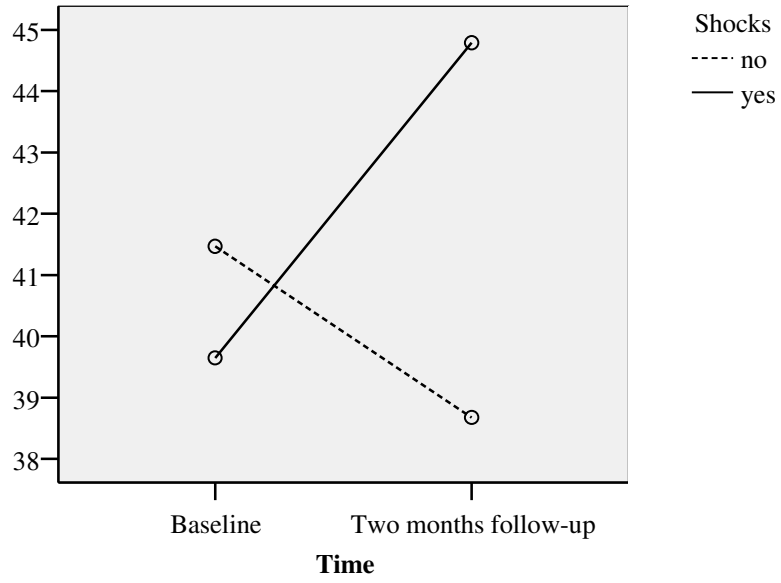
Type D personality was significantly related to anxiety sensitivity, with Type D patients scoring higher on anxiety sensitivity than non-Type D patients (18.8±10.2 versus 12.1±8.5, $p < .0001$). Similarly, significantly more Type D patients reported increased feelings of anxiety sensitivity compared to non-Type Ds (48% versus 22%, $p < .0001$). However, the biserial correlation coefficient between Type D personality and anxiety sensitivity was 0.42, indicating no multicollinearity and permitting these variables to be included simultaneously in the regression model.

**Personality and self-reported symptoms of anxiety**

Repeated measures ANCOVA analysis showed no significant effect of time (Wilks' Lambda = 0.99, $F$ (1, 298) = 2.75, $p = .098$), indicating that baseline levels of anxiety did not differ from follow-up levels, adjusting for anxiety sensitivity, Type D personality, shocks, gender, marital status, education, ICD indication, and age. Two interaction effects were found. First, a significant time by shocks effect (Wilks' Lambda = 0.97, $F$ (1, 298) = 9.27, $p = .003$) was found, with the plot in Figure 1 showing almost equal levels of anxiety at baseline, but at follow-up higher levels for the patients who had experienced a shock. Second, the time by age (Wilks' Lambda = 0.98, $F$ (1, 298) = 4.82, $p = .029$) effect was significant. Additional analysis using the dichotomized variable age $\leq 65$ instead of the continuous variable age showed that younger patients experience similar levels of anxiety across time points, but older patients experience less anxiety at baseline and equal levels at follow-up. Both Type D personality (Wilks' Lambda = 0.99, $F$ (1, 298) = 1.93, $p = .17$) and anxiety sensitivity (Wilks' Lambda = 1.0, $F$ (1, 298) = 0.26, $p = .61$) did not interact with time nor was there a significant interaction between time and any of the other variables.

The main effect of Type D personality was significant ($F$ (1, 298) = 33.42, $p < .0001$), with Type Ds scoring significantly higher on self-reported anxiety as compared to non Type Ds across both time points. Similarly, the main effect of anxiety sensitivity was significant ($F$ (1, 298) = 66.31, $p < .0001$). In contrast, the main effect of shocks was not significant ($F$ (1, 298) = 1.07, $p = .30$). Low education was associated with higher anxiety levels across time points ($F$ (1, 298) = 8.62, $p = .004$). None of the other variables displayed a main effect.

***Figure 1.*** *Estimated marginal means of self-reported anxiety as a function the experience of a shock.*




**Personality and interviewer-ratings of anxiety**

Mean levels of interviewer-rated anxiety varied as a function of Type D personality and anxiety sensitivity, but not of shocks (Figure 2). A series of univariable linear regression analyses were used to examine the predictive value of personality and shocks for interviewer-ratings of anxiety. Type D personality ($\beta$ = .24, $p$ = .001) and anxiety sensitivity ($\beta$ = .24, $p$ = .001) were significant predictors of interviewer-ratings of anxiety, whereas shocks were not ($\beta$ = .04, $p$ = .59). These two personality variables also predicted interviewer-rated anxiety in multivariable analyses (Table 3). None of the covariates were significantly associated with interviewer-rated anxiety at follow-up. It is important to note that this interview group comprised only 5 patients who had experienced a shock.

***Figure 2.*** *Levels of interviewer-rated anxiety at follow-up, stratified by shocks, Type D personality, and anxiety sensitivity*

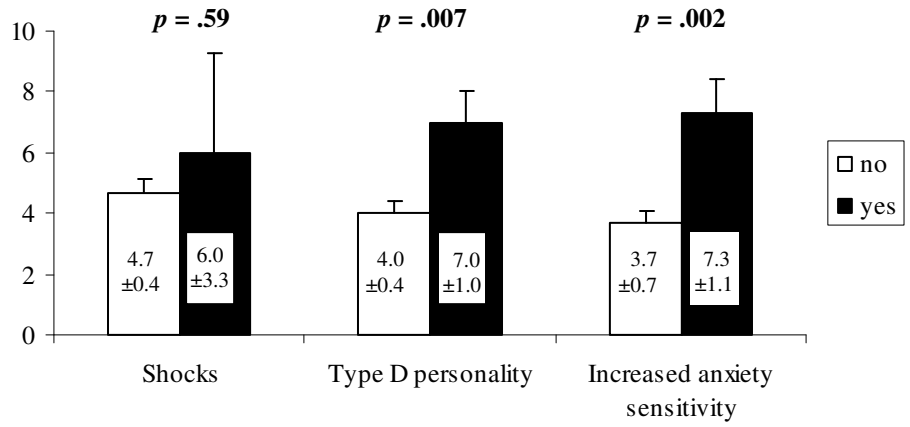



***Table 3.*** *Multivariate predictors of interviewer-rated anxiety at two months following ICD implantation*

| | **Interviewer-rated anxiety** | |
|---|---|---|
| | ***β*** | ***p*** |
| **Type D personality** | **.18** | **.021** |
| **Anxiety sensitivity** | **.19** | **.016** |
| Shocks | .01 | .90 |
| **Demographics** | | |
| Female | .05 | .58 |
| No partner | -.01 | .90 |
| Low education* | .03 | .71 |
| Age | -.09 | .25 |
| **Clinical variables** | | |
| Secondary prevention | .05 | .50 |
| Ischemic heart disease† | .06 | .45 |
| Comorbidity‡ | .08 | .27 |

* Secondary education or less, † Previous MI, PCI, CABG, ‡ Lung, renal, and/or rheumatic disease, and/or diabetes

**DISCUSSION**

This short-term follow-up study in ICD patients examined personality type and ICD shocks in relation to anxiety. Anxiety is an important issue in ICD patients, since over one third of the patients in this study still experienced clinically elevated levels of anxiety two months following the ICD implantation. Both self-reported anxiety as well as interviewer-rated anxiety were independently predicted from Type D personality and anxiety sensitivity, whereas shocks did not exert a significant main effect on either anxiety outcome. However, levels of self-reported anxiety at baseline were equal for shocked versus non-shocked patients, but at two months follow-up, the shocked patients experienced higher levels of self-reported anxiety as compared to the non-shocked patients.

Previous studies regarding the role of shocks for anxiety have reported inconsistent results[2-5]. Personality may play a role in this relationship, but this could not be examined in this study due to the low number of shocks and consequently reduced power. Our results indicate that patients who have experienced one or more shocks may develop symptoms of anxiety (as measured by the STAI), although the severity of these symptoms may not be on the level of a clinical diagnosis of anxiety (as measured by the HAM-A). These results should be interpreted with caution because of the short-term follow-up period and subsequent reduced number of shocks, especially in the interview group.

It is important to note that the decreased prevalence of shocks, as well as the number of shocks per patient, may have influenced our results. The declined prevalence of shocks may in part be due to an increasing proportion of primary ICD implantations. Moreover, increasing use of antitachycardia pacing as initial therapy for ventricular tachycardias will diminish the occurrence of shocks[23]. In general, in our population we programmed antitachycardia pacing for slow and fast VT in all ICD patients. The prevalence of patients who have experienced $\geq$ 1 shocks between implantation and 2 months follow-up was 5% only, which implies reduced power to detect differences. Besides the prevalence and consequently reduced power, the number of shocks may also be of importance in predicting anxiety. The CIDS trial found that receiving $\geq$ 5 shocks was related to poorer emotional functioning, whereas < 5 shocks was not[24]. Because of the small number of participants receiving a shock, we used the distinction of 0 shocks versus

≥ 1 shocks, which may have influenced the results. Therefore, future research should further focus on the role of shocks for anxiety, using different distinctions.

Our results regarding personality factors are in line with and expand previous research, with one previous cross-sectional study showing an independent association between Type D personality and symptoms of anxiety, independent of shocks[5] and another study showing a large effect size (> 0.8) for the impact of Type D personality on anxiety[12]. Our study also showed an independent risk of anxiety sensitivity for state anxiety, which has not been described before. Moreover, the effects of Type D personality and anxiety sensitivity were independent of each other, indicating that both personality constructs have their own effect on symptoms of anxiety. Therefore, in future research on anxiety, it is important to take into account the role of personality.

The level as well as the proportion of patients experiencing high levels of anxiety significantly diminished from baseline to 2 months following the implantation. However, ANCOVA for repeated measures showed no significant change in anxiety levels across time points. Previous studies also have shown that anxiety did not significantly decrease from implantation to follow-up, which was 12 months in these studies[25, 26]. However, one study did show that the proportion of patients experiencing clinically elevated levels of anxiety decreased from 61% to 42% at 12 months follow-up[25]. In these studies, the increased number of shocks or the worsening of the clinical status of the patient may account for the nonsignificant decrease in anxiety over the 12 month period. Hence, levels of anxiety may decrease in the ICD population, indicating that patients can gain some relief with an ICD. Future studies may further investigate this issue.

Secondary prevention was not associated with anxiety. A few studies have investigated the relationship between ICD indication and anxiety, reporting also no difference between primary and secondary prevention[2, 27]. Similarly, primary and secondary prevention ICD patients did not differ on health-related quality of life following ICD implantation[9, 27, 28]. Considering the paucity of studies, future research is warranted to further examine the relationship between indication and psychological well-being.

This study has a number of limitations. First, a follow-up period of two months is rather short and our results should be replicated in studies using a longer follow-up period. Next, the prevalence of shocks was only 5% ($n$ = 16), which may indicate insufficient

power to find a major effect for shocks. Similarly, the relationship between anxiety and the experience of shocks could not be examined. Future studies with a longer follow-up period may have adequate power to research the influence of shocks. Finally, the attrition rate (16%), as well as the significant differences between patients with and without complete data may indicate limited generalizability. In addition, the limited generalizability also applies for the results of the interviewer-ratings of anxiety, although with the exception of shocks and secondary prevention, no systematic differences were found between the interview and mail only group. Despite these limitations, this is the first study to show that Type D personality and anxiety sensitivity exert major independent effects on both self-reported as well as interviewer-rated anxiety, while shocks contributed to an increase in self-reported anxiety.

Important clinical implications can be inferred from these results. Identification of patients with a Type D personality or high in anxiety sensitivity is important, because these patients are at increased risk to experience anxiety and anxiety may precipitate ventricular arrhythmias[6, 7]. In cardiology practice, the DS14 may be used to screen for Type D personality, because this is a short questionnaire and easy to score with well-defined cut-off points to determine the presence of Type D personality[8]. Regarding anxiety sensitivity, the 16-item ASI may be used[14], but there are no established cut-off points to determine the presence of increased anxiety sensitivity. Future research may focus on the ASI and its cut-offs. Furthermore, the importance of self-reported anxiety was stressed with this study, since prevalences of self-reported anxiety were higher as compared to prevalences of interviewer-rated anxiety. Hence, interviewer-rated anxiety may result in an underestimation of anxiety problems.

A recent review on psychological interventions in ICD patients showed that a multi-factorial approach including a cognitive behavioral component paired with exercise training is likely to be most successful[29]. However, appropriate psychosocial interventions for Type D personality and anxiety sensitivity per se have not been examined to date. Since our results showed that the experience of shocks may lead to an increase in symptoms of anxiety, it may be essential to support patients who have experienced a shock in order to diminish the risk that they develop symptoms of anxiety. Sears and colleagues[30] recently showed that structured interventions including ICD education and

cognitive-behavioral strategies may reduce psychological distress in ICD patients who received a shock.

In conclusion, both Type D personality and anxiety sensitivity were independent predictors of self-reported anxiety at baseline and 2 months following ICD implantation as well as interviewer-rated levels of anxiety at 2 months following ICD implantation. The experience of a shock was related to an increase in self-reported symptoms of anxiety from baseline to 2 months following ICD implantation, but not to interviewer-rated levels of anxiety at 2 months follow-up. Identification and support of ICD patients with Type D personality, increased anxiety sensitivity, and shocks is very important. Future research on anxiety in ICD patients should take shocks, as well as these personality factors, into account.

***ACKNOWLEDGEMENTS***

*This study was supported by the Netherlands Organization for Scientific Research, The Hague, The Netherlands with a VICI grant (453-04-004) to Dr. Johan Denollet.*

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*Chapter 3*

# Psychological Reaction to Potential Malfunctioning of Implantable Defibrillators

**Van den Broek KC, Denollet J, Nyklíček I, van der Voort PH. Psychological reaction to potential malfunctioning of implantable defibrillators. Pacing Clin Electrophysiol 2006;29:953-6**

**ABSTRACT**

**Background** Psychological problems following implantable cardioverter defibrillator (ICD) implantation are diverse and include increased levels of anxiety. Anxiety may even rise further when possible malfunctioning of an ICD is announced, with a higher risk of serious ventricular arrhythmias and death as a consequence. Following the public statement of Medtronic, all patients in the Netherlands with the specific Medtronic ICD were contacted for extra device evaluation. The aim of this exploratory study was to determine whether the proportion of ICD patients with high levels of anxiety would increase after this extra device evaluation.

**Methods** Patients were recruited from an ongoing prospective study on psychological effects of ICD implantation. Thirty-three patients completed the State subscale of the State-Trait Anxiety Inventory (STAI) before and after extra device evaluation. The STAI can identify patients with high levels of anxiety.

**Results** A high level of anxiety was experienced by 2 patients (6.1%) at baseline and 8 patients (24.2%) at follow-up ($p$ = .031). Hence, ICD patients were significantly more likely to experience high levels of anxiety following the public statement of potential malfunctioning of their device.

**Conclusion** A public statement regarding device safety may increase levels of anxiety among ICD patients. Given the potential triggering effect of high levels of anxiety on arrhythmias, psychological support may be considered for some of the ICD patients after such public statement.

## INTRODUCTION

Implantation of implantable cardioverter defibrillators (ICDs) is increasingly common in patients who have experienced serious ventricular arrhythmias or in those patients who are at risk for such arrhythmias[1]. Psychological problems following ICD implantation are diverse and include increased levels of anxiety[2-4]. However, symptoms of anxiety may even rise further when possible malfunction of an ICD is announced. Recently, the safety of ICDs has been questioned[5]; for example, Medtronic (Minneapolis, MN, USA) sent out a news report regarding the possibility of rapid battery depletion in some models of the Marquis and Maximo series[6]. Patients may have different psychological reactions to these public statements about the safety of devices and to the options or advice regarding replacement. Some patients may experience acute stress and anxiety, with a higher risk of ventricular arrhythmias as a consequence[7].

In the Netherlands all patients with an ICD of the Marquis or Maximo series were contacted for extra device evaluation. The aim of this exploratory study was to determine whether the number of ICD patients with high levels of anxiety would increase after this extra device evaluation.

## METHOD

### Patients

In the Catharina Hospital in Eindhoven, the Netherlands, ICD patients were approached, who (i) had been called for the extra device evaluation of their Medtronic Marquis series ICD, and (ii) were enrolled in a larger ongoing 18-month prospective study on psychological effects of ICD implantation, which started in May 2003 ($N$ = 39). Of these patients, 35 (90%; 28 men and 7 women) returned their questionnaire; two patients were excluded from analyses because of missing data. This procedure resulted in a final sample of 33 patients. After the extra device evaluation, 5 (15%) had their ICD replaced and the remaining patients were recommended to perform regular self-checks of their device by a handheld magnet. Criteria for ICD replacement were: (i) having experienced an ICD shock the year prior to the extra device evaluation and/or (ii) pacemaker-dependency. The study was approved by the medical ethics committee of the participating hospital. The

study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent.

**Self-report measures and procedure**

At baseline, that is, following ICD implantation, patients completed the State subscale of the State-Trait Anxiety Inventory (STAI)[8] as part of the ongoing study. After the extra device evaluation, patients completed the STAI scale once again. This self-report scale measures the current presence of symptoms of anxiety. The scale consists of 20 statements that ask people to describe how they feel at a particular moment in time (e.g., 'I feel upset', 'I feel calm'), which can be rated on a 4-point intensity scale ranging from *1-not al all* to *4-very much so*. Ten items are positively worded and 10 items are negatively worded. Scores can range from 20, that is, low level of state-anxiety to 80, that is, high level of state-anxiety. The Dutch version of the STAI has good reliability (α ranges from 0.87 to 0.92) and validity[8]. The STAI was also used in recent studies on (i) the influence of psychological distress on ICD patients' report of atrial fibrillation symptoms[9], and (ii) the effect of behavioral intervention on psychological adjustment post-ICD implantation[10].

**Statistical analysis**

Given the relatively small sample and wide ranges of anxiety scores, we used a nonparametric test (i.e., McNemar's Chi-Square test) to compare the proportion of patients with high levels of anxiety at baseline and after extra device evaluation. The upper quartile score on the STAI (≥ 56) was used to identify patients with markedly increased anxiety scores following extra device evaluation. In previous research[11], we found that a score of 56 on the state-scale of the STAI corresponds to the 90% percentile in patients who were recovering from an acute coronary event. Moreover, this score is at least half a standard deviation above the mean STAI-state scores obtained among panic disorder patients[12], once again indicating clinically relevant levels of anxiety.

**RESULTS**

The mean time between assessment of anxiety at baseline and after device evaluation was 14 ±4 months with a range from 5 to 20 months. Sociodemographic and clinical baseline characteristics of the patients are shown in Table 1. The mean age in this patient group was 60 ±11 years. Of these 33 patients, 29 (88%) had a partner, 15 (46%) had received higher education, and 25 (76%) had a history of ischemic heart disease.

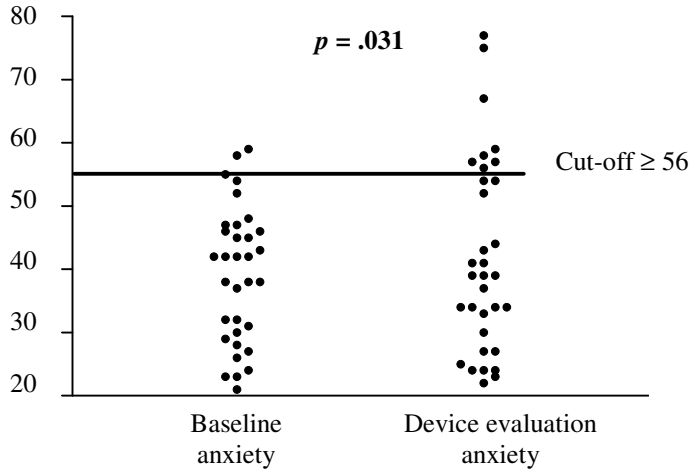
***Table 1.*** *Sociodemographic and clinical characteristics*

| | |
|---|---|
| Age, mean (SD) | 60 (±11) |
| Female | 6 (18%) |
| Partner | 29 (88%) |
| High education | 15 (46%) |
| Employment | 7 (21%) |
| Current smoking | 5 (15%) |
| History of ischemic heart disease* | 25 (76%) |
| Indication for ICD | |
| Primary prevention | 8 (24%) |
| Secondary prevention | 25 (76%) |
| Months since implant and Medtronic's news report, mean (SD) | 14 (±4) |

* e.g., previous AMI, PCI or CABG

The mean level of anxiety rose from 39.1 (±10.73) at baseline to 42.0 (±15.34) after extra device evaluation. The mean anxiety level after device evaluation corresponds to the upper quintile of the Dutch general population[8], and indicates clinically relevant symptoms of anxiety. High levels of anxiety were experienced by 2 patients (6.1%) at baseline and by 8 patients (24.2%) at follow-up ($p$ = .031) (Figure 1). Hence, ICD patients were significantly more likely to experience high levels of anxiety following the public statement of possible malfunctioning of their device.

***Figure 1.*** *Symptoms of anxiety in ICD patients before and after extra device evaluation*




**DISCUSSION**

Significant differences were found in ICD patients regarding levels of anxiety before and after the extra device evaluation following a public statement from Medtronic about the possibility of a short-circuit in the battery; that is, a larger proportion of ICD patients was found to have high levels of anxiety after extra device evaluation as compared to their baseline anxiety level. Psychological distress, including anxiety, has been shown to predict ventricular arrhythmias requiring shocks in ICD patients[7, 13, 14]. In addition, preliminary evidence suggests that behavioral[15] or psychopharmacological[16] intervention may decrease the risk of ventricular arrhythmias in these patients. Psychological distress and anxiety are at least as strong as ICD shocks in reducing quality of life post-ICD implantation[17]. Anxiety may also increase atrial fibrillation symptoms, causing a further decline in quality of life[9]. Given the detrimental effects of anxiety on ventricular arrhythmias and quality of life, ICD patients should be monitored more frequently after an anxiety-evoking event such as a news report about the safety of an ICD.

Although cardiologists or nurses may not feel very comfortable in managing anxiety problems in ICD patients[18], our findings indicate that managing these problems may be important in patients who are being called for extra device evaluation because of potential malfunctioning. There is evidence that specific behavioral intervention may be

indicated for ICD patients with high levels of anxiety. For example, a structured nursing intervention resulted in a significant and stable reduction in anxiety post-ICD implantation[10]. Cognitive behavioral therapy may also be an effective way of reducing anxiety[19] and ventricular arrhythmias[15] among ICD patients.

The present findings should be interpreted with some caution because of the small number of patients. The strength of this explorative study is the fact that patients are participating in an ongoing study, so that baseline data were available. To the best of our knowledge, no other studies including such data have been published.

Currently, a number of steps are being taken to provide clear guidelines for the notification of medical device malfunctioning. These steps should result in the reassurance of patients that ICD therapy is reliable and effectively regulated[20]. In his commentary, Maisel has proposed a number of changes to this notification process, e.g., "manufacturers should annually publish detailed data on device reliability"[21]. In addition, the Heart Rhythm Society (HRS) has formed a task force on device performance and in September 2005 a conference was organized about the current policy and possible improvements. In April 2006, a document regarding recommendations on performance policies for pacemakers and ICDs was released by the HRS[22]. In a report issued on March 20, 2006, a Guidant-commissioned panel made recommendations to "strengthen postmarket surveillance of the products, to actively pursue any potential device-related problems and be completely open with clinicians and the public about safety issues"[23]. The present data suggest that this policy also needs to account for possible psychological consequences for patients of making news regarding safety of devices public.

## CONCLUSION

ICD patients were significantly more likely to experience high levels of anxiety after a public statement about possible malfunctioning of ICDs as compared to their baseline anxiety level. Given the potential triggering effect of anxiety on arrhythmias and its detrimental effect on quality of life, psychological support may be considered for some of the ICD patients after such a public statement.

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*Chapter 4*

# Diabetes and Type D Personality Predict Chronic Anxiety in Cardioverter-Defibrillator Patients: A Multi-Center Study

**Pedersen SS, Van den Broek KC, Theuns DAMJ, Erdman RAM, Alings M, Meijer A, Jordaens L, Denollet J. Diabetes and Type D personality predict chronic anxiety in cardioverter-defibrillator patients: a multi-center study.** ***Submitted for publication.***

**ABSTRACT**

**Background** Little is known about the prevalence of chronic anxiety in patients with an implantable cardioverter defibrillator (ICD). In a multi-center study, we examined 1) the prevalence of patients with chronic anxiety, and 2) the predictors of chronic anxiety at 12 months.

**Methods** ICD patients ($N$ = 222; 81.1% males; mean±SD age = 60.8±10.4 years) recruited from three hospitals, who were anxious at the time of implantation, comprised the sample for the current study. Patients completed the Type D Scale at baseline and the State-Trait Anxiety Inventory (state measure) at baseline and 12 months. A cut-off ≥ 40 on the STAI was used to indicate probable levels of clinical anxiety.

**Results** At 12 months, 51.8% (115/222) patients were still anxious. Diabetes (OR = 4.57; 95% CI 1.65-12.66; $p$ = .003) and Type D personality (OR = 2.81; 95% CI 1.48-5.36; $p$ = .002) were independent predictors of 12-month anxiety, adjusting for demographic and clinical variables including appropriate ICD therapy during follow-up. The prevalence of anxiety at 12 months in the 118 patients with no risk factors was 39.8%, whereas the prevalence was 65.4% in the 104 patients with either diabetes or Type D ($p$ < .001).

**Conclusions** More than 50% of ICD patients anxious at the time of implantation were still anxious at 12 months, indicating a high level of chronicity. Diabetes and Type D personality were independent predictors of chronic anxiety. ICD patients anxious at the time of implantation should be closely monitored and offered adjunctive psychosocial intervention if symptoms do not remit spontaneously in order to prevent adverse health outcomes.

## INTRODUCTION

Implantable cardioverter defibrillator (ICD) therapy for the treatment of life-threatening arrhythmias is generally well accepted by patients, although a subgroup experiences probable clinical levels of anxiety and depression[1-4]. Anxiety seems to be more prevalent in cardioverter-defibrillator patients than depression, with prevalence rates of anxiety reported from 24-87% compared to 24-33% for depressive symptoms[1]. In the general cardiovascular literature, anxiety has been associated with adverse health outcomes, including decreased quality of life[5,6] and increased morbidity and mortality[7,8]. There is also evidence to suggest that general psychological distress and anxiety may precipitate arrhythmic events[9-12]. Therefore, it is important to know the determinants of anxiety following ICD implantation in order to identify high-risk patients and optimize secondary prevention.

Psychological distress may decrease in the first year following implantation with an ICD[1-13], indicating that patients adapt to ICD therapy over time. However, examining changes in overall mean scores over time may mask variability in intraindividual changes and impede the identification of patients who experience chronic levels of distress and potentially may have a greater risk of adverse health outcomes[14]. Importantly, ICD patients who experience anxiety both at the time of implantation and at later follow-up may be distinctly different from those whose anxiety levels may resolve. We are not aware of any studies in ICD patients that have examined patients who are prone to experience chronic anxiety.

Therefore, in a multi-center study focusing on patients who were anxious at the time of implantation, we examined 1) the prevalence of chronic anxiety at 12-month follow-up, and 2) the demographic, clinical and psychological predictors of chronic anxiety.

## METHODS

### Patient sample

Patients implanted with an ICD ($N$ = 222; 81.1% males; mean±SD age = 60.8±10.4 years) between May 2003 and December 2006 at the Erasmus Medical Center, Rotterdam, Catharina Hospital, Eindhoven, and Amphia Hospital, Breda, The Netherlands, comprised

the sample for the current study. Patients included in the Erasmus Medical Center were part of the ongoing *Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter Defibrillator: A prospective Study (MIDAS)*[15]. Exclusion criteria were significant cognitive impairments (e.g., dementia), life-threatening comorbidities (e.g., cancer), a history of psychiatric illness other than affective/anxiety disorders, and insufficient knowledge of the Dutch language.

Initially, 587 ICD patients agreed to participate, but 22 (3.7%) were not included in the analyses due to missing data on self-report measures or clinical variables. These excluded patients were compared with the remaining 565 patients on all demographic and clinical variables, but no statistically significant differences were found. For the purpose of the current study, we included 273 patients who were anxious at baseline, as measured by a score $\geq 40$ on the STAI. Of these patients, 18 died during follow-up and 33 patients had no score on the STAI at 12 months, leaving 222 patients in the analyses.

The study protocol was approved by the medical ethic committees of the participating hospitals. The study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent.

**Measures**

*Demographic and clinical variables*

Demographic variables included gender, age, marital status (single versus having a partner) and low education (secondary education or less). Information on clinical variables included ICD indication (primary versus secondary), etiology (ischemic versus non-ischemic), cardiac resynchronization therapy (CRT), diabetes, smoking, cardiac medication, and appropriate ICD therapy (i.e., both antitachycardia pacing episodes and shocks) for ventricular arrhythmias (i.e., ventricular tachycardia or ventricular fibrillation) during the 12-month follow-up period. Information on these variables was obtained from the patients' medical records, with the exception of smoking which was obtained by means of self-report.

*Anxiety*

Symptoms of anxiety were assessed with the 20-item state scale of the State-Trait Anxiety Inventory (STAI)[16,17]. Each item is rated on a 4-point Likert scale from *1-not al all* to *4-very much so*, with a score range of 20 to 80. A high score indicates high levels of anxiety, with a score ≥ 40 indicating probable levels of clinical anxiety[18,19]. The STAI is a valid and reliable scale, with Cronbach's α ranging from 0.87 to 0.92[16]. The STAI state scale was administered at baseline (i.e., between 1 day prior to ICD implantation and 3 weeks post implantation) and at 12 months.

*Type D personality*

Type D personality was assessed with the 14-item Type D Scale (DS14)[20]. Items are answered on a 5-point Likert scale ranging from *0-false* to *4-true*. The 14 items contribute to two subscales, negative affectivity (e.g., 'I often feel unhappy'; 7 items) and social inhibition (e.g., 'I am a closed kind of person'; 7 items). A standardized cut-off ≥ 10 on both subscales identifies patients with a Type D personality[20,21]. The DS14 was originally developed in cardiac patients and is a valid and reliable measure, with Cronbach's alpha of 0.88/0.86 and 3-month test-retest reliability $r = 0.72/0.82$ for the negative affectivity and social inhibition subscales, respectively[20]. The stability of Type D personality has been confirmed in a large sample of patients with acute myocardial infarction[22]. It is the combination of a high score on both negative affectivity and social inhibition that incurs an increased risk of adverse clinical events rather than the single traits[23]. In addition, Type D is not confounded by cardiac disease severity and measures of anxiety and depression[22, 24]. The DS14 was administered at baseline.

**Statistical analyses**

The Chi-square test (Fisher's exact test when appropriate) was used to examine between group differences on dichotomous variables and Student's *t*-test for independent samples for differences on continuous variables. Multivariable logistic regression analysis was used to determine predictors of 12-month anxiety, adjusted for gender, age, education, marital status, Type D personality, diabetes, etiology, ICD indication, CRT, smoking, and appropriate ICD therapy during follow-up. In a secondary multivariable analysis, we also

adjusted for cardiac medication (i.e., amiodarone, beta-blockers, diuretics, ACE-inhibitors, statins, and digoxin) to examine whether this would change the results, although this model was essentially over fitted due the large number of covariates relative to the number of patients with anxiety at 12-month follow-up. All tests were two-tailed, and a *p*-value < .05 was used to indicate statistical significance. For the results of the logistic regression analysis, odds ratios (OR) and their corresponding 95 percent confidence intervals (CI) are reported. All data were analyzed using SPSS.14.0 for Windows (SPSS Inc., Chicago, Illinois).

## RESULTS

### Patient characteristics

At 12 months, 51.8% (115/222) patients were still anxious. Patient demographic and clinical baseline characteristics stratified by anxiety at 12 months are presented in Table 1. Patients with chronic anxiety were more likely to have diabetes (20.2% versus 8.7%; $p = .029$) and a Type D personality (44.7% versus 28.0%; $p = .015$) than patients whose anxiety remitted by 12 months. There was a trend for CRT ($p = .06$), appropriate ICD therapy for ventricular arrhythmias ($p = .055$) and age ($p = .08$), with patients with chronic anxiety more likely receiving CRT, having experienced ICD therapy for ventricular arrhythmias during follow-up, and being older.

### Independent predictors of 12-month anxiety

The independent predictors of 12-month anxiety are presented in Table 2. Diabetes (OR = 4.57; 95% CI 1.65-12.66; $p = .003$) and Type D personality (OR = 2.81; 95% CI 1.48-5.36; $p = .002$) were independent predictors of 12-month anxiety, adjusting for all other demographic and clinical variables. The overall results did not change when adding cardiac medication (i.e., amiodarone, beta-blockers, diuretics, ACE-inhibitors, statins, and digoxin) to the multivariable analysis (results not shown), apart from the use of ACE-inhibitors (OR = 0.47; 95% CI 0.22-0.99; $p = .047$) being protective of anxiety at 12 months.

***Table 1.*** *Patient baseline characteristics stratified by anxiety at 12 months**

| Characteristics | Anxious (*n* = 115) | Non-anxious (*n* = 107) | *p* |
|---|---|---|---|
| **Demographics** | | | |
| Male gender | 80.9 | 81.3 | 1.00 |
| Age, mean ±SD | 62.0 ±9.6 | 59.5 ±11.0 | .08 |
| Single/no partner | 13.9 | 9.3 | .40 |
| Lower education[1] | 60.9 | 61.5 | 1.00 |
| **Clinical** | | | |
| Smoking | 19.1 | 14.0 | .40 |
| **Diabetes** | **20.2** | **8.7** | **.029** |
| Secondary indication | 48.7 | 45.8 | .77 |
| Ischemic etiology | 71.3 | 70.1 | .96 |
| CRT | 38.1 | 25.5 | .06 |
| Appropriate ICD therapy during follow-up | 25.0 | 13.6 | .055 |
| **Medication** | | | |
| Amiodarone | 25.7 | 25.5 | 1.00 |
| Beta-blockers | 78.8 | 84.9 | .32 |
| Diuretics | 64.6 | 58.5 | .43 |
| ACE-inhibitors | 69.9 | 75.5 | .44 |
| Statins | 69.8 | 69.0 | 1.00 |
| Digoxin | 15.9 | 12.3 | .56 |
| **Psychological** | | | |
| **Type D personality** | **44.7** | **28.0** | **.015** |

Results are presented as percentages unless otherwise indicated, CRT = cardiac resynchronization therapy, [1] Secondary education or less (≤ 13 years of education)

***Table 2.*** *Predictors of anxiety at 12 months**

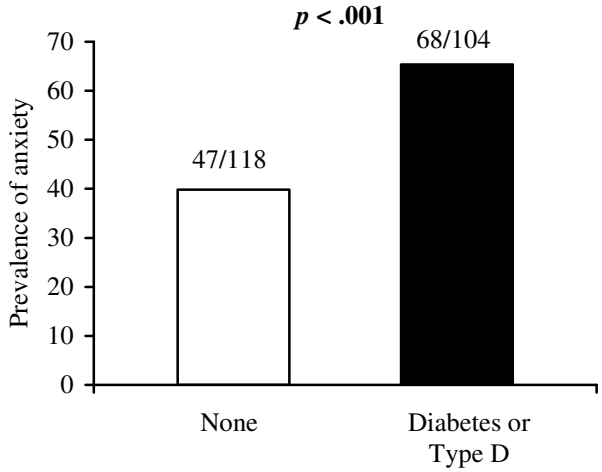
| Predictor variables | OR | 95% CI | *p* |
|---|---|---|---|
| **Demographics** | | | |
| Male gender | 0.93 | 0.42-2.09 | .87 |
| Age | 1.03 | 0.99-1.06 | .13 |
| Single/no partner | 1.16 | 0.44-3.10 | .77 |
| Lower education[1] | 0.93 | 0.50-1.75 | .82 |
| **Clinical** | | | |
| Smoking | 1.68 | 0.76-3.69 | .20 |
| **Diabetes** | **4.57** | **1.65-12.66** | **.003** |
| Secondary indication | 1.33 | 0.69-2.60 | .40 |
| Ischemic etiology | 0.81 | 0.38-1.72 | .58 |
| CRT | 1.80 | 0.88-3.68 | .11 |
| Appropriate ICD therapy during follow-up | 1.94 | 0.86-4.37 | .11 |
| **Psychological** | | | |
| **Type D personality** | **2.81** | **1.48-5.36** | **.002** |

* Multivariable logistic regression analysis, CRT = cardiac resynchronization therapy, [1] Secondary education or less (≤ 13 years of education)

**Prevalence of anxiety at 12 months stratified by diabetes and Type D personality**

Given that Type D personality and diabetes were the two most prominent predictors of anxiety at 12 months, we created 2 groups based on the presence of none versus one (i.e., either Type D or diabetes) of these risk factors. Anxiety at 12 months stratified by none versus one of these risk factors is presented in Figure 1. The prevalence of anxiety in the 118 patients with no risk factors was 39.8%, whereas the prevalence was 65.4% in the 104 patients with either diabetes or Type D ($p < .001$).

***Figure 1***. *Anxiety at 12 months stratified by risk factors (total numbers are listed on top of bars; anxiety was indicated by a STAI score ≥ 40)*




**DISCUSSION**

In the current study, we found that 50% of ICD patients suffering from anxiety at baseline also experienced probable levels of clinical anxiety at 12 months post implantation, indicating a high level of chronicity. Diabetes and Type D personality were both independent predictors of chronic anxiety, with the presence of anxiety being significantly higher in patients with one of these risk factors compared to none. ICD therapy for ventricular arrhythmias was not significantly associated with chronic anxiety, although there was a trend.

The study of anxiety in the context of ICD patients has received considerable attention[1-4, 13, 25, 26], likely due to the unique feature of the device compared to any other intervention in clinical cardiology, namely its capacity to provide shocks to terminate life-threatening ventricular arrhythmias. For this purpose, device-specific questionnaires have been developed, such as the Florida Patient Acceptance Survey[27] and the ICD Concerns Questionnaire[28, 29], to tap into the fears that patients have about the device providing a shock. However, generally studies have focused on prevalence rates or mean anxiety scores over time, which may mask intraindividual changes and the identification of

patients who may experience chronic levels of distress[14]. Therefore, we selected patients who were anxious already at baseline in order to examine the level of chronicity at 12 months and the profile of chronically anxious patients. To our knowledge, this is the first study to use such an approach to anxiety in ICD patients. We found that once anxiety was manifest at the time of implantation, 50% of patients had symptoms that did not remit spontaneously during the 12-month follow-up period. This level of chronicity is similar to that found in a recent study of patients treated with percutaneous coronary intervention (PCI), as part of the RESEARCH registry[30].

Diabetes and having a Type D personality typified patients experiencing chronic levels of anxiety in the current study. In PCI patients, Type D has also been associated with chronic anxiety adjusting for demographic and clinical risk factors, including stent type[30]. In previous studies of the MIDAS population, we also showed that Type D personality but not ICD indication was a predictor of poor quality of life at 3 months[15], and that clustering of Type D with ICD concerns was associated with increased anxiety at 6 months follow-up[13]. Type D has also been shown to independently predict self-reported as well as interviewer-rated levels of anxiety[26]. Diabetes has previously been associated with the onset of depressive symptoms in PCI patients[31] and co-morbid diabetes and angina with anxiety in outpatients with chronic heart failure[32]. Increased anxiety in diabetic versus non-diabetic ICD patients found in the current study may reflect the toll of having to deal with multiple somatic diseases[33], although we cannot rule out that the association may also represent a chance finding.

The high level of chronicity of anxiety found in the current study may have clinical implications, as anxiety and general psychological distress have been associated with an increased risk of ventricular arrhythmias[9-12]. Anxiety may potentiate pathological processes that increase the risk of ventricular arrhythmias and sudden cardiac death through reduced heart rate variability[34], which is an important risk factor for sudden cardiac death[35]. Distress may also be related to increases in T-wave alternans[36, 37], which is an important predictor for ventricular arrhythmias and death[38]. Although anxiety levels in ICD patients generally have been shown to diminish and reach a plateau after 1 year[1], this pattern may be different for shocked patients[39] and patients whose ICD may be subject to malfunctioning and recall[40]. The present study suggests that patients who are

anxious at the time of ICD implantation should be closely monitored and offered adjunctive psychosocial intervention if anxiety symptoms do not remit spontaneously. Screening for emotional distress in ICD patients at regular intervals has also been advocated by others to track changes in distress over time[41]. In terms of the clinical management of these patients, they should be offered adjunctive psychosocial intervention, using a multi-factorial approach incorporating an educational component on the ICD, cognitive behavioral therapy, problem-solving skills, and exercise[42]. Such an approach would also be cost-effective, as it would provide adjunctive intervention to those patients who need it the most and who are also likely to benefit the most.

The results of this study should be interpreted with some caution. First of all, we had no information on participation in cardiac rehabilitation and the use of psychopharmaca, which may have influenced anxiety levels. Second, due to the small number of patients with the co-occurrence of diabetes and Type D personality ($n$ = 9), we were not able to deduce whether these patients are particularly prone to experience chronic anxiety compared to patients with one or no risk factors. Third, the number of patients with anxiety at follow-up was insufficient to also adjust for medication use, which would lead to over fitting of the multivariable regression model. Nevertheless, in secondary analysis adjustment for medication did not change the overall results. Finally, we used a generic rather than a disease-specific measure to assess anxiety, with the likelihood that levels of anxiety would have been higher if assessed with a disease-specific measure, as it taps into symptoms that are more pertinent to patients.

In conclusion, more than 50% of ICD patients who were anxious at baseline still suffered from anxiety 12 months post implantation, indicating a high level of chronicity. Diabetes and Type D personality were independent predictors of chronic anxiety, as indicated by a 2- to 4-fold increased risk of experiencing anxiety both at baseline and at 12-month follow-up. Patients who are anxious at the time of implantation should be closely monitored and offered adjunctive psychosocial intervention if symptoms do not remit spontaneously[42]. It may be important to prevent that anxiety becomes chronic, as these patients may be at increased risk of poor quality of life, life-threatening arrhythmias or sudden cardiac death.

***ACKNOWLEDGEMENTS***

*We would like to thank Agnes Muskens-Heemskerk and Eefje Postelmans for inclusion of the patients into the study and Simone Traa, Martha van den Berg, Vivianne Sterk, Jolien Diekhorst, Marjan Traa, and Marie-Anne Mittelhaeuser for help with data management. This research was supported with a VENI grant (451-05-001) to Dr. Susanne S. Pedersen and a VICI grant (453-04-004) to Dr. Johan Denollet, from the Netherlands Organization for Scientific Research, The Hague, The Netherlands.*

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*Chapter 5*

# Trajectories of Anxiety and Depressive Symptoms in Patients with an Implantable Defibrillator

**Van den Broek KC, Smith ORF, Meijer A, Alings M, Denollet J, Nyklíček I. Trajectories of anxiety and depressive symptoms in patients with an implantable defibrillator.** ***Submitted for publication.***

**ABSTRACT**

**Background** A subgroup of patients experiences anxiety and depressive symptoms following implantable cardioverter defibrillator (ICD) implantation, but little is known about the course of these symptoms. Therefore, we examined 1) trajectories of anxiety and depressive symptoms in the first year post-implantation and 2) the predictors of these trajectories.

**Methods** ICD patients ($N$ = 312, 16.7% females, 62.8% ≥ 60 years) completed the STAI (state-version) and BDI at baseline, and at 2 and 12 months post-implantation. Anxiety sensitivity (Anxiety Sensitivity Index), Type D personality (Type D Scale), and self-deception (Marlowe-Crowne scale) were also measured at baseline. SAS procedure TRAJ was used to examine trajectories over a 12-month period and multinomial logistic regression to examine predictors of these trajectories.

**Results** Four distinct trajectories were found for both anxiety and depressive symptoms, that is, respectively very low (8.0%), low (53.2%), mildly (35.3%), and severely (3.5%) anxious groups and parallel groups for depression (respectively, 38.1%, 36.9%, 17.0%, and 8.0%). Trajectories were relatively stable, although particularly within depression classes some statistically significant change was observed. Multinomial regression analyses showed that anxiety sensitivity ($OR_{\text{mildly anxious}}$ = 3.76, $p$ < .001) and Type D personality ($OR_{\text{mildly anxious}}$ = 2.09, $p$ = .03; $OR_{\text{severely anxious}}$ = 17.46, $p$ = .001; $OR_{\text{severely depressed}}$ = 4.11, $p$ = .005) were the most prominent predictors of anxiety and depression groups.

**Conclusions** Anxiety and, to a lesser extent, depression trajectories tend to be stable in the first year post-implantation, with anxiety sensitivity and Type D personality being the most prominent predictors of these trajectories. Psychological screening may be implemented in hospitals to identify patients at risk for chronic anxiety and depression.

## INTRODUCTION

Ventricular arrhythmias are the most important cause of sudden cardiac death[1]. The main treatment to prevent sudden cardiac death in survivors of these arrhythmias, and also in patients at risk, is implantation with an implantable cardioverter defibrillator (ICD)[2]. ICDs can terminate ventricular arrhythmias by antitachycardia pacing (ATP) or high-voltage shocks[3]. Randomized trials have shown that the ICD is 20% to 60% more beneficial in reducing mortality rates as compared to antiarrhythmic drugs[2, 4] in secondary as well as primary prevention patients[2]. However, a substantial subgroup of patients experiences psychological problems, including anxiety, depression, impaired quality of life, and avoidance behaviors[5-7]. Anxiety may be the most important emotion, but depression also is prevalent, with diagnosable levels being experienced by 13%-38% and 10%-15% of ICD patients, respectively[5]. ICD shocks may also lead to increased distress, although results are contradictory[8-13].

Little is known about the course of anxiety and depressive symptoms in ICD patients. These levels may decrease after ICD implantation to 6[14] and 12[15] months follow-up, and in case of anxiety even to 30 months follow-up[16]. Other studies suggest that levels remain stable over various periods within 1 month and 5 years post-implantation[8, 9, 17, 18], although one study found that anxiety levels increased from 6 to 12 months post-implantation[14]. It is important to note that all these studies used mean scores in their analyses. This approach does not allow for the identification of subgroups with high levels of anxiety and depression. Identification and treatment of these patients is very important, as increased levels of anxiety and depression may precipitate ventricular arrhythmias in ICD patients[19, 20].

The aims of the current study were to 1) determine whether different trajectories of anxiety and depressive symptoms exist in subgroups of ICD patients over the 12-month period following ICD implantation and 2) determine predictors of these trajectories, using several demographic, clinical, and psychological variables.

## METHODS

### Patient sample

Patients hospitalized between May 2003 and December 2006 for implantation with an ICD were included from two referral hospitals in the Netherlands (Catharina Hospital, Eindhoven; Amphia Hospital, Breda). Inclusion criteria were implantation with an ICD and age between 18 and 80 years. Exclusion criteria were significant cognitive impairments (e.g., dementia), life-threatening comorbidities (e.g., cancer), and insufficient knowledge of the Dutch language.

The study was approved by the medical ethic committees of both participating hospitals. The study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent.

### Procedure and psychological measures

Patients completed self-report questionnaires on anxiety and depressive symptoms at 3 time points, that is, between 0 and 3 weeks following ICD implantation and subsequently at 2 and 12 months following ICD implantation. Questionnaires on Type D personality, anxiety sensitivity, and self-deception were completed at the first time-point only.

*State-anxiety*

The State-Trait Anxiety Inventory (STAI) was used to assess general symptoms of anxiety[21]. The STAI is a self-report measure consisting of two 20-item scales developed to measure the level of general state and trait anxiety. In the current study, we only used the state measure. Each item is rated on a 4-point Likert scale from *1-not al all* to *4-very much so*. Ten items measure the presence of anxiety and 10 items the absence of anxiety. After recoding the anxiety absence items, scores range from 20, that is, low level of state-anxiety to 80, that is, high level of state-anxiety, were scores above 40 indicate increased levels of anxiety[21]. The STAI has been demonstrated to have adequate validity and reliability, with Cronbach's α ranging from 0.87 to 0.92[21].

*Depressive symptoms*

The Beck Depression Inventory (BDI) is a 21-item self-report measure developed to assess the presence and severity of depressive symptoms[22]. Each item is rated on a Guttmann scale from *0* to *3*. The BDI is a reliable and valid measure of depressive symptomatology and the most frequently used self-report measure of depressive symptoms in cardiac patients. Clinically relevant levels are present when scoring ≥ 10[22, 23].

*Type D personality*

The DS14 was used to assess Type D personality and contains the 7-item scales negative affectivity (e.g., "I often feel unhappy") and social inhibition (e.g., "I am a closed kind of person")[24]. Items are answered on a 5-point Likert scale, ranging from *0-false* to *4-true*, with total scores ranging from 0-28 for both subscales. Patients scoring ≥ 10 on both subscales are classified as Type D[24, 25]. The DS14 has good reliability, with Cronbach's alpha being 0.88 and 0.86 and three-month test-retest reliability being 0.72 and 0.82, for negative affectivity and social inhibition, respectively. Recently, the DS14 was shown to be a stable measure of Type D personality over an 18-month period[26], and scores were not affected by cardiac disease severity or symptoms of anxiety and depression[26, 27]. Type D personality has been found to predict adverse cardiac events, including mortality[28-30].

*Anxiety sensitivity*

Anxiety sensitivity was measured using the 16-item Anxiety Sensitivity Index (ASI), designed to assess sensitivity and fear of anxiety symptoms, e.g., "It scares me when I feel faint" and "When I am nervous, I worry that I might be mentally ill"[31]. Items are rated on a five-point Likert scale from *0-very little* to *4-very much*. Total scores are obtained by summing the scores on the 16 items, that is, total scores range from 0 to 64, with higher scores reflecting greater sensitivity and fear of anxiety symptoms. In our study, the reliability of the ASI was good, with Cronbach's $\alpha = 0.89$. Since there is no standardized cut-off for the ASI, we used a median split (i.e., ASI ≥ 12) to dichotomize ASI scores. Anxiety sensitivity is associated with an enhanced risk of clinically relevant levels of anxiety in ICD patients[12]. As a final point, it is important to distinguish anxiety sensitivity;

that is, the beliefs that anxiety symptoms have negative effects, from anxiety; that is, the frequency of occurrence of anxiety symptoms[31].

*Self-deception*

The Marlowe-Crowne Social Desirability Scale is a valid and reliable measure of self-deception[32, 33]. Originally, this scale consists of 33 items, but three items were omitted that were judged as being typical of an American population. We applied a previously reported cut-off score (≥ 22) to classify patients as high in self-deception[34]. Self-deception in combination with very low anxiety scores is predictive of adverse cardiac events, including mortality[35].

**Demographic and clinical variables**

Demographic and clinical variables were obtained from medical records. Demographic variables included gender, age (dichotomized using a median split, that is, ≥ 60 years), marital status (i.e., having a partner versus not having a partner), and education (low education, that is secondary school or less versus higher education). Clinical variables were obtained from medical records and included ICD indication (primary versus secondary prevention), etiology (ischemic versus non-ischemic), comorbidity (lung, renal, or rheumatic disease and/or diabetes versus none), and appropriate ICD therapies (i.e., ATP or shocks) for ventricular arrhythmias.

**Statistical Analyses**

Differences between patients who were excluded from analyses versus included in analyses were examined with a Chi-square test.

SAS procedure TRAJ was used to examine trajectories of symptoms of anxiety and depression in ICD patients over a 12-month period[36]. TRAJ fits a finite mixture model (or latent class model) to identify classes of individuals following similar patterns of behavior over time. The model assumes unobserved latent variables to explain the associations among observed scores and can be seen as a categorical equivalent of factor analysis. To determine the optimal number of trajectories, the Bayesian Information Criterion (BIC) was used, with a higher BIC indicating a better fit. However, a difference of less than 3

will favor the least complex model. BIC is often used for comparing models, as it trades off model fit and model complexity.

For comparison between classes we used the Chi-square test for discrete variables. Adjusted Standardized Residuals (ASRs) were used to identify groups responsible for significant differences. A residual greater than 2.0 was taken to indicate a significantly higher frequency, and a residual less than -2.0 was considered to indicate a significantly lower frequency, than expected if the independence hypothesis was true[37]. Cohen's *d* was used as a measure of clinical significance. Cohen has defined effect sizes as small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$). Multinomial logistic regression was used to assess whether demographic, medical, and personality variables were predictors of trajectories of symptoms of anxiety and depression. A similar approach has previously been used in myocardial infarction[38], percutaneous coronary intervention[39], and peripheral arterial disease[40] patients.

## RESULTS

### Patient characteristics

Of the 355 ICD patients who agreed to participate, 25 (7.0%) died within 12 months and 18 (5.1%) had too many missing values on self-report or clinical data, resulting in a final sample of 312 patients (87.9%). The proportion of patients with a Type D personality was significantly higher among patients who were excluded from analyses as compared to included patients (39.0% versus 20.5%; $\chi^2 = 7.09$; df = 1, $p = .008$). There was also a trend for excluded patients to more often have no partner (20.9% versus 11.8%; $\chi^2 = 2.79$; df = 1, $p = .095$) and score low on self-deception (69.0% versus 53.4%; $\chi^2 = 3.69$; df = 1, $p = .055$). No other significant differences were found between excluded and included patients. Table 1 (second column) shows the baseline characteristics of included patients.

***Table 1.*** *Patient characteristics stratified by anxiety class*

| **Baseline variable** | **Total (*N* = 312)** % (*n*) | **Very low anxious (*n* = 25)** % (*n*) | **Low anxious (*n* = 166)** % (*n*) | **Mildly anxious (*n* = 110)** % (*n*) | **Severely anxious (*n* = 11)** % (*n*) | ***p*-value** |
|---|---|---|---|---|---|---|
| Female sex | 17 (52) | 16 (4) | 16 (26) | 18 (20) | 18 (2) | .96 |
| Age ≥ 60 yrs | 63 (196) | 64 (16) | 59 (98) | 70 (77) | 46 (5) | .18 |
| Having no partner | 12 (37) | 8 (2) | 12 (20) | 12 (13) | 18 (2) | .85 |
| **Low educational level*** | 48 (151) | **44 (11)** | **40 (66)** | **62 (68)** | **55 (6)** | **.003** |
| Secondary indication | 48 (149) | 60 (15) | 45 (75) | 47 (52) | 64 (7) | .38 |
| Ischemic etiology | 72 ( 226) | 72 (18) | 68 (113) | 78 (86) | 82 (9) | .27 |
| Comorbidity** | 34 (107) | 40 (10) | 31 (51) | 38 (42) | 36 (4) | .50 |
| ATP/shocks | 18 (57) | 20 (5) | 15 (25) | 22 (24) | 27 (3) | .38 |
| **Anxiety sensitivity** | 53 (164) | **4 (1)** | **42 (70)** | **76 (84)** | **82 (9)** | **<.001** |
| **Type D personality** | 21 (64) | **4 (1)** | **13 (22)** | **30 (33)** | **82 (9)** | **<.001** |
| **Self-deception** | 47 (146) | **68 (17)** | **52 (87)** | **36 (40)** | **18 (2)** | **.002** |

* Secondary school or less, ** Lung disease, renal failure, rheumatoid arthritis, diabetes

***Table 2.*** *Patients characteristics stratified by depression class*

| | **Total** (***N* = 312**) | **Very low depressed** (***n* = 119**) | **Low depressed** (***n* = 115**) | **Mildly depressed** (***n* = 53**) | **Severely depressed** (***n* = 25**) | |
|---|---|---|---|---|---|---|
| **Baseline variable** | **% (*n*)** | **% (*n*)** | **% (*n*)** | **% (*n*)** | **% (*n*)** | ***p*-value** |
| Female sex | 17 (52) | 13 (16) | 17 (20) | 23 (12) | 16 (4) | .51 |
| Age≥60 yrs | 63 (196) | 61 (72) | 67 (77) | 60 (32) | 60 (15) | .72 |
| Having no partner | 12 (37) | 11 (13) | 10 (11) | 19 (10) | 12 (3) | .37 |
| Low educational level* | 48 (151) | 42 (50) | 50 (57) | 53 (28) | 64 (16) | .20 |
| Secondary indication | 48 (149) | 56 (66) | 44 (51) | 36 (19) | 52 (13) | .09 |
| **Ischemic etiology** | 72 ( 226) | **64 (76)** | **75 (86)** | **83 (44)** | **80 (20)** | **.04** |
| **Comorbidity**** | 34 (107) | **27 (32)** | **34 (39)** | **47 (25)** | **44 (11)** | **.04** |
| ATP/shocks | 18 (57) | 16 (19) | 16 (18) | 26 (14) | 24 (6) | .24 |
| **Anxiety sensitivity** | 53 (164) | **32 (38)** | **61 (70)** | **66 (35)** | **84 (21)** | **<.001** |
| **Type D personality** | 21 (64) | **8 (10)** | **24 (27)** | **23 (12)** | **64 (16)** | **<.001** |
| **Self-deception** | 47 (146) | **59 (70)** | **47 (54)** | **34 (18)** | **16 (4)** | **<.001** |

* Secondary school or less, ** Lung disease, renal failure, rheumatoid arthritis, diabetes

***Figure 1.*** *Observed trajectories of anxiety symptoms (STAI)*

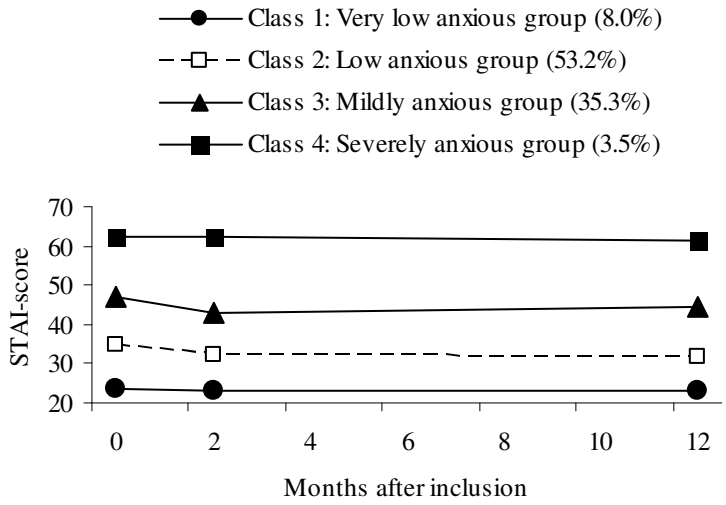
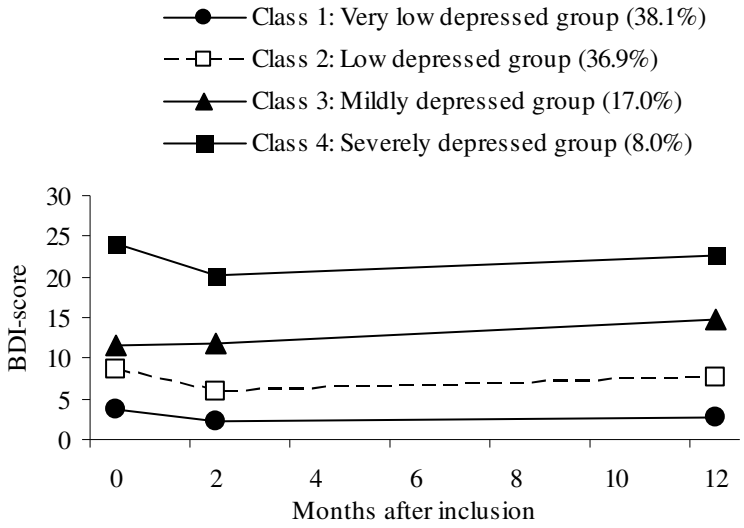



***Figure 2.*** *Observed trajectories of depressive symptoms (BDI)*



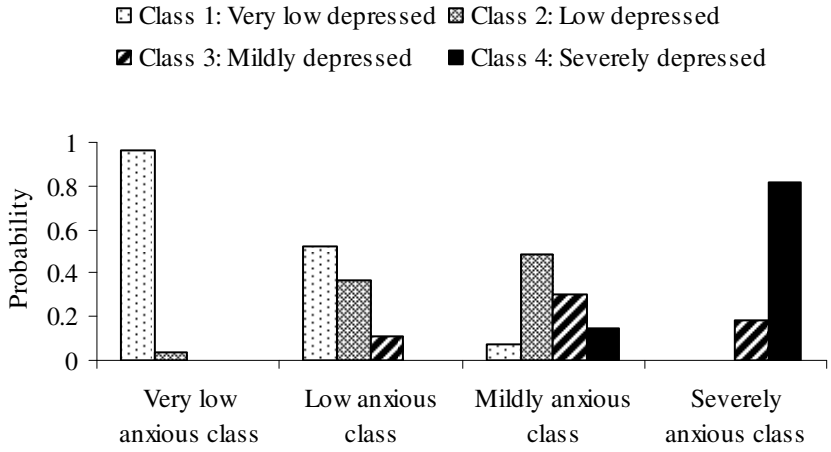
**Trajectories of anxiety and depression**

As displayed in figures 1 and 2, latent class analyses resulted in four distinct trajectories for both symptoms of anxiety (BIC = -3222) and depression (BIC = -2650). The first class was labeled as respectively the very low anxious group and the very low depressed group. Scores for anxiety and depression for the second class were slightly higher as compared to the first class but did not reach clinical significant levels; hence, they were classified as respectively low anxious and low depressed. The third class was described as mildly anxious and mildly depressed because scores within these trajectories were slightly higher as compared to cut-off scores to indicate clinically relevant levels. Finally, the fourth class was labeled as severely anxious and severely depressed because scores within these classes were far higher as compared to the cut-off scores for clinically relevant levels. Since the low anxious group (53.2% of the patients) and the low depressed group (36.9% of the patients) comprised a large percentage of patients and approximate total sample averages of anxiety and depression scores, these two groups were used as reference categories in the multinomial regression analyses.

Trajectories for anxiety were relatively stable, although some within-class change was observed for two subgroups. A significant decrease was observed between baseline and 2-months follow-up for both the low anxiety class (Cohen's $d$ = -0.32) and the mild anxiety class (Cohen's $d$ = -0.51). Trajectories of depression were somewhat more variable. For the depression classes, a significant quadratic pattern was observed in the very low depressed class (Cohen's $d_{\text{baseline-2months}}$ = -0.50; Cohen's $d_{\text{2months-12months}}$ = 0.20), the low depressed class (Cohen's $d_{\text{baseline-2months}}$ = -1.03; Cohen's $d_{\text{2months-12months}}$ = 0.64), and the severely depressed class (Cohen's $d_{\text{baseline-2months}}$ = -0.80; Cohen's $d_{\text{2months-12months}}$ = 0.43). A significant linear increase was found in the mildly depressed class (Cohen's $d_{\text{baseline-12months}}$ = 0.84).

The Spearman rank order correlation coefficient ($r_s$) between the anxiety classes and depression classes equals 0.63 ($p < .001$) suggesting a considerable overlap between the trajectories of anxiety and depression. This association is visualized in Figure 3, which shows the conditional probabilities of being in a depression class given the anxiety class.

***Figure 3.*** *Probability of depression class conditional of anxiety class*




**Patient characteristics stratified by anxiety and depression class**

Demographic, clinical, and personality characteristics stratified by anxiety class are shown in Table 1 and by depression class in Table 2. Differences were found between anxiety groups on educational level ($\chi^2$ = 13.9; df = 3, $p$ = .003), anxiety sensitivity ($\chi^2$ = 62.4; df = 3, $p$ < .001), Type D personality ($\chi^2$ = 40.7; df = 3, $p$ < .001), and self-deception ($\chi^2$ = 15.0; df = 3, $p$ = .002). Patients in the very low anxious and the low anxious groups were more likely to be self-deceptive (ASR = 2.2 resp. ASR = 2.1) but less likely to have high anxiety sensitivity (ASR = -5.1 resp. ASR = -4.0) or to have a Type D personality (ASR = -2.2 resp. ASR = -3.5) than would be expected from the independence hypothesis, whereas the opposite is true for patients in the mildly and severely anxious groups. Patients in the mildly anxious group were more likely to have a lower educational level (ASR = 3.6).

Differences were found between depression groups on prevalence of ischemic etiology ($\chi^2$ = 8.4; df = 3, $p$ = .04), comorbidity ($\chi^2$ = 8.1; df = 3, $p$ = .04), anxiety sensitivity ($\chi^2$ = 38.8; df = 3, $p$ < .001), Type D personality ($\chi^2$ = 39.9; df = 3, $p$ < .001), and self-deception ($\chi^2$ = 19.9; df = 3, $p$ < .001). Patients in the very low depressed group were more likely to be self-deceptive (ASR = 3.3) but less likely to have ischemic etiology (ASR = -2.7), comorbidities (ASR = -2.1), high anxiety sensitivity (ASR = -5.8)

or a Type D personality (ASR = -4.3) than would be expected from the independence hypothesis. Patients in the severely depressed group were more likely to have high anxiety sensitivity (ASR = 3.5) and a Type D personality (ASR = 5.5), but were less likely to be self-deceptive (ASR = -3.2).

No association was found between classes of anxiety ($\chi^2$ = 3.1; df = 3, $p$ = .38) or depression ($\chi^2$ = 4.2; df = 3, $p$ = .24) and the occurrence of either ATP or shock between baseline and 12-months follow-up.

**Predictors of anxiety and depression trajectories**

Variables that were significantly associated with one of the anxiety or depression symptom trajectories were entered into a multivariable model. Multivariable predictors of anxiety and depression symptom trajectories are presented in Table 3. The estimates are reported in odds ratios (OR), using respectively the low anxious group, and the low depressed groups as the reference categories.

Low anxiety sensitivity was a predictor of both the very low anxious class (OR = 0.06; 95%CI 0.01-0.47, $p$ < .001) and the very low depressed class (OR = 0.35; 95%CI 0.20-0.61, $p$ < .001) membership. In addition, Type D personality was associated with a low probability of being in the very low depressed class (OR = 0.33; 95%CI 0.14-0.76, $p$ = .01). Anxiety sensitivity and Type D personality were the most prominent predictors of elevated symptoms of anxiety and depression over time, with odds ratios varying from 2.09 to 17.46 (Table 3). Finally, low educational level was associated with being mildly anxious (OR = 2.44; 95%CI 1.42-4.20, $p$ = .001). No significant associations were found for indication, etiology, and self-deception.

***Table 3.*** *Multivariable associations of baseline covariates with trajectories of anxiety [A] and depression [B].*

| **[A]** | **Very low anxious** | | **Mildly anxious** | | **Severely anxious** | |
|---|---|---|---|---|---|---|
| **Covariate** | **OR** | ***p*-value** | **OR** | ***p*-value** | **OR** | ***p*-value** |
| **Low educational level*** | ns | ns | **2.44** | **.001** | ns | ns |
| **Anxiety sensitivity** | **0.06** | **.007** | **3.76** | **<.001** | ns | ns |
| **Type D personality** | ns | ns | **2.09** | **.03** | **17.46** | **.001** |
| Self-deception | ns | ns | ns | ns | ns | ns |

| **[B]** | **Very low depressed** | | **Mildly depressed** | | **Severely depressed** | |
|---|---|---|---|---|---|---|
| **Covariate** | **OR** | ***p*-value** | **OR** | ***p*-value** | **OR** | ***p*-value** |
| Ischemic etiology | ns | ns | ns | ns | ns | ns |
| Comorbidity** | ns | ns | ns | ns | ns | ns |
| **Anxiety sensitivity** | **0.35** | **<.001** | ns | ns | ns | ns |
| **Type D personality** | **0.33** | **.01** | ns | ns | **4.11** | **.005** |
| Self-deception | ns | ns | ns | ns | ns | ns |

* Secondary school or less, ** Lung disease, renal failure, rheumatoid arthritis, diabetes

## DISCUSSION

To our knowledge, this is the first study which examined trajectories of anxiety and depressive symptoms in ICD patients in the first year post-implantation. Our results suggest four distinct classes of both anxiety and depression symptoms, mainly based on absolute levels, ranging from low to severe levels, rather than differences regarding change over time. Anxiety symptoms, and to a lesser extent, depressive symptoms showed relatively stable trajectories, with depression scores showing some significant within-class changes. Anxiety and depression trajectories had considerable overlap. Importantly, ICD indication and ATPs or shocks were unrelated to anxiety and depressive symptoms trajectories. Type D personality and anxiety sensitivity were the most important predictors of trajectories.

Results of the current study extend previous research, as we identified different trajectories of anxiety and depressive symptoms and found them to vary across subgroups of patients. Despite statistical significant within-class change, mainly due to small standard-deviations, we concluded that the four trajectories of anxiety and depressive symptoms were relatively stable over time, because the ranking of the trajectories did not change over time. The largest changes are consistent with previous studies which found a decrease of symptoms after implantation[14-16], but our results are mainly in line with studies showing a stable course of anxiety and depression from 1 month to 5 years post-implantation[8, 9, 17, 18]. However, these studies examined only overall mean scores. We also found that most subgroups of patients, defined by their symptom trajectories, show a relatively stable course of symptoms. The proportion of patients experiencing at least mild levels of anxiety symptoms (38.8%) was higher as compared to the proportion of patients experiencing at least mild levels of depressive symptoms (25.0%), which is in line with previous research in ICD patients[5, 8, 17]. The overlap between anxiety and depressive symptoms trajectories concur with results of previous studies[41]. Our results are rather salient, considering the chronicity of mild and severe levels of anxiety and depression in a substantial subgroup of patients.

ICD indication was unrelated to anxiety and depression, although it seems likely that resuscitated patients and non-resuscitated patients with ventricular arrhythmias may experience higher levels of distress as compared to other patients. All other studies

regarding ICD indication and patient-centered outcomes also reported negative findings[8, 11-13, 42-44]. However, future research may investigate whether the effect of ICD indication on patient-centered outcomes may be influenced by other factors relating to these outcomes, including Type D personality and anxiety sensitivity.

Occurrence of appropriate ICD therapies during the first year post-implantation was also included in the model, despite the fact that this variable is not a constant, as ICD therapies can occur after implantation at any time. Studies have shown that shocks may lead to increased anxiety and depression, although results are not conclusive[8-13]. Anxiety and depression may also precipitate ventricular arrhythmias[19, 20]. Therefore, if statistical differences had been found, causality could not be inferred. Our results seem to suggest that ATPs and shocks are not associated with increased distress; however these non-significant results may be due to limited power to detect differences.

Type D personality predicted persistent severe levels of anxiety and depressive symptoms. In addition, Type D personality, and also anxiety sensitivity and low educational level, predicted chronic mildly anxious symptoms. The predictive value of Type D personality for momentary anxiety and depressive symptoms in ICD patients has also been shown by others[43, 45]. Our results extend these findings by showing a predictive effect regarding trajectories over a 12-month period.

The results of this study should be interpreted with caution. First, generalizability may be limited as 12.1% of initially participating patients had to be excluded due to death or missing values and these patients differed significantly or marginally from included patients with respect to Type D personality, marital status, and self-deception. Second, baseline questionnaires were completed between 0 and 3 weeks post-implantation, which means that baseline levels do not reflect pre-treatment levels. Third, the power to detect a differential effect of ATPs and shocks was limited.

Identification of patients with mild and severe levels of anxiety and depressive symptoms is important, because our results demonstrate chronicity of these symptom levels from the time of implantation. Moreover, previous research in ICD patients suggests that anxiety is related to low treatment satisfaction[46], impaired quality of life[47], feelings of disability[11], pain intensity of ICD shocks[48], and ventricular arrhythmias[20]. Considering the stability, anxiety and depression levels may already be measured at the

time of implantation. It is essential to support these patients, as anxiety and depression may precipitate ventricular arrhythmias[19, 20]. Treatment of anxiety may be best realized by cognitive behavioral therapy in combination with exercise training[49]. In addition, it may be timely to standardize screening for Type D personality in hospitals, as we and others have found that ICD patients with a Type D personality are at increased risk to experience high levels of anxiety[43, 45], and previous research has also found that Type D patients are at increased risk for morbidity and mortality[28-30]. Screening may be realized during hospitalization for ICD implantation, by use of the Type D scale (DS14), which consists of 14 items only[24].

Several points may be addressed in future research. First, anxiety sensitivity is mostly neglected in ICD research, but our current and previous[12] findings suggest an association with clinically relevant levels of anxiety. Therefore, to clarify the role of anxiety sensitivity, this personality disposition may be incorporated in future studies. Second, because this is the first study to examine trajectories of anxiety and depressive symptoms in ICD patients, future studies need to replicate our findings and it may also be important to look at the prognostic value of trajectories. Third, baseline levels of anxiety and depressive symptoms did not reflect pre-treatment levels as questionnaires were completed between 0 and 3 weeks post-implantation. Finally, randomized controlled trials are needed to examine adequate interventions for anxiety and depressive symptoms in ICD patients. Interventions aimed at patients with a Type D personality may be of particular interest.

In conclusion, four trajectories of anxiety and depressive symptoms were identified and comprised very low, low, mild, and severe symptom levels. These trajectories tended to be relatively stable in the first year following ICD implantation. Anxiety sensitivity and Type D personality were the most prominent predictors of these trajectories, whereas ATPs and shocks were not associated with trajectories. Psychological screening may be implemented in hospitals to identify patients at risk for chronic anxiety and depression.

***ACKNOWLEDGEMENTS***

*We would like to thank Eefje Postelmans for inclusion of the patients into the study and Martha van den Berg (MSc), Vivianne Sterk, Jolien Diekhorst (MSc), Marjan Traa, and Marie-Anne Mittelhaeuser for help with data management. This study was supported by the Netherlands Organization for Scientific Research, The Hague, The Netherlands with a VICI grant (453-04-004) to Dr. Johan Denollet.*

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*PART II*

# The Role of Anxiety in the Outcome of ICD Treatment

*Chapter 6*

# Anxiety Predicts Poor Perceived Health in Patients with an Implantable Defibrillator

**Van den Broek KC, Nyklíček I, Denollet J. Anxiety predicts poor perceived health in patients with an implantable defibrillator. Psychosomatics, *in press*.**

**ABSTRACT**

Implantation with an implantable cardioverter defibrillator (ICD) may cause psychological problems, including anxiety. The objective was to examine whether general anxiety and disease-specific anxiety differentially predict poor perceived health in ICD patients. Patient concerns about the ICD and feelings of disability were independently predicted by general as well as disease-specific anxiety. Clinical anxiety was predicted by general anxiety only, while cardiopulmonary symptomatology was predicted by disease-specific anxiety. Identifying and supporting ICD patients with different anxiety symptoms is important. Future research should examine the differential predictive value of different forms of anxiety towards medical endpoints as well as possible interventions for disease-related anxiety.

## INTRODUCTION

The implantable cardioverter defibrillator (ICD) constitutes the main therapy in the treatment of life-threatening arrhythmias. The ICD is superior to antiarrhythmic drugs in reducing mortality rates[1, 2]. Furthermore, ICDs are proven to be efficacious in reducing the risk for sudden cardiac death in patients who receive the ICD for secondary as well as primary prevention[3, 4]. Despite these clear medical benefits, treatment with an ICD may be stressful in a subgroup of patients, most often due to concerns about a future ICD shock, although previous studies report inconsistent results regarding the impact of ICD shocks on psychological adaptation[5-8]. Conversely, some studies report that it is the survived cardiac arrest or the underlying arrhythmia disease that leads to psychological maladjustment rather than the treatment[5, 9, 10]. Nevertheless, psychological problems such as anxiety[8, 11, 12] and depression[8, 11] are frequently experienced by patients in the months or even years after ICD implantation.

In cardiovascular research, the importance of such patient-centered outcomes is increasingly acknowledged. The working group of America's National Heart, Lung, and Blood Institute reported in 2005 on the need for more patient-centered care, including the assessment of patient-centered health-status outcomes[13]. In addition, they recommended conducting studies aimed at identifying important determinants of patient-centered health status.

Patient-centered research in ICD patients has frequently focused on anxiety, since the prevalence of clinically significant levels of anxiety vary from 13 to 46%[7, 8, 11, 12, 14, 15]. This shows that anxiety is a common negative emotion following ICD implantation. Moreover, emotions such as anxiety increase the risk for potential lethal arrhythmias and therefore ICD shocks[16-18]. Although this indicates the importance to study the concept of anxiety more deeply, most studies focused on general anxiety instead of specific disease-related anxiety. Previous studies on disease-related anxiety in ICD patients concentrated on anxiety sensitivity (i.e., sensitivity to and fear of symptoms of autonomic arousal[11, 19] or patients' anxiety or concerns about the ICD[6, 12, 20, 21]). Disease-related anxiety overlaps with general anxiety[6] but both constructs are differentially associated with outcomes. For instance, anxiety sensitivity is more strongly related to quality of life than general anxiety[11]. In sum, these studies suggest that the distinction between general and disease-

specific anxiety is important and should receive more attention in research on the prevalence and role of anxiety in ICD patients.

The aim of the current study is to examine whether general anxiety and disease-specific anxiety differentially predict poor perceived health outcomes. First, the differential assessment of anxiety by a general and a disease-specific measurement of anxiety was investigated. Next, the differential predictive power of disease-specific anxiety versus general anxiety regarding perceived health outcomes was determined.

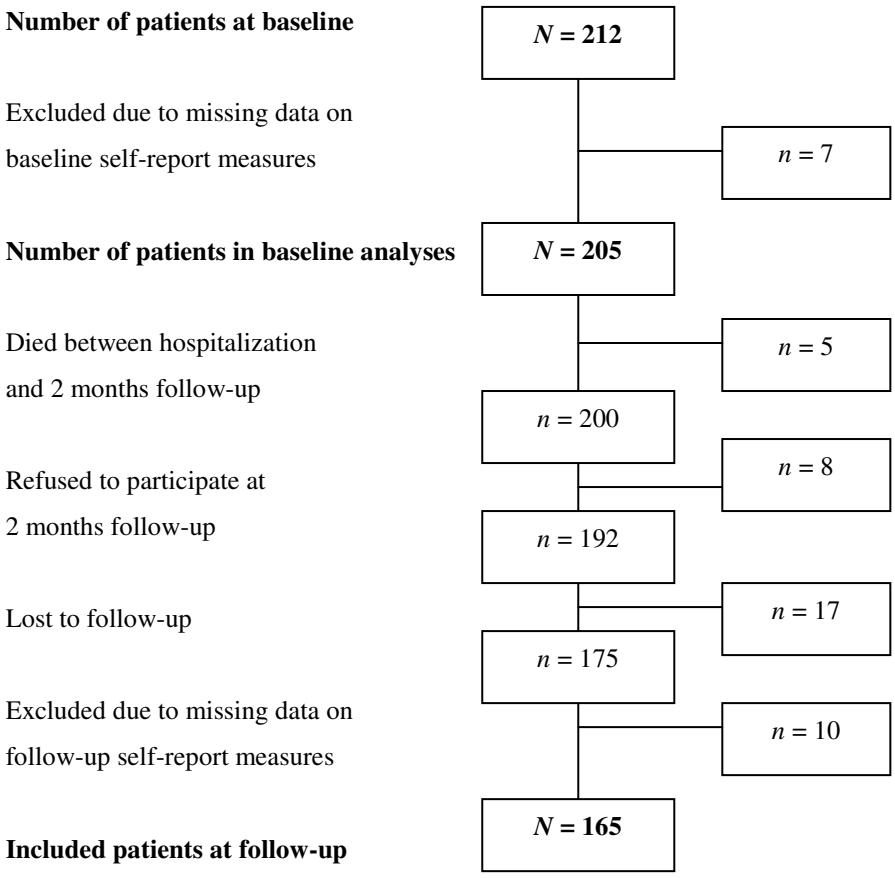
## METHODS

### Patient population and design

Patients hospitalized between May 2003 and July 2006 for implantation with an ICD were included from two teaching hospitals in the Netherlands (Catharina Hospital, Eindhoven; Amphia Hospital, Breda). Inclusion criteria were implantation with an ICD, technical ICD follow-up in the treatment center, and age between 18 and 80 years. Exclusion criteria were significant cognitive impairments (e.g., dementia), severe comorbidities (e.g., cancer), and inability to read and understand Dutch. Patients completed self-report measures on general and specific anxiety at baseline. Self-reports on feelings of disability, cardiopulmonary complaints, and ICD concerns were completed at 2 months follow-up. In addition, a diagnostic interview was administered to determine the severity of anxiety at this time. The two months follow-up period was adopted due to logistic reasons. Two months following ICD implantation, patients visited the outpatient clinic for a routine control. To minimize patient burden, we combined our study with these visits to the hospital. Of the original 212 patients who were included at baseline, 165 (78%) patients remained in the study at 2 months follow-up. The main reasons for exclusion were loss to follow-up and missing data on self-report measures (Figure 1).

The study was approved by the medical ethic committees of the participating hospitals. The study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent.

***Figure 1.*** *Flowchart of patient selection*




**Demographic and clinical characteristics**

Demographic variables included sex, age, marital status, educational level, and working status. Clinical variables included ICD indication, shocks between implantation and follow-up, comorbidity (lung disease, renal disease, rheumatic disease, or diabetes mellitus), cardiac history (previous myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery), smoking, psychotropic medication, and days between implantation and completion of the baseline questionnaire. Clinical variables were obtained from the medical records, except for smoking and psychotropic medication which were measured by self-report.

**Symptoms of anxiety at baseline**

*General anxiety*

The State-Trait Anxiety Inventory (STAI) was used to assess general symptoms of anxiety[22]. The STAI is a self-report measure consisting of two 20-item scales developed to measure the level of general state and trait anxiety. In the current study, we only used the state measure, because the purpose in this study was to assess the current presence of symptoms of anxiety at baseline and not anxiety as a stable trait. Each item is rated on a 4-point Likert scale from *1-not at all* to *4-very much so*. Ten items measure the presence of anxiety and 10 items the absence of anxiety. After recoding the anxiety absence items, scores can range from 20, that is, low level of state-anxiety to 80, that is, high level of state-anxiety. The STAI has been demonstrated to have adequate validity and reliability, with Cronbach's α ranging from 0.87 to 0.92[22].

*Disease-related anxiety*

The 18-item Cardiac Anxiety Questionnaire (CAQ) was specifically designed to measure heart-focused anxiety, which refers to the fear of cardiac-related stimuli and sensations based upon their perceived negative consequences[23]. Answers are rated on a 5-point Likert scale, ranging from *0-never* to *4-always*. A total score is computed as the mean of the relative frequency ratings for each of the 18 items. Subscale scores are computed similarly. The CAQ comprises three subscales: *Fear and worry* about heart sensations (α = 0.83), *Cardioprotective avoidance* of activities that could bring on symptoms (α = 0.82), and *Heart-focused attention* and monitoring of cardiac–related stimuli (α = 0.69)[23]. Higher scores indicate higher cardiac anxiety.

**Poor perceived health outcomes at two months follow-up**

*Feelings of disability and cardiopulmonary complaints*

The Health Complaints Scale (HCS) is a self-report measure on cognitive and somatic health complaints[24]. Of the cognitive health complaints scale, we included the subscale feelings of disability and of the somatic health complaints the subscale cardiopulmonary complaints, which are both answered on a 5-point Likert scale ranging from *0-not at all* to *4-extremely*. The subscale feelings of disability contains 6 items, e.g., "able to take on

much more work formerly" and the subscale cardiopulmonary complaints contains 5 items, e.g., "stabbing pain in heart or chest". Both scales have good internal consistency ($\alpha = 0.91$ and 0.80, respectively) and validity[24].

*Patient concerns about the ICD*

Patient concerns about the ICD were measured by the ICD-Concerns questionnaire (ICDC)[6]. Originally, the 20-item ICDC was developed in British ICD patients[25]. The ICDC was adapted to Dutch language and reduced to 8 items as a result of factor analyses[6]. All items were related to concerns about the ICD firing. Items are scored on a 5-point Likert scale from *0-not at all* to *4-very much so*. Total scores range from 0-32. The ICDC has good internal consistency ($\alpha = 0.91$) and validity[6].

**Clinical anxiety at two months follow-up**

The Hamilton Rating Scale for anxiety (HAM-A) is a 14-item semi-structured interview and is a psychiatric standard for the assessment of current severity of anxiety symptoms[26]. The items comprise the symptoms of anxiety, including anxious mood, tension, insomnia, and several somatic symptoms. The interviewer has to rate the severity of the symptoms on a scale from *0-not present* to *4-very severe/incapacitating*. Scores range from 0 to 56, with a score above 17 indicating significant anxiety[26]. The validity and reliability are good, with $\alpha$ ranging from 0.82 to 0.92, and interrater reliability (i.e., intraclass coefficient) ranging from 0.74 to 0.98[26-28]. The HAM-A has been used as an outcome measure of general anxiety in previous studies on ICD patients[29, 30].

**Statistical analysis**

Since the STAI is considered a measure of general anxiety, whereas the CAQ is supposed to measure specific heart-focused anxiety, factor analyses were performed on STAI and CAQ items to verify this differential assessment of anxiety components. Bartlett's test of sphericity and the Kaiser-Meyer-Olkin index were used to determine whether it was appropriate to perform factor analyses on these items. To determine the number of factors to retain, we used the criteria of Eigen values > 1 and scree plot analyses. Varimax rotation was applied to further examine the orthogonal dimensions of anxiety. The

resulting dimensions of the CAQ were subjected to reliability analyses in order to investigate the possibility to abbreviate this scale, because in clinical and epidemiological research, it is preferable to have a limited number of items. Item-total correlations and Cronbach's α were calculated to identify redundant items in CAQ. Correlations between the STAI and the new CAQ scales, and the outcomes feelings of disability, cardiopulmonary complaints, patient concerns about the ICD, and clinical severity of anxiety were computed to investigate the degree to which these measures are related bivariately before entering them in multivariate analyses.

A series of univariate linear regression analyses were performed to examine the predictive value of the following potential confounders: sex, age, marital status, education, work status, indication for ICD implantation, shocks, cardiac history, comorbidity, smoking (self-report), psychotropic medication (self-report), and days between implantation and completion of baseline questionnaire. Those potential confounders showing at least a marginal effect ($p < .10$) were subsequently entered in multivariable linear regression analyses, in which the independent predictive value of the anxiety dimensions was examined.

All statistical analyses were performed using SPSS 14.0 for Windows.

## RESULTS

### Patient characteristics

Baseline demographic and clinical characteristics of the ICD patients as well as mean scores on the questionnaires and the interview are displayed in Table 1. The study population consisted of 26 women (12.7%) and 179 men (87.3%) with a mean age of 62.1 (±10.6). An equal number of patients received their ICD for reasons of primary and secondary prevention. There were 144 (70.2%) patients with a history of ischemic heart disease and 73 (35.6%) patients had comorbid diseases, like lung disease, renal disease, rheumatic disease, or diabetes.

***Table 1.*** *Patient characteristics*

| | ***N* (%)** | **Mean (SD)** | **Range** |
|---|---|---|---|
| **Demographics** | | | |
| Age | | 62.1 (10.6) | 24-79 |
| Female | 26 (12.7) | | |
| No partner | 24 (11.7) | | |
| Low education | 45 (22.0) | | |
| No work | 155 (75.6) | | |
| **Clinical variables** | | | |
| Primary indication | 102 (49.8) | | |
| ≥1 shock since implantation[2] | 7 (4.2) | | |
| History of ischemic heart disease[3] | 144 (70.2) | | |
| Comorbidity[4] | 73 (35.6) | | |
| Current smoking | 39 (19.0) | | |
| Use of psychotropic medication | 33 (16.1) | | |
| Days[5] | | 7.7 (6.8) | 0-21 |
| **Predictor variables** | | | |
| STAI absence of anxiety | | 26.8 (7.5) | 11-40 |
| STAI presence of anxiety | | 16.3 (5.8) | 10-38 |
| CAQ total score | | 1.1 (0.8) | 0-4 |
| CAQ Fear | | 1.2 (0.9) | 0-4 |
| CAQ Avoidance | | 1.4 (1.1) | 0-4 |
| CAQ Heart-focused attention | | 0.7 (0.8) | 0-4 |
| **Outcome variables[2]** | | | |
| Feelings of disability (HCS) | | 7.0 (6.4) | 0-24 |
| Cardiopulmonary complaints (HCS) | | 2.9 (3.5) | 0-19 |
| Patient concerns about the ICD (ICDC) | | 5.9 (6.6) | 0-32 |
| Clinical anxiety (HAM-A) | | 4.6 (5.3) | 0-24 |

[1] Data are presented as percentages, unless specified as mean (SD); [2] Based on patients at 2-months follow-up ($n$ = 165); [3] Previous MI, PCI, CABG; [4] Lung, renal, rheumatic disease, and/or diabetes; [5] Days between ICD implantation and completion of baseline questionnaire.

STAI = State-Trait Anxiety Inventory; CAQ = Cardiac Anxiety Questionnaire; HCS = Health Complaints Scale; ICDC = ICD-Concerns questionnaire; HAM-A = Hamilton Rating Scale for Anxiety.

**Dimensions of general versus disease-specific anxiety**

To explore whether the STAI and CAQ items assess different aspects of anxiety, we performed factor analyses on the total sample ($N$ = 205). Bartlett's test of sphericity ($p < .0001$) and the Kaiser-Meyer-Olkin index (0.885) indicated that it was appropriate to perform factor analyses on these items. Eight components had eigenvalues above 1.00 (12.30, 4.93, 2.26, 2.05, 1.51, 1.16 1.10, and 1.01), but the scree plot showed a clear break between the fourth and fifth component. The resulting four factors were subjected to Varimax rotation. Table 2 displays the factor loadings.

The first component covers the items of the STAI which measure absence of anxiety. The second component contains the 5 items of the CAQ subscale Heart-Focused Attention and 6 items of the CAQ subscale Fear. The third component covers the STAI items which measure presence of anxiety. Finally, the fourth component includes the items of the CAQ subscale Avoidance and also one item of the CAQ subscale Fear. CAQ item 13 had no loading on any of the four factors. The extraction of these four factors shows the differential measurement of general anxiety by the STAI and heart-specific anxiety by the CAQ.

**Avoidance and Fear measures of anxiety**

The above described factor analyses yielded two components of the CAQ. To identify redundant items in the CAQ, we calculated item-total correlations and Cronbach's α. Since items 1, 14, 15, 16, and 17 of component 2 had the highest item-total correlations and the lowest α-values when the item was deleted, these items were selected for the new subscale labeled Fear. This scale consists of 1 item from the previous subscale Heart-Focused Anxiety (item 1) and 4 items from the subscale Fear (items 14-17). Cronbach's α of the new Fear subscale was 0.88. The item-total statistics of the other CAQ component showed clearly that CAQ item 18 had the lowest item-total correlations and the highest α-values if this item was deleted from the scale. Omitting this item resulted in a new 5-item scale, which exactly comprised the initial CAQ subscale Avoidance. Hence, this name was retained. Results of the item-total correlations of the new subscales and α values are displayed in Table 3.

***Table 2.*** *Factor loadings of the STAI and CAQ items after varimax rotation (N = 205)*

| SCALE "Item" (number) | Components: | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| STAI "Feel pleasant" (20) | | .83 | | | |
| STAI "Feel self-confident" (11) | | .82 | | | |
| STAI "Feel content" (16) | | .79 | | | |
| STAI "Feel comfortable" (10) | | .78 | | | |
| STAI "Feel at ease" (5) | | .77 | | -.31 | |
| STAI "Feel satisfied" (8) | | .77 | | | |
| STAI "Am relaxed" (15) | | .74 | | -.34 | |
| STAI "Feel steady" (19) | | .74 | | | |
| STAI "Feel calm" (1) | | .68 | | | |
| STAI "Feel secure" (2) | | .64 | | -.31 | |
| CAQ "Get frightened" (16) | | | .81 | | |
| CAQ "Might have heart attack" (14) | | | .81 | | |
| CAQ "Difficulty concentrating" (15) | | | .73 | | .35 |
| CAQ "Pay attention" (1) | | | .72 | | |
| CAQ "Feel heart in chest" (8) | | | .63 | | |
| CAQ "Check by doctor" (17) | | | .62 | | |
| CAQ "Check my pulse" (6) | | | .58 | | |
| CAQ "Awakening by chest pain" (4) | | | .56 | | |
| CAQ "Awakening by racing heart" (3) | | | .55 | | |
| CAQ "Normal test, still worry" (10) | | | .52 | | |
| CAQ "Safe around hospital" (11) | | | .51 | | .32 |
| CAQ "Do not believe symptoms" (13)* | | | | | |
| STAI "Am jittery" (13) | | -.33 | | .73 | |
| STAI "Feel nervous" (12) | | -.37 | | .71 | |
| STAI "Worry over misfortunes" (7) | | | | .68 | |
| STAI "Feel frightened" (9) | | | | .66 | |
| STAI "Feel strained" (4) | | -.41 | | .64 | |
| STAI "Feel upset" (6) | | | | .64 | |
| STAI "Feel confused" (18) | | | | .63 | |
| STAI "Feel indecisive" (14) | | | | .62 | |
| STAI "Am worried" (17) | | | .31 | .62 | |
| STAI "Am tense" (3) | | -.40 | | .61 | |
| CAQ "Avoid exercise" (7) | | | | | .84 |
| CAQ "Avoid physical exertion" (2) | | | | | .82 |
| CAQ "Take it easy" (5) | | | | | .74 |
| CAQ "Avoid activities: sweat" (12) | | | | | .73 |
| CAQ "Avoid activities: heart beat" (9) | | | .45 | | .67 |
| CAQ "Tell family" (18) | | | | | .34 |
| | **% of Variance** | **18.14** | **15.13** | **13.58** | **10.01** |
| | **Cronbach's α** | **0.94** | **0.88** | **0.91** | **0.85** |

* no factor loadings; STAI = State-Trait Anxiety Inventory; CAQ = Cardiac Anxiety Questionnaire

***Table 3.*** *New subscales of the CAQ: item-rest correlations and factor loadings (N = 205)*

| | Item-total correlations | Factor loadings 1 | 2 |
|---|---|---|---|
| **CAQ Fear** | | | |
| When I have chest discomfort or when my heart is beating fast: | | | |
| ... I get frightened (16) | .81 | .85 | |
| ... I worry that I might have a heart attack (14) | .85 | .88 | |
| ... I have difficulty concentrating on anything else (15) | .79 | .81 | |
| ... I like to be checked out by a doctor (17) | .59 | .66 | |
| I pay attention to my heart beat (1) | .56 | .67 | |
| **Cronbach's α** | **.88** | | |
| **CAQ Avoidance** | | | |
| I avoid exercise or other physical work (7) | .74 | | .84 |
| I avoid physical exertion (2) | .76 | | .82 |
| I take it easy as much as possible (5) | .66 | | .78 |
| I avoid activities that make me sweat (12) | .69 | | .72 |
| I avoid activities that make my heart beat faster (9) | .69 | | .70 |
| **Cronbach's α** | **.88** | | |
| **% of variance** | | 12.39 | 11.82 |

**Univariate analyses**

After removing patients who did not meet inclusion criteria for follow-up measurements, 165 patients remained in analyses (Figure 1). Included patients differed significantly from excluded patients regarding several baseline characteristics. Excluded patients were younger (58.3±13.9 versus 63.0±9.4, $t(203) = -2.6$, $p = .011$), had more days between implantation and completion of baseline questionnaire (10.7±8.0 versus 7.0±6.3 days, $t(203) = 3.2$, $p = .002$), and reported higher scores on STAI presence of anxiety (18.6±8.0 versus 15.7±4.9, $t(203) = 2.9$, $p = .005$), CAQ Fear (1.5±1.1 versus 1.1±0.8, $t(203) = 3.1$, $p = .003$), and CAQ Avoidance (1.8±1.2 versus 1.3±1.0, $t(203) = 2.5$, $p = .017$).

The obtained mean score of 5.9 (±5.3) on patient concerns about the ICD is lower compared to a previous study, which reported a mean score of 8.18[6]. The mean score on clinical anxiety was 4.6 and there were only 7 (4.2%) patients who experienced clinically significant levels of anxiety, that is, a score > 17 on the HAM-A[26].

Correlations between STAI and the new CAQ scales with feelings of disability, cardiopulmonary complaints, patient concerns about the ICD, and clinical anxiety at two months following ICD implantation were all significant (Table 4).

***Table 4.*** *Correlations between STAI and CAQ subscales and their correlations with perceived health measures (N = 165)*

| | **STAI absence of anxiety** | **STAI presence of anxiety** | **CAQ Avoidance** | **CAQ Fear** |
|---|---|---|---|---|
| STAI absence of anxiety | | -.63*** | -.22** | -.30*** |
| STAI presence of anxiety | | | .32*** | .34*** |
| CAQ Avoidance | | | | .45*** |
| CAQ Fear | | | | |
| | | | | |
| Feelings of disability | -.42*** | .48*** | .45*** | .35*** |
| Cardiopulmonary complaints | -.23** | .29*** | .31*** | .22** |
| Patient concerns about the ICD | -.24** | .35*** | .18* | .29*** |
| Clinical anxiety | -.30*** | .45*** | .24** | .27*** |

* $p < .02$ (2-tailed); ** $p < .005$ (2-tailed); *** $p < .0001$ (2-tailed).

Univariate linear regression analyses showed that of the potential confounding variables low education ($\beta = .13$, $p = .088$), shocks ($\beta = .16$, $p = .040$), and comorbidity ($\beta = .23$, $p = .003$) were (marginally) associated with feelings of disability. No work ($\beta = .17$, $p = .033$), previous cardiac disease ($\beta = .13$, $p = .094$), and comorbidity ($\beta = .24$, $p = .002$) predicted cardiopulmonary complaints. Shocks ($\beta = .31$, $p < .0001$) was the only variable that significantly predicted patient concerns about the ICD. Finally, smoking ($\beta = .17$, $p = .031$) and use of psychotropic medication ($\beta = .20$, $p = .009$) were significantly related to clinical anxiety. These variables were adjusted for in multivariable analyses.

**Multivariable regression model**

Multiple linear regression analyses were performed to determine the independent predictive value of STAI and CAQ scales. As shown in Table 4, the highest correlation between these scales was 0.63, indicating that multicollinearity would not appear in the analyses[31].

The results of multiple linear regression analyses are shown in Table 5. Feelings of disability were significantly and independently predicted by STAI absence of anxiety ($\beta$ = -.22, $p$ = .009), STAI presence of anxiety ($\beta$ = .22, $p$ = .011), and CAQ Avoidance ($\beta$ = .28, $p$ < .0001). The covariates shocks ($\beta$ = .15, $p$ = .017) and comorbidity ($\beta$ = .20, $p$ = .002) remained also independent predictors in the multivariable model. Cardiopulmonary complaints were predicted only by CAQ Avoidance ($\beta$ = .17, $p$ = .049) and comorbidity ($\beta$ = .19, $p$ = .014), not by the STAI. Patient concerns about the ICD were predicted by STAI presence of anxiety ($\beta$ = .25, $p$ = .010), CAQ Fear ($\beta$ = .17, $p$ = .043), and shocks ($\beta$ = .27, $p$ < .0001). Finally, the only significant and independent predictor of clinical anxiety was STAI presence of anxiety ($\beta$ = .37, $p$ < .0001). In other words: STAI absence of anxiety predicted feelings of disability; STAI presence of anxiety predicted feelings of disability as well, but also patient concerns about the ICD and clinical anxiety. CAQ Avoidance was significantly and independently associated with feelings of disability and cardiopulmonary complaints and CAQ Fear showed only an independent relation with patient concerns about the ICD.

**DISCUSSION**

This is the first study which examined the differential independent predictive value of general anxiety versus disease-related anxiety for poor perceived health outcomes. Our results confirm our hypothesis that different dimensions of general and specific anxiety predict different outcomes in ICD patients. We found that clinical anxiety was only predicted by a general measure of anxiety (from the STAI), while cardiopulmonary symptomatology was only predicted by a disease-specific measure of anxiety (from the CAQ). In turn, patient concerns about the ICD and feelings of disability were independently predicted by both general as well as disease-specific measures of anxiety. Moreover, three out of four anxiety dimensions predicted feelings of disability, indicating significant and independent predictive value of those dimensions. These results demonstrate the importance of differentiating between general and disease-specific anxiety.

***Table 5***. *Multivariable predictors of feelings of disability, cardiopulmonary complaints, concerns about the ICD, and severity of anxiety (n = 165)*[1]

| | **Feelings of disability** | | **Cardio-pulmonary symptoms** | | **Patient concerns about the ICD** | | **Clinical anxiety** | |
|---|---|---|---|---|---|---|---|---|
| **Predictors** | ***ß*** | ***p*** | ***ß*** | ***p*** | ***ß*** | ***p*** | ***ß*** | ***p*** |
| **STAI absence of anxiety** | -.22 | **.009** | -.08 | .38 | -.05 | .57 | -.01 | .90 |
| **STAI presence of anxiety** | .22 | **.011** | .15 | .13 | .25 | **.010** | .37 | **<.0001** |
| **CAQ Avoidance** | .28 | **<.0001** | .17 | **.049** | .04 | .61 | .04 | .61 |
| **CAQ Fear** | .08 | .25 | .05 | .53 | .17 | **.043** | .11 | .20 |
| **Demographics** | | | | | | | | |
| Low education | .08 | .25 | .03 | .67 | .01 | .86 | -.04 | .60 |
| Working | -.06 | .40 | .04 | .65 | -.14 | .07 | -.02 | .84 |
| **Clinical variables** | | | | | | | | |
| **Received ≥ 1 shock since implantation** | .15 | **.017** | -.04 | .63 | .27 | **<.0001** | -.01 | .95 |
| History of ischemic heart disease[2] | .02 | .73 | .08 | .28 | .07 | .33 | .04 | .55 |
| **Comorbidity**[3] | .20 | **.002** | .19 | **.014** | .06 | .39 | .07 | .34 |
| Current smoking | -.00 | .96 | .03 | .67 | -.01 | .92 | .03 | .71 |
| Using psychotropic medication | -.08 | .20 | -.07 | .35 | -.06 | .45 | .12 | .10 |

[1] Linear regression analyses; [2] Previous MI, PCI, CABG; [3] Lung, renal, rheumatic disease, and/or diabetes.
STAI = State-Trait Anxiety Inventory; CAQ = Cardiac Anxiety Questionnaire

Previous studies have also discriminated general from disease-specific anxiety, but simultaneous associations with outcome measures have not been examined, except for shocks. Our result that shocks are independently related to patient concerns about the ICD has been found in some[6, 20] but not all[12, 21] studies. It is important to note that one study found general anxiety to be predicted by previous shocks, whereas specific concerns following insertion of an ICD were not[21]. The discrepancies in the results of the different studies could in part be due to the use of different measures for assessing worries and concerns about the ICD. The questionnaire we used, that is, the ICDC, was previously used in the study of Pedersen et al[6]. They also reported that shocks received since implantation were related to specific patient concerns about the ICD.

Correlations between general anxiety and disease-specific anxiety vary between 0.42 and 0.61 in previous research[6, 21]. Since these correlations are moderate to high, they show that 18% to 37% of the variance is shared between both dimensions of anxiety, but that each construct has unique aspects.

Disease-specific anxiety and avoidance of behaviors of which the patient believes it triggers shocks, can limit the frequency and intensity of activities of daily life[32]. Our results elaborate on this previously reported finding as disease-specific anxiety was most importantly related to feelings of disability and uniquely to cardiopulmonary complaints. Overall, these results suggest that physical complaints and functional impairment in ICD patients may be a result of disease-specific anxiety enhancing avoidance of physical activities. In line with this, previous studies have shown that patients with disease-specific anxiety may recover more slowly than patients without disease-specific anxiety[23, 33].

The CAQ has previously been described as an 18-item screening instrument for identifying patients with disease-specific anxiety[23]. However, in clinical and epidemiological research, questionnaires should contain a limited number of items. This study reported on two new 5-item CAQ subscales, which may be useful as a screening tool. However, before the two new subscales can be used in the clinical setting, the scales should be validated in future research.

The present findings may have a number of clinical implications. First, identifying patients with general anxiety or disease-specific anxiety is important, since psychological distress, including anxiety, may precipitate ventricular arrhythmias and therefore ICD

shocks[16, 17, 34]. Second, since feelings of disability were predicted by presence as well as absence of anxiety, it may be important to not only use total STAI-state scores, but also the sub scores. More specifically, clinicians may focus on positive answers regarding presence of anxiety, but also on low scores on the items reflecting absence of anxiety, e.g., 'feel calm' and 'feel at ease'. Next, two RCT trials using ICD patients have demonstrated the positive effect of comprehensive cardiac rehabilitation including an exercise programme on general anxiety[35-37]. Since patients with disease-specific anxiety may avoid physical exercise because of anxiety to elicit cardiac symptoms[33], including arrhythmias and ICD shocks[32], these patients may also benefit from rehabilitation in which physical exercise may be supplemented by a psychological intervention aimed at reducing this disease-specific anxiety. However, future research is warranted to examine appropriate interventions for both general as well as disease-specific anxiety.

These results should be interpreted with some caution. Initially, 212 patients agreed to take part in the study, but follow-up analyses were based on 165 (78%) patients, mainly due to loss to follow-up and missing self-report data. The excluded patients were younger, had more days between implantation and completion of the questionnaire, and had higher scores on three of the anxiety indices. The loss of 47 subjects and the differences between excluded and included patients may have influenced the results and may have a negative impact on the generalizability. However, since excluded patients experienced more anxiety at baseline, the differential predictive value of general versus disease-specific anxiety found in this study is more likely to be an underestimation than an overestimation. Future research is warranted to replicate our findings. Nevertheless, this is the first study that explicitly determined the differential and independent predictive value of general anxiety versus disease-specific anxiety for poor perceived health outcomes.

Future research should also examine the differential predictive value towards hard medical endpoints, such as mortality, morbidity, and ICD shocks. Research may focus on ICD patients or on the broader range of patients with cardiovascular disease. Following the distinction of both anxiety dimensions, future research should also focus on possible interventions for disease-specific anxiety.

***ACKNOWLEDGEMENTS***

*This study was supported by the Netherlands Organization for Scientific Research, The Hague, The Netherlands with a VICI grant (453-04-004) to Dr. Johan Denollet.*

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*Chapter 7*

# Anxiety and Onset of Ventricular Arrhythmias in Patients with an Implantable Defibrillator: A Multicenter Study

**Van den Broek KC, Theuns DAMJ, Nyklíček I, Jordaens L, Alings M, Meijer A, Denollet J, Pedersen SS. Anxiety and onset of ventricular arrhythmias in patients with an implantable defibrillator.** ***Submitted for publication.***

**ABSTRACT**

**Background** Clinical factors increase the risk for ventricular arrhythmias, but little is known about the role of psychological factors. In this multicenter study, we examined whether increased levels of anxiety triggered ventricular arrhythmias in implantable cardioverter defibrillator (ICD) patients.

**Methods** Patients ($N$ = 565; 81% males; mean age = 60.4±11.4 years) completed the STAI (state-version) at the time of implantation. Ventricular arrhythmias were defined as appropriate ICD therapies (i.e., antitachycardia pacing or shocks for ventricular arrhythmias) during the 12-month follow-up period. Endpoints were ≥ 1 arrhythmia, ≥ 5 arrhythmias, and ≥ 1 shock.

**Results** 21.6% of patients experienced ≥ 1 arrhythmia, 8.0% ≥ 5 arrhythmias, and 11.2% ≥ 1 shock. Patients with the ICD for secondary prevention were at a 2.2-fold risk (95% CI 1.43-3.27; $p < .0001$) of experiencing ≥ 1 arrhythmia during follow-up, whereas no main effect was found for anxiety. However, increased anxiety was an independent predictor of patients who experienced ≥ 5 arrhythmias (OR = 2.3; 95% CI 1.21-4.48; $p = .012$); other independent predictors were secondary prevention (OR = 2.5; 95% CI 1.33-4.88; $p = .005$) and ischemic etiology (OR = 0.46; 95% CI 0.23-0.92; $p = .028$). Secondary prevention was also associated with a 2.8-fold risk (95% CI 1.58-4.78; $p < .0001$) for shocks. Analyses included anxiety, age, gender, indication, and ischemic etiology.

**Conclusions** Secondary prevention was predictive for all three endpoints. Increased anxiety and ischemic etiology were related to ≥ 5 ventricular arrhythmias. It may be important to identify and treat patients at high risk for anxiety, as their increased risk of arrhythmias may lead to adverse health outcomes, including poor quality of life.

## INTRODUCTION

Mortality from cardiovascular disease is caused by sudden cardiac death in about 50% of cases[1], with 84% being attributable to ventricular arrhythmias[2]. Clinical factors, including low left ventricular ejection fraction (LVEF), QRS duration, and atrial fibrillation[3], New York Heart Association (NYHA) Class III[4] or IV[5], and vigorous exercise[1, 6] have been shown to increase the risk of ventricular arrhythmias, but psychological factors may also play a role[7].

The implantable cardioverter defibrillator (ICD) has become the therapy of choice for the treatment of life-threatening arrhythmias in patients who have experienced a previous arrest and in patients at risk due to reduced LVEF[8, 9], with ICD implantation being associated with a 20-60% reduction in mortality as compared to antiarrhythmic drugs[9, 10]. The beneficial effects of the ICD have led to an expansion in the indications for ICD to include both primary and secondary prevention[8]. As a consequence, the number of implantations has increased substantially and this rise is projected to continue in the future[10]. Given this increase in the number of ICD patients, knowledge of precipitating factors of life-threatening arrhythmias is essential for the identification of high-risk patients in order to optimize the clinical management of these patients.

Despite preliminary evidence that psychological factors may play a role in the onset of ventricular arrhythmias, there is a paucity of studies investigating the role of psychological factors as precipitants in ICD patients[11-14]. Anxiety may trigger ventricular arrhythmias in ICD patients, although this finding was not consistently found across studies[11, 12, 14]. Furthermore, patients with high levels of trait anxiety are at increased risk of experiencing anxiety-triggered arrhythmias[13].

The objective of this multicenter study was to determine whether increased levels of anxiety trigger the onset of ventricular arrhythmias during a 12-month period in ICD patients.

## METHODS

### Patient sample

Patients hospitalized between May 2003 and December 2006 for ICD implantation were included from three teaching hospitals in the Netherlands (Erasmus Medical Center,

Rotterdam; Catharina Hospital, Eindhoven; Amphia Hospital, Breda). Patients included in the Erasmus Medical Center were part of the ongoing study entitled "*Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter Defibrillator: A prospective Study* (MIDAS)". Exclusion criteria were significant cognitive impairments (e.g., dementia), life-threatening comorbidities (e.g., cancer), history of psychiatric illness other than affective/anxiety disorders, and insufficient knowledge of the Dutch language. Patients who died during the 12-month follow-up period were included in the analyses, since they could also have experienced ventricular arrhythmias during the follow-up period.

The study was approved by the medical ethic committees of the participating hospitals. The study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent.

**Measures**

*Demographic and clinical variables*

Demographic variables included gender, age, marital status (single versus having a partner), low education (secondary education or less), and unemployment. Clinical variables included indication for ICD treatment (primary versus secondary prevention), underlying cardiac disease (ischemic versus non-ischemic etiology), pharmacological treatment, and cardiovascular risk factors including diabetes and smoking. These variables were obtained from the patients' medical records, with the exception of smoking which was obtained from self-report.

*Anxiety*

The State-Trait Anxiety Inventory (STAI) was used to assess general symptoms of anxiety[15]. The STAI is a self-report measure consisting of two 20-item scales developed to measure the general level of state and trait anxiety. In the current study, we only used the state measure. Each item is rated on a 4-point Likert scale from *1-not al all* to *4-very much so*. Ten items measure the presence of anxiety and 10 items the absence of anxiety. After recoding the anxiety absence items, scores range from 20 (i.e., low level of state-anxiety) to 80 (i.e., high level of state-anxiety). The STAI has been demonstrated to have adequate

validity and reliability, with Cronbach's α ranging from 0.87 to 0.92[15]. To indicate clinically elevated levels of general anxiety, a cut-off ≥ 40 was used. This cut-off was previously used in studies on ICD[16] and patients with myocardial infarction.[17] Patients completed the STAI in the period between 1 day prior to ICD implantation and 3 weeks following ICD implantation.

**Study endpoints**

Ventricular arrhythmias comprised the primary study endpoint, which was defined as appropriate ICD therapies, that is antitachycardia pacing episodes (ATP) or shocks, delivered for ventricular tachyarrhythmia or ventricular fibrillation during the 12-month follow-up period. Only the most aggressive treatment per episode was counted, such that if a patient experienced a ventricular arrhythmia for which first ATPs were delivered and then shocks, this episode was counted as a shock. The primary endpoint of ventricular arrhythmias was further subdivided using a cut-off ≥ 5 ventricular arrhythmias, analogous to the Canadian Implantable Defibrillator Study (CIDS)[18] and other studies[19, 20]. These studies showed that a threshold number of shocks (i.e., ≥ 5 shocks) may be necessary in order for shocks to influence emotional functioning. Likewise, psychological distress may play a differential role in predicting patients who experience ≥ 1 versus ≥ 5 ventricular arrhythmias. The secondary endpoint was appropriate shocks (0 versus ≥ 1). Due to limited power, this outcome was not further subdivided. Information on the study endpoints was obtained from the patients' medical records.

**Statistical analyses**

Differences between patients who were included versus excluded in analyses were examined using the Chi-square test for dichotomous variables and Student's *t*-test for independent samples for continuous variables. The Kaplan-Meier method was used to graphically present the time to first ventricular arrhythmia for patients high versus low in anxiety. The log-rank test was applied to test for statistically significant differences between groups. To examine the influence of anxiety on the onset of ventricular arrhythmias, a series of univariable logistic regression analyses were performed, followed by multivariable logistic regression analysis. In the multivariable analyses, we decided a

priori to include gender[7], age[7], ICD indication[5, 21, 22], and ischemic etiology[23] as covariates. All tests were two-tailed, and a $p$-value < .05 was used to indicate statistical significance. All data were analyzed using SPSS.14.0 for Windows (SPSS Inc., Chicago, Illinois).

## RESULTS

### Patient characteristics

Initially, 587 ICD patients agreed to participate, but 22 (3.7%) were not included in the analyses due to missing data on self-report measures ($n$ = 14) or clinical variables ($n$ = 8). These excluded patients were compared with the remaining 565 patients on all demographic and clinical variables, but no statistically significant differences were found. Demographic and clinical baseline characteristics of the 565 ICD patients are presented in Table 1, as a function of the total sample and stratified by ≥ 1 arrhythmias and ≥ 5 arrhythmias.

### Anxiety as a precipitant of ventricular arrhythmias (univariable analysis)

Of the 565 patients included in the analyses, 122 (21.6%) had experienced at least 1 episode and 45 (8.0%) at least 5 episodes with ATP or shocks for ventricular arrhythmias during the 12-month follow-up period; 63 (11.2%) patients had experienced at least 1 shock and 36 (6.4%) had died. Mean anxiety levels in these patients were 41.18, 44.58, 42.16, and 41.39, respectively, with the proportion of patients with increased anxiety being 52.5%, 66.7%, 56.3%, and 50%, respectively.

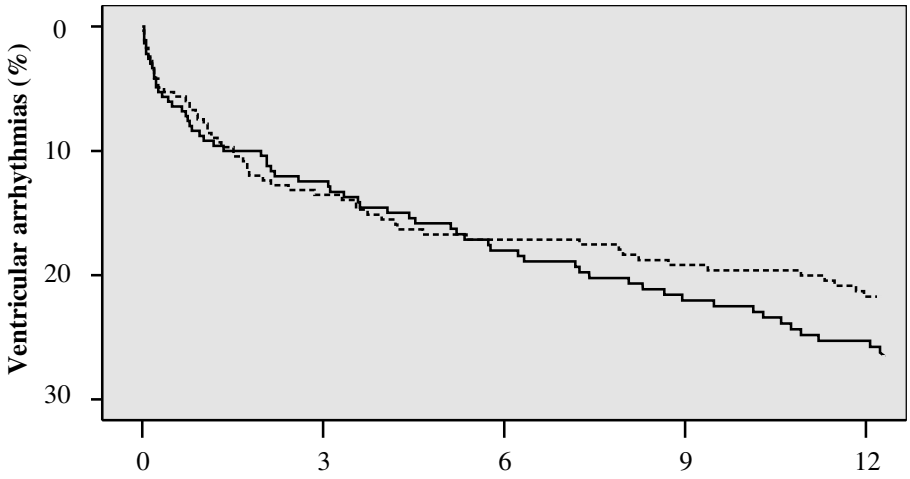
The Kaplan-Meier curves for time to first ATP or shock, stratified by high versus low anxiety, are shown in Figures 1 and 2 for ≥ 1 episode and ≥ 5 episodes, respectively. The Log Rank test for ≥ 1 episode was not significant ($\chi^2$ = 1.10, df = 1, $p$ = 0.29), indicating that the proportion of patients with ≥ 1 episode was equal among patients with high versus low levels of anxiety. In contrast, the Log rank test for ≥ 5 episodes was significant ($\chi^2$ = 6.48, df = 1, $p$ = .011), with more high anxious patients experiencing ≥ 5 episodes as compared to low anxious patients.

***Table 1.*** *Demographic and clinical baseline characteristics (N = 565)*

| | | ≥ 1 ventricular arrhythmias | | | ≥ 5 ventricular arrhythmias | | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **% (*n*)** | **No (*n*=443)** | **Yes (*n*=122)** | ***p*** | **No (*n*=520)** | **Yes (*n*=45)** | ***p*** |
| **Demographic characteristics** | | | | | | | |
| Males | 81.1% (458) | 80.4% | 83.6% | ns | 80.4% | 88.9% | ns |
| Age (Mean ±SD) | 60.41 ±11.41 | 60.33 | 60.73 | ns | 60.50 | 59.38 | ns |
| Single/No partner | 9.7% (55) | 8.8% | 13.1% | ns | 9.4% | 13.3% | ns |
| Lower education* | 54.4% (304) | 54.8% | 52.9% | ns | 55.0% | 47.7% | ns |
| Unemployed | 71% (396) | 70.2% | 73.8% | ns | 71.0% | 71.1% | ns |
| **Clinical characteristics** | | | | | | | |
| Smoking | 14.5% (82) | 13.6% | 18.0% | ns | 14.1% | 20.0% | ns |
| Diabetes | 13.0% (71) | 12.6% | 14.4% | ns | 12.5% | 18.6% | ns |
| **Secondary prevention** | **44.2% (250)** | **40.2%** | **59.0%** | **<.0001** | **42.5%** | **64.4%** | **.004** |
| Ischemic etiology | 66.2% (374) | 67.0% | 63.1% | ns | 67.1% | 55.6% | ns |
| **Medication** | | | | | | | |
| ACE-inhibitor | 68.1% (376) | 67.3% | 71.1% | ns | 68.1% | 68.2% | ns |
| Amiodarone | 23.5% (130) | 24.5% | 19.8% | ns | 23.0% | 29.5% | ns |
| Beta-blocker | 80.8% (447) | 81.5% | 78.5% | ns | 80.9% | 79.5% | ns |
| Digoxin | 13.6% (75) | 12.8% | 16.5% | ns | 13.6% | 13.6% | ns |
| Diuretic | 63.8% (352) | 64.5% | 61.2% | ns | 64.2% | 59.1% | ns |
| Statin | 62.6% (346) | 63.2% | 60.3% | ns | 63.1% | 56.8% | ns |
| **Anxiety** | | | | | | | |
| Anxiety scores (Mean±SD) | 39.62 ±11.84 | | | | | | |
| Probable clinical levels (STAI ≥ 40) | 48.3% (273) | | | | | | |

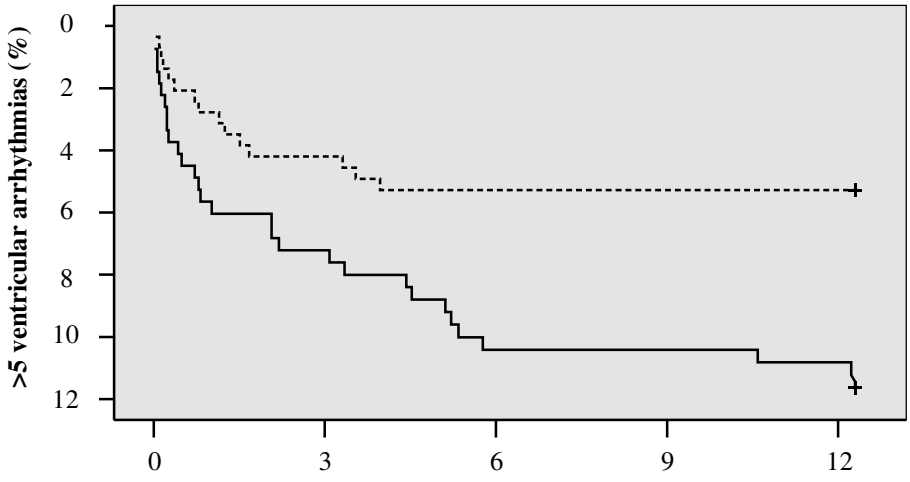
* Secondary education or less (≤ 13 years of education), ATP = antitachycardia pacing

***Figure 1.*** *Kaplan-Meier curve for ventricular arrhythmias for which appropriate ATPs or shocks were delivered for patients with high versus low anxiety*




| Number at risk | | | | | |
|---|---|---|---|---|---|
| Low anxiety (*dotted*) | 292 | 254 | 245 | 240 | 233 |
| High anxiety (*solid*) | 273 | 240 | 227 | 218 | 208 |

***Figure 2.*** *Kaplan-Meier curve for more than 5 ventricular arrhythmias for which appropriate ATPs or shocks were delivered for patients with high versus low anxiety*




| Number at risk | | | | | |
|---|---|---|---|---|---|
| Low anxiety (*dotted*) | 292 | 279 | 276 | 276 | 276 |
| High anxiety (*solid*) | 273 | 253 | 245 | 245 | 242 |

Secondary indication was the only significant predictor of ≥ 1 ventricular arrhythmias at follow-up (OR = 2.23; 95% CI 1.48-3.36; $p < .0001$). Anxiety was not significantly associated with ≥ 1 arrhythmia (OR = 1.19; 95% CI 0.80-1.78; p = .39). Secondary indication was also the only significant predictor of > 1 appropriate shocks (OR = 2.82; 95% CI 1.62-4.90; $p < .0001$). In contrast, increased anxiety (OR = 2.28; 95% CI 1.20-4.34; $p = .012$) and secondary indication (OR = 2.62; 95% CI 1.37-5.00; $p = .004$) were both associated with an increased risk of ≥ 5 ventricular arrhythmias; there was also a trend for ischemic etiology, with patients with ischemic heart disease having a lower risk of experiencing ≥ 5 arrhythmias (OR = 0.59; 95% CI 0.32-1.09; $p = 0.094$).

**Anxiety as a precipitant of ventricular arrhythmias (multivariable analysis)**

In multivariable analyses, we included increased anxiety, age, male, secondary indication, and ischemic etiology a priori as predictor variables. Using ≥ 1 ventricular arrhythmias as the endpoint (Table 2, left column), patients with a secondary indication were at a 2.2-fold risk of experiencing an arrhythmia during follow-up. In the second analysis, secondary indication was associated with a 2.8-fold risk (95% CI 1.58-4.78; $p < .0001$) for appropriate shocks; no other significant predictors were found (data not shown). In the third analysis, increased anxiety, secondary indication, and ischemic etiology were significant independent predictors of ≥ 5 ventricular arrhythmias (Table 2, right column). A trend was found for gender, with male patients having a 2.4-fold increased risk for experiencing ≥ 5 ventricular arrhythmias. In sum, secondary indication was predictive for all three endpoints. Patients with increased anxiety had an increased risk of experiencing ≥ 5 ventricular arrhythmias, while patients with ischemic etiology had a decreased risk.

***Table 2.*** *Multivariable model of predictors of ventricular arrhythmias*

| | **≥ 1 ventricular arrhythmias** | | | **≥ 5 ventricular arrhythmias** | | |
|---|---|---|---|---|---|---|
| | **OR** | **95% CI** | ***p*** | **OR** | **95% CI** | ***p*** |
| **Increased anxiety** | 1.20 | 0.80-1.82 | .37 | **2.33** | **1.21-4.48** | **.012** |
| Male | 1.26 | 0.73-2.20 | .41 | 2.35 | 0.88-6.32 | .090 |
| Age | 1.01 | 0.99-1.03 | .47 | 1.00 | 0.97-1.03 | .96 |
| **Secondary prevention** | **2.16** | **1.43-3.27** | **<.0001** | **2.54** | **1.33-4.88** | **.005** |
| **Ischemic etiology** | 0.70 | 0.44-1.11 | .13 | **0.46** | **0.23-0.92** | **.028** |

## DISCUSSION

The objective of the current prospective multicenter study was to examine whether anxiety comprises a precipitant of arrhythmic events at 12 months follow-up in cardioverter defibrillator patients. Patients with probable clinical anxiety had a 2.3-fold increased risk of experiencing ≥ 5 ventricular arrhythmias within the first 12 months following ICD implantation, whereas anxiety was not a predictor of ≥ 1 events. Patients with a secondary indication were also at increased risk for experiencing ≥ 5 ventricular arrhythmias, with the risk being 2.5-fold, whereas patients with ischemic etiology had a decreased risk. In addition, secondary indication was an independent predictor for ≥ 1 ventricular arrhythmias (2.2-fold risk) and ≥ 1 shock (2.8-fold risk).

The results of the current study are in line with some previous studies in ICD patients. Dunbar and colleagues[11] found that self-reported anxiety at 1 and 3 months was predictive for ventricular arrhythmias (i.e., appropriate ATPs and shocks) within 1-3 months and 3-6 months follow-up, respectively. However, since the total mood disturbance score at baseline and 6 months follow-up did not predict arrhythmias in the consecutive 2 and 3 months, respectively, the authors did not specify total mood disturbance, despite the possibility that one of the separate mood disturbances could have been significant. Lampert and colleagues[12] investigated predictors for appropriate shocks. In line with our results, they found that appropriate shocks were not predicted by anxiety, which was measured using a 5-point intensity scale. It may be important to note that the Dunbar et al.[11] study included clinical risk factors in the multivariable models when predicting total mood disturbance (but not in the models on separate mood states), whereas the Lampert et al.[12] study did not. Taken together, anxiety may be predictive for ventricular arrhythmias as defined by appropriate ATPs or shocks, but not for shocks alone. However, we have no explanation why anxiety in the current study was only a predictor of arrhythmic events when these were stratified by ≥ 5 and not a predictor of ≥ 1 events.

In the current study, secondary indication was related to all study endpoints, which is in line with other studies finding that secondary indication is associated with appropriate ICD discharges for ventricular arrhythmias[5, 21, 22]. We also found that patients with ischemic etiology had a lowered risk to experience ≥ 5 ventricular arrhythmias, but

not ≥ 1 event or shocks alone. We have no explanation for this finding, since an ischemic and infarcted myocardium provides an excellent substrate for developing arrhythmias[23]. To our knowledge, the predictive value of age and gender for ≥ 5 ventricular arrhythmias has not yet been examined. Comparable to our results, previous studies did not find a significant association between male gender and ≥ 1 ventricular arrhythmias[22], although one study found an increased risk for older age and a trend for male gender[7].

Little is known about the pathways through which psychological factors in general and anxiety in particular may lead to the onset of ventricular arrhythmias. Disturbances in the autonomic nervous system may comprise one mechanism, as patients with anxiety or anxiety disorders[24] exhibit reduced heart rate variability, which is an important risk factor for sudden cardiac death[24, 25]. As shown in experimental studies, general mental stress may lead to ventricular arrhythmias[26], as mental stress may shorten the VT cycle length and may influence the termination of VTs, thereby creating a more dangerous arrhythmia[27]. Mental stress is also related to increases in T-wave alternans[28, 29], which is an important predictor for ventricular arrhythmias and death[30].

In clinical practice, it may be timely to introduce a standard screening procedure in order to identify ICD patients at risk of clinical levels of anxiety and anxiety disorders, given that our findings and those of others[11] show that anxiety may trigger arrhythmic events. In addition, anxiety is more pronounced than depression in ICD patients, with estimated levels ranging from 13% to 38%[31]. Furthermore, anxiety increases avoidance behaviors, in turn leading to a more sedentary lifestyle, which is counterproductive for cardiac patients[31-34]. Anxiety has also been associated with poor quality of life in patients with general cardiovascular disease[35]. A recent review of psychosocial intervention studies in ICD patients indicated that anxiety can be reduced in these patients and may best be realized using a multifactorial approach, including a cognitive behavioral component paired with exercise training[14].

The results of the current study should be interpreted with some caution due to the following limitations. First, anxiety was measured at baseline only. Alteration in anxiety levels during the follow-up period may have additional prognostic information to a single snapshot measure. Although this has not been examined in ICD patients to our knowledge, one study in myocardial infarction patients reported that a single measure of

depression was predictive for cardiovascular death[36], whereas another study suggested that persistent depression may be more important than remittent depression for all-cause mortality[37]. Second, generalizability may be limited due to excluded patients who had missing data on self-report measures or clinical variables. However, these patients did not differ from included patients on all demographic and clinical variables. Third, VTs without therapy were not included. Fourth, the number of shocks was too few to subdivide this endpoint further into ≥ 5 shocks. Fifth, we did not have information on the cause of death for those patients who died during the 12-month follow-up period. Hence, we were not able to determine whether death may be attributed to a cardiac cause, including ventricular arrhythmia. Sixth, ≥ 5 ICD therapies may be associated with aggressive programming of the device, leading to unnecessary therapies for possibly non-sustained arrhythmias. However, we had no information about the device programming, but as there were no differences on baseline characteristics between patients who did and did not experience ≥ 5 ICD therapies, nor were there any differences in the prevalence of patients experiencing ≥ 5 ICD therapies between the three hospitals, it may be assumed that there was no aggressive programming. Finally, information on LVEF and NYHA class were not available for a substantial part of patients; hence, we could not adjust for these variables in multivariable analyses.

Future research is warranted to further explore the role of psychological factors as precipitants of ventricular arrhythmias, adopting a broader focus, as depression[12], anger[11], fatigue[11], vigor[11], and confusion[13] have also been related to the onset of ventricular arrhythmias. Personality may also be of importance, as Burg et al.[13] showed that the state of anger and anxiety as triggers of arrhythmias were related to their corresponding trait measures. These studies should incorporate LVEF and NYHA class, as they may serve as confounders on the relationship between psychological factors and ventricular arrhythmias. Research should also be devoted to the study of the physiological mechanisms that may account for this relationship, including potential moderators.

In conclusion, results of the current study suggest an important role for increased self-reported anxiety as a trigger of arrhythmic events the first 12 months following ICD implantation. Patients with secondary indication were also at increased risk, whereas patients with ischemic etiology were at decreased risk. These findings indicate that

patients with increased levels of anxiety should be identified in clinical practice, with the option of offering them adjunctive psychosocial intervention to reduce anxiety. Further research is warranted to increase our knowledge of the link between psychological factors and ventricular arrhythmias, as well as mechanisms and moderators of this relationship in order to optimize secondary prevention in ICD patients.

***ACKNOWLEDGEMENTS***

*This research was supported with a VENI grant (451-05-001) to Dr. Susanne S. Pedersen and a VICI grant (453-04-004) to Dr. Johan Denollet from the Netherlands Organization for Scientific Research, The Hague, The Netherlands. We would like to thank Eefje Postelmans and Agnes Muskens-Heemskerk for inclusion of the patients into the study and Martha van den Berg (MSc), Vivianne Sterk, Jolien Diekhorst (MSc), Marjan Traa, and Marie-Anne Mittelhaeuser for help with data management.*

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*Chapter 8*

# Increased Risk of Ventricular Arrhythmia in Implantable Defibrillator Patients with Increased Anxiety and a Type D Personality

**Van den Broek KC, Nyklíček I, Van der Voort PH, Alings M, Meijer A, Denollet J. Increased risk of ventricular arrhythmia in implantable defibrillator patients with increased anxiety and a Type D personality.** ***Submitted for publication*****.**

**ABSTRACT**

**Background** Little is known about the role of psychological factors in the occurrence of life-threatening arrhythmias. We examined anxiety, depression, and Type D personality (tendency to experience increased negative emotions paired with a tendency to inhibit the expression of these emotions) as predictors of ventricular arrhythmias in implantable cardioverter defibrillator (ICD) patients.

**Methods** ICD patients (*N* = 324, 83% males, age = 62.0±10.5 years) completed questionnaires on anxiety (STAI), depressive symptoms (BDI), and Type D personality (DS14) at baseline (i.e., 0-3 weeks post-implantation). The endpoint was occurrence of ventricular arrhythmias, defined as appropriate ICD therapies, in the first year post-implantation.

**Results** Appropriate ICD therapies were experienced by 21% (*n* = 68) of patients. Increased anxiety (OR = 1.46; 95% CI 0.86-2.50; *p* = .17) and depression (OR = 1.13; 95% CI 0.65-1.97; *p* = .67) did not predict arrhythmias, but there was a trend for Type D personality (OR = 1.71; 95% CI 0.94-3.11; *p* = .078). The combined presence of anxiety and Type D personality significantly predicted ventricular arrhythmias (OR = 2.39; 95% CI 1.28-4.47; *p* = .006). Stepwise logistic regression analysis confirmed that this interaction was significant; depressive symptoms did not have an incremental prognostic value. Adjusting for gender, age, and ischemic etiology, the combined presence of anxiety and Type D personality was associated with a 2.3-fold risk (95% CI 1.20-4.35; *p* = .012) and secondary prevention with a 2.1-fold risk (95% CI 1.20-3.66; *p* = .009) to experience arrhythmias.

**Conclusions** Anxious Type D patients and secondary prevention patients are at increased risk of experiencing ventricular arrhythmias in the first year post-ICD implantation. Type D patients with increased anxiety post-implantation may be identified and offered support.

## INTRODUCTION

Implantable cardioverter defibrillator (ICD) treatment provides an opportunity to study factors associated with ventricular arrhythmias, which are the most common cause of sudden cardiac death[1]. Guidelines advocate ICD implantation in patients who have survived life-threatening arrhythmias and in patients with severe left ventricular dysfunction[2, 3]. The ICD does not prevent ventricular arrhythmias, but can terminate ventricular arrhythmias by antitachycardia pacing (ATP) or high-voltage shocks[4]. However, sudden cardiac death due to ventricular arrhythmias may still occur in a proportion of ICD patients[5]. Another important issue refers to possible increased emotional distress in shocked patients[6]. These patients may experience more anxiety[7-10], depression[11], and impaired quality of life[12] as compared to non-shocked patients, although some studies did not find this association[13-15]. For these reasons and also because patient selection for ICD implantation remains controversial, better knowledge of risk factors for ventricular arrhythmias is required[1, 16]. Possible clinical risk factors include ischemic heart disease[1], New York Heart Association Class III[17] or IV[18], vigorous exercise[19], low left ventricular ejection fraction, QRS duration, and atrial fibrillation[20]. Psychological factors may play a role, but little is known about their influence[21-24].

Few studies have evaluated the role of psychological factors as precipitants of ventricular arrhythmias in ICD patients[21-24]. Depression has been associated with an increased risk for appropriate shocks[21], while others found that anxiety[22] (but not depression and anger) or anger[23] (but not sadness and anxiety) may trigger ventricular arrhythmias. Personality traits may also increase the risk of emotion-triggered appropriate shocks in ICD patients[24]. Taken together, anxiety, depression, and personality predicted ventricular arrhythmias in some studies, but evidence is not conclusive.

Therefore, the objective of the current study was to examine the role of anxiety, depression, and personality traits as predictors of ventricular arrhythmias over the 12-month period following ICD implantation, adjusting for gender, age, ICD indication, and etiology.

## METHODS

### Patient sample

Patients who underwent ICD implantation between May 2003 and December 2006 were included from two referral hospitals in the Netherlands (Catharina Hospital, Eindhoven; Amphia Hospital, Breda). Inclusion criteria were implantation with an ICD and age between 18 and 80 years. Exclusion criteria were significant cognitive impairments (e.g., dementia), life-threatening comorbidities (e.g., cancer), and insufficient knowledge of the Dutch language. Patients who died during the 12-month follow-up period were not excluded from the analyses, since these patients could also have experienced ventricular arrhythmias during their follow-up period. The study was approved by the medical ethics committees of both participating hospitals. The study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent.

### Psychological measures

Patients completed questionnaires on anxiety, depressive symptoms, and personality in the period between 1 day prior to ICD implantation and 3 weeks following ICD implantation.

*Anxiety*

The State-Trait Anxiety Inventory (STAI) was used to assess general symptoms of anxiety[25]. In the current study, we only used the state measure, because the purpose in this study was to assess the current presence of symptoms of anxiety at baseline. The STAI state version consist of 20 items and each item is rated on a 4-point Likert scale from *1-not al all* to *4-very much so*, with total scores ranging from 20-80, with higher scores indicating higher levels of state-anxiety. The STAI has adequate validity and reliability, with Cronbach's α ranging from 0.87 to 0.92[25]. To indicate clinically elevated levels of general anxiety, a cut-off ≥ 40 was used, which was previously used in studies on ICD[26].

*Depressive symptoms*

The Beck Depression Inventory (BDI) is a 21-item self-report measure developed to assess the presence and severity of depressive symptoms[27]. Each item is rated on a Guttmann scale from *0* to *3*. The BDI is a reliable and valid measure of depressive

symptomatology and the most frequently used self-report measure of depressive symptoms in cardiac patients. Scores ≥ 10 were used to indicate clinically relevant levels of depression[27, 28].

*Type D personality*

The Type D scale (DS14) was used to assess Type D personality. Type D patients tend to experience increased negative emotions (e.g., worry and have a gloomy view of life) paired with emotional non-expression[29]. The DS14 contains two 7-item scales, negative affectivity (e.g., "I often feel unhappy") and social inhibition (e.g., "I am a closed kind of person")[29]. Items are answered on a 5-point Likert scale, ranging from *0-false* to *4-true*, with total scores ranging from 0-28 for both subscales. Patients scoring ≥ 10 on both subscales are classified as Type D[29, 30]. The DS14 has good reliability, with Cronbach's alpha being 0.88 and 0.86 and three-month test-retest reliability being 0.72 and 0.82, for negative affectivity and social inhibition, respectively[29]. The DS14 is a stable personality measure over an 18-month period[31] and scores are not confounded by cardiac disease severity or symptoms of anxiety and depression[31, 32]. Previous studies have shown an association between Type D personality and adverse clinical outcome, including mortality and morbidity[33-36]. Type D personality was included in this paper to examine its main effects and interaction effects with anxiety and depressive symptoms for arrhythmias.

**Demographic and clinical variables**

Demographic variables included gender and age. Clinical variables included ICD indication (primary versus secondary prevention) and etiology (ischemic versus non-ischemic). These variables were obtained from medical records.

**Ventricular arrhythmias**

Ventricular arrhythmias were defined by appropriate ICD therapies, either ATPs or shocks, which were delivered for ventricular tachycardia or ventricular fibrillation, over a 12-month period, beginning with ICD implantation. Only the most aggressive treatment per episode was counted, meaning that if a patient experienced a ventricular arrhythmia for which first ATPs were delivered and then shocks, this episode was only counted as 1

shock. The occurrence of appropriate ATPs and shocks were obtained from medical records.

**Statistical analyses**

Differences between groups were examined with a Chi-square test (Likelihood ratio were appropriate) for dichotomous variables and a *t*-test for independent samples for continuous variables. To enhance clinical interpretability, anxiety and depression scores were dichotomized. A series of univariable logistic regression analyses were performed to determine whether anxiety, depressive symptoms, Type D personality, and the interaction effects anxiety by depressive symptoms, anxiety by Type D personality, and depressive symptoms by Type D personality predicted ventricular arrhythmias in the first year following ICD implantation. A subsequent stepwise regression (backward method) was applied to determine the most important psychological predictor of arrhythmias; because of suppressor effects, the backward method is preferable to the forward method[37]. The initial regression model contains all psychological variables; in each subsequent step a variable is deleted until the best model is reached. Next, a multivariable logistic regression analysis (enter method) was performed, including the psychological predictor(s), age, gender, ICD indication, and etiology. However, in order to determine whether ICD indication and etiology could be entered simultaneously, a Chi-square test was applied. The Kaplan-Meier method was applied to graphically present the time to first ventricular arrhythmia and the log-rank test was performed to test for significant differences between the groups. All data were analyzed using SPSS.14.0 for Windows and a *p*-value of .05 was used to indicate statistical significance.

**RESULTS**

**Patient characteristics**

Of the 345 patients who agreed to participate in the study, 324 (93.9%) patients were included in the analyses. Patients who were not included had missing data on self-report measures ($n$ = 12) or clinical variables ($n$ = 9). Table 1 shows demographic and clinical characteristics of the 324 patients included in the study.

***Table 1.*** *Baseline characteristics of 324 patients included in the analyses*

| **Characteristics** | **% (*n*)** |
|---|---|
| **Demographic and Clinical** | |
| Males | 82.7% (268) |
| Age; mean±SD | 62.0±10.5 |
| Secondary prevention | 46.6% (151) |
| Ischemic etiology | 72.2% (234) |
| **Psychological** | |
| Anxiety scores (STAI); mean±SD | 39.2±8.8 |
| Depressive symptoms (BDI); mean±SD | 11.6±6.8 |
| Increased anxiety (i.e., STAI ≥ 40) | 46.9% (152) |
| Increased depressive symptoms (i.e., BDI ≥ 10) | 34.6% (112) |
| Type D personality (DS14) | 22.8% (74) |

SD = standard deviation, ATP = antitachycardia pacing, DS14 = Type D Scale, BDI = Beck Depression Inventory, STAI = State-Trait Anxiety Inventory

**Ventricular arrhythmias**

During the first year post-implantation, 68 patients (21%) experienced ventricular arrhythmias with appropriate therapies and 22 patients (6.8%) died. Of the 68 patients, 51.5% of patients only had appropriate ATP episode(s), 25.0% only had shocks, and 23.5% had both ATPs and shocks. The median number of appropriate ICD therapies was 2, with a range from 1 to 1100 episodes.

**Anxiety, depressive symptoms, Type D personality, and ventricular arrhythmias**

Univariable logistic regression analyses showed that secondary prevention ($p$ = .005) was a significant predictor of occurrence of ventricular arrhythmia, but not gender ($p$ = .23), age ($p$ = .65), or etiology ($p$ = .34) (Table 2). Increased anxiety ($p$ = .17) and depression ($p$ = .67) did not predict arrhythmias, but there was a trend for Type D personality ($p$ = .078). In addition, the combined presence of anxiety and Type D personality significantly predicted ventricular arrhythmias ($p$ = .006).

***Table 2.*** *Univariable predictors of ventricular arrhythmias*

| | Ventricular arrhythmias | | |
|---|---|---|---|
| **Variables** | **OR** | **95% CI** | ***p**** |
| **Demographic and Clinical** | | | |
| Male | 0.99 | 0.96-1.01 | .23 |
| Age | 0.85 | 0.43-1.70 | .65 |
| **Secondary prevention** | **2.18** | **1.26-3.77** | **.005** |
| Ischemic etiology | 0.76 | 0.42-1.35 | .34 |
| **Psychological** | | | |
| Anxiety | 1.46 | 0.86-2.50 | .17 |
| Depressive symptoms | 1.13 | 0.65-1.97 | .67 |
| **Type D personality** | **1.71** | **0.94-3.11** | **.078** |
| **Psychological Interactions** | | | |
| Anxiety by Depression | 1.19 | 0.65-2.17 | .58 |
| **Anxiety by Type D personality** | **2.39** | **1.28-4.47** | **.006** |
| Depression by Type D personality | 1.69 | 0.85-3.37 | .14 |

*$p \leq .09$ are presented in bold face

**Independent predictors of ventricular arrhythmias**

The predictive effect of the combined presence of increased anxiety and Type D personality was confirmed in a backward stepwise regression model ($p = .006$), including anxiety, depressive symptoms, Type D personality, and their interaction effects; all other variables did not add incremental prognostic value.

ICD indication was not associated with etiology, as about 70% of patients in both indication groups had ischemic etiology ($\chi^2 = 0.23$, df = 1, $p = .63$). Hence, these variables could be entered at the same time. In the multivariable logistic regression analysis (enter model), adjusting for gender, age, secondary prevention, and ischemic etiology, the interaction between anxiety and Type D personality remained significant with a 2.3-fold risk. In addition, secondary prevention was associated with a 2.1-fold risk to experience ventricular arrhythmias (Table 3).

***Table 3.*** *Multivariable predictors of ventricular arrhythmias*

| | Ventricular arrhythmias | | |
|---|---|---|---|
| | **OR** | **95% CI** | ***p*** |
| Male | 1.06 | 0.51-2.22 | .88 |
| Age | 0.99 | 0.96-1.102 | .44 |
| **Secondary prevention** | **2.10** | **1.20-3.66** | **.009** |
| Ischemic etiology | 0.77 | 0.41-1.47 | .43 |
| **Anxiety by Type D personality** | **2.29** | **1.20-4.35** | **.012** |

**Ventricular arrhythmias in anxious Type D patients**

Stratification by anxiety and Type D personality yielded 4 groups, that is a non-anxious non-Type D group ($n$ = 156, 48.1%), an anxious non-Type D group ($n$ = 94, 29%), a non-anxious Type D group ($n$ = 16, 4.9%), and an anxious Type D group ($n$ = 58, 17.9%). Figure 1 shows that the incidence of ventricular arrhythmias significantly differed across these groups (Likelihood ratio = 9.13, df = 3, $p$ = .028), with the anxious Type D group showing the highest incidence. The incidence of arrhythmia did not differ across the first three groups (Likelihood ratio = 2.06, df = 2, $p$ = .36). Of note, the incidence was rather low in the small non-anxious Type D group. The three groups were merged and compared with the anxious Type D group, which yielded a significant difference (Likelihood ratio = 7.07, df = 1, $p$ = .008), with 34.5% of the anxious Type D group versus 18.0% of the reference group experiencing ventricular arrhythmias. Kaplan-Meier curves for the time to first ventricular arrhythmia for anxious Type D patients versus the other patients are shown in Figure 2. The log-rank test was significant ($p$ = .004), with anxious Type D patients experiencing earlier and more often ventricular arrhythmia as compared to other ICD patients.

***Figure 1.*** *Proportion of patients who had experienced ventricular arrhythmia, stratified by anxiety and Type D personality status*

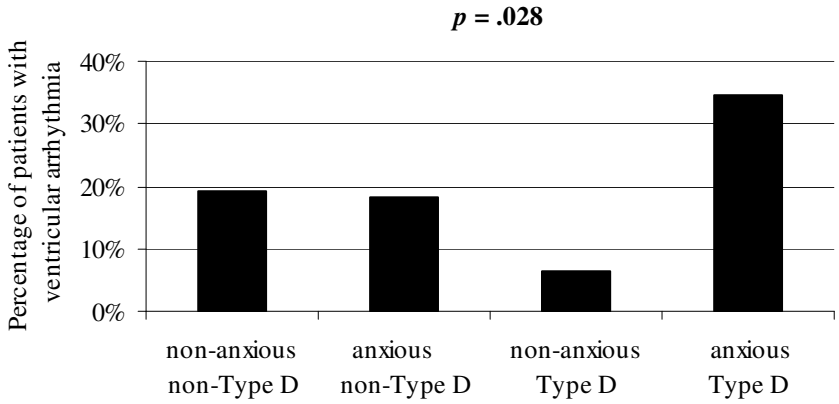
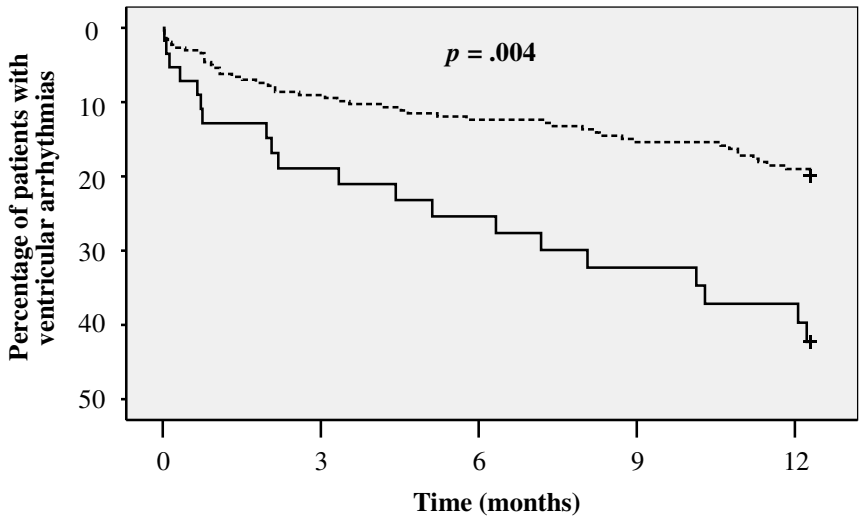



***Figure 2.*** *Kaplan-Meier curve for time to first ventricular arrhythmia in Type D patients with increased anxiety*




| Number at risk | | | | | |
|---|---|---|---|---|---|
| Other groups (*dotted*) | 266 | 242 | 234 | 227 | 218 |
| Anxious Type Ds (*solid*) | 58 | 47 | 44 | 41 | 37 |

**DISCUSSION**

In this prospective study, we examined whether ventricular arrhythmia in ICD patients was predicted by anxiety, depressive symptoms, Type D personality, or their interaction effects. Only the interaction between anxiety and Type D personality was significant, with anxious Type D patients having a 2.3-fold independent risk to experience ventricular arrhythmias in the first year following ICD implantation. This risk was comparable to the 2.1-fold risk for patients with a secondary prevention. Gender, age, and etiology were not significantly related to ventricular arrhythmias. Stratifying patients according to anxiety and personality status showed a significant difference, with almost 35% of the anxious Type D patients experiencing ventricular arrhythmias as compared to 18% among other patients.

Our results provide additional insight to prior research on predictors of ventricular arrhythmias. Incorporation of various psychological variables has been done by Lampert et al.[23] and Dunbar et al.[22], but they did not enter these variables simultaneously. Dunbar et al.[22] reported that anxiety precipitated ventricular arrhythmias (including ATPs and shocks) but Lampert et al.[23] reported no predictive role of anxiety for ventricular arrhythmias (only shocks). In line with the latter study, our results showed that anxiety alone did not predict arrhythmias (ATPs and shocks). Only in combination with the Type D personality, anxiety predicted the occurrence of arrhythmias, which was independent of age, gender, indication, and etiology. Moderate to high levels of depressive symptoms have been linked to appropriate shocks in the Whang et al. study[21], however, Dunbar et al.[22] did not find a precipitating role of mild depressive symptoms for appropriate ATPs and shocks, which is in line with our study. Burg et al.[24] reported that anxiety-triggered ICD shocks were highly present in patients who scored high on trait-anxiety as a stable personality trait. The present findings confirm that personality may be important in moderating the effects of anxiety on the occurrence of ventricular arrhythmias. As this is the first study to show such effect for Type D personality, more research is needed to substantiate this finding.

Type D personality has been studied extensively in cardiac patients and is associated with adverse clinical outcome, including mortality and morbidity[33-36]. Type D personality has also shown to be of value in arrhythmia research, being associated with

outcomes such as anxiety, depressive symptoms, and health-related quality of life[8, 9, 13, 38, 39]. Regarding ventricular arrhythmia, there was a trend for Type D personality alone, but the present findings clearly suggest a predictive effect of Type D personality in ICD patients with elevated anxiety following implantation. Therefore, a part of the relationship between Type D personality and morbidity and mortality might be due to an enlarged risk of ventricular arrhythmias in those Type D patients who experience elevated anxiety levels.

The pathways or mechanisms linking emotions and personality traits in general, and anxiety and Type D personality in particular, to arrhythmias are not well-known and should be explored further in future research. Stress may be associated with increased sympathetic tone and its detrimental effects on arrhythmia[40, 41]. Experimental studies have shown that general mental stress may induce increased T-wave alternans[42], which are associated with ventricular arrhythmias and death[43]. Mental stress may also shorten the cycle length of ventricular tachycardia and consequently result in more difficult termination of this arrhythmia[44].

Of the confounding variables, secondary prevention was significantly predictive for ventricular arrhythmias, whereas gender, age and ischemic etiology were not. The findings on indication, gender, and age are in line with results from previous research[18, 22, 45, 46], although older and male patients may be at increased risk for ventricular arrhyhmias[47]. As ischemic etiology has been identified as a precipitant of ventricular arrhythmias[1], it is difficult to explain the nonsignificant finding.

Approximately half of the patients had increased anxiety, a third increased depression, and a quarter of patients was classified as Type D. In addition, about 80% of Type D patients also had increased levels of anxiety. These prevalences are in line with previous research in ICD patients[7, 8, 15] and confirm that anxiety may be more prevalent in ICD patients as compared to depressive symptoms.

Screening for anxious Type D patients may be standardized in clinical practice, as anxiety and Type D personality have been associated with adverse outcomes in ICD patients[10, 13, 15, 48, 49]. Anxiety has been related to occurrence of arrhythmias[22] and this study more specifically showed that Type D patients with increased anxiety may have an enlarged risk for arrhythmias. The 20-item STAI and 14-item DS14 may be used as

screening tools for general anxiety and Type D personality, respectively, as these measures have good psychometric properties and standard cut-off scores[25, 29, 30]. Next, identified high-risk patients may be offered adequate behavioral support. A recent review indicates that cognitive-behavioral therapy paired with exercise training may be most useful to diminish anxiety symptoms in ICD patients[50]. Interventions for Type D personality have not yet been examined, but these may aim at changing coping styles for dealing with negative emotions. As only a few studies have focused on psychological intervention in ICD patients[50] and no study has investigated interventions for Type D patients, more research is needed on this topic.

This study has several limitations. First, it was not possible to control for clinical variables such as ejection fraction and NYHA class, because these data were not available for many patients. Second, ventricular arrhythmias without therapy were not included. Third, although the prevalence of arrhythmias in the non-anxious Type D group was rather low, this was probably related to the small number of patients in this group. Fourth, as cause of death is not known for most of the patients, it is unknown, though unlikely, whether death was attributable to ventricular arrhythmia.

In conclusion, results of this prospective study suggest that Type D patients with increased levels of anxiety and patients with a secondary prevention are at increased risk to experience ventricular arrhythmias in the first year following ICD implantation. In clinical practice, patients with increased anxiety and Type D personality should be identified and offered adequate support. Future studies may focus on the mechanisms and pathways linking anxiety and personality traits to ventricular arrhythmias.

***ACKNOWLEDGEMENTS***

*We would like to thank Eefje Postelmans for inclusion of the patients into the study and Martha van den Berg (MSc), Vivianne Sterk, Jolien Diekhorst (MSc), Marjan Traa, and Marie-Anne Mittelhaeuser for help with data management. This study was supported by the Netherlands Organization for Scientific Research, The Hague, The Netherlands with a VICI grant (453-04-004) to Dr. Johan Denollet.*

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*Chapter 9*

# Psychological Intervention Following Implantation of an Implantable Defibrillator: A Review and Future Recommendations

**Pedersen SS, Van den Broek KC, Sears SF. Psychological intervention following implantation of an implantable defibrillator: a review and future recommendations. Pacing Clin Electrophysiol 2007;30:1546-54.**

**ABSTRACT**

**Background** The medical benefits of the implantable cardioverter defibrillator (ICD) are unequivocal, but a subgroup of patients experiences emotional difficulties following implantation. For this subgroup, some form of psychological intervention may be warranted. This review provides an overview of current evidence on the efficacy of psychological intervention in ICD patients and recommendations for future research.

**Methods** We searched the PubMed and PsycInfo databases in the period between January 1980 and April 2007, using a set of a priori determined keywords. Based on the search and a hand search of the reference lists of the included articles, we identified nine studies that fulfilled the inclusion criteria.

**Results** The majority of studies used a randomized controlled trial design, but studies varied considerably in sample size, response rate, attrition rate, and type of intervention. However, most interventions were multifactorial, using cognitive behavioral therapy as one of the mainstays of treatment. Overall, psychological interventions seem to have little impact on shocks and heart rate variability. Some studies found a decrease in depressive symptoms and gains in quality of life, but the most notable effects are seen in improved exercise capacity and reductions in anxiety. Effect sizes for changes in anxiety in the intervention group ranged from small to large compared to small in the usual care group, using Cohen's effect size index.

**Conclusions** Preliminary evidence from small-scale intervention trials suggests that psychological intervention is worthwhile in ICD patients. Nevertheless, large-scale, well-designed trials are warranted to substantiate these findings. A multifactorial approach using a cognitive behavioral component paired with exercise training is likely to be the most successful.

## INTRODUCTION

The superiority of the implantable cardioverter defibrillator (ICD) compared to anti-arrhythmic drugs for the prevention of sudden cardiac death (SCD) both in primary[1,2] and secondary prevention is well established[3,4], with risk reductions ranging from 50%-63%[5]. Nevertheless, a subgroup of patients experiences emotional difficulties, with symptoms of anxiety and depression varying from 24%-87%[6]. Anxiety may exist on a continuum from normalized fear, generalized anxiety, and panic disorder to post-traumatic stress disorder[6,7], with 13-38% of ICD patients experiencing clinical levels[8].

Generally, the manifestation of emotional distress in ICD patients has been attributed to shocks[6]. However, the Canadian Implantable Defibrillator Study (CIDS) indicated that a threshold ≥ 5 shocks is required[3], whereas the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial showed that one shock is sufficient to lead to decreased quality of life (QoL) and increased patient concerns[9]. Other studies show that catastrophic cognitions, such as attributing ICD shocks to the progression of disease and impending risk of SCD[10], concerns about the ICD firing[10, 11], and the *distressed* (Type D) personality (i.e., the tendency to experience increased negative emotions paired with the non-expression of these emotions) may be more important determinants of emotional distress than shocks[12].

There is also preliminary evidence to suggest that distress may precipitate arrhythmic events[13,14]. For some patients, a vicious cycle may ensue, with ICD implantation leading to anxiety and depression in turn precipitating arrhythmic events and leading to more distress. ICD patients may be particularly prone to developing anxiety post implantation due to fears of the ICD firing and associated catastrophic cognitions, with some patients interpreting a shock as a sign of danger and progression of disease[6]. Being caught in this vicious cycle may lead to detrimental effects of a secondary nature, including avoidance behavior, not returning to work, reduced sexual activity, physical inactivity, and impaired QoL[6, 8].

Both anxiety and depression comprise risk factors for adverse prognosis in coronary artery disease[15,16]. More importantly, emotional distress in some ICD patients does not remit spontaneously but persists over time[17,18]. For these patients, psychological intervention on its own or combined with pharmacotherapy may be warranted in order to

reduce distress and adverse secondary outcomes. Given the exponential rise in ICD implantations and its projected increase in the future[19], knowledge of psychological interventions and their efficacy is important for secondary prevention in this distinct patient group.

The only review on psychological interventions in ICD patients was published in 2003[20]. However, the search period extended only until 2002, with new studies having been published since then. The current review (i) provides an up-to-date overview of psychological intervention studies in ICD patients, (ii) evaluates their efficacy in terms of reducing distress and the occurrence of ventricular arrhythmias, and (iii) provides recommendations for future research.

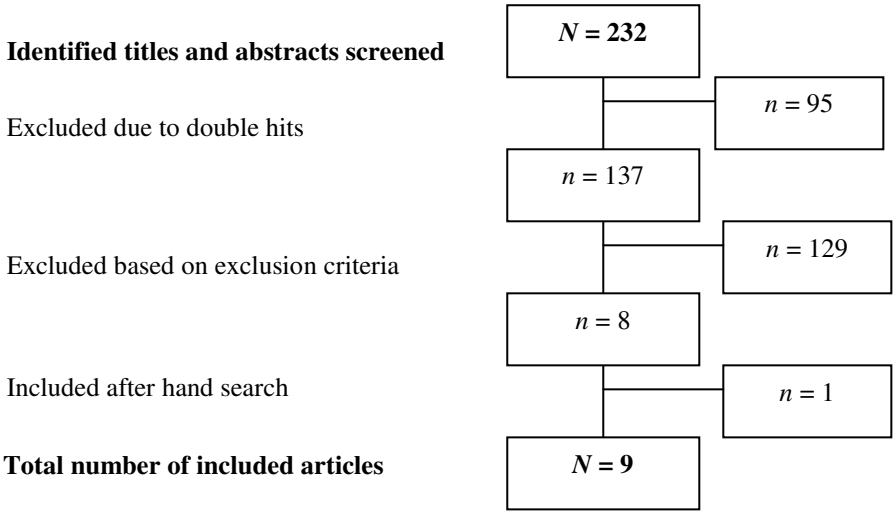
**METHODS**

The databases PubMed and PsycInfo were searched in the period between January 1980 and April 2007, using a combination of the following search terms: *implantable defibrillator, psychological, psychosocial, intervention, rehabilitation, therapy,* and *treatment outcome*. We included articles in the review irrespective of their design, as long as the study was empirical, included an intervention and a comparison group, the intervention had a psychological component, and the article was published in a peer-reviewed English journal. Hence, studies that evaluated multifactorial interventions (e.g., comprising psychotherapy and/or exercise in addition to a psychological component) also qualified for inclusion. Reviews, case studies, and descriptive studies were excluded, as were studies based on mixed patient groups (i.e., if only part of the patients had received an ICD). In addition to the computer search, the reference list of the included articles was hand searched. The second author (KCB) conducted the computer search and eliminated double hits; subsequently, the first (SSP) and the second author (KCB) reviewed the abstracts and decided on whether an article qualified for inclusion based on the inclusion criteria. The hand search was conducted by the first (SSP) and the second author (KCB). No other hand searches were conducted.

The search resulted in 232 hits. After removing double hits, the number of studies was reduced to 137. Weighing the remaining studies against the inclusion criteria reduced the number to 8. A hand search of the reference list of these studies identified one

additional study. See Figure 1 for an overview of the selection. Due to the limited number of studies, their heterogeneity, and the relatively small sample sizes, it was not possible to conduct a meta-analysis. However, we aimed to comply with the criteria for the reporting of Meta-analysis of Observational Studies in Epidemiology (MOOSE) to the extent that it was possible[21]. We chose to use the MOOSE criteria given that studies used a mix of designs (i.e., experimental or observational).

***Figure 1.*** *Flowchart of the literature selection*




**RESULTS**

The current review is based on nine studies, with studies reporting on the same sample in different publications being listed under the first author and as one study. See Table 1 for an overview. In the following section, we provide a description of the included studies in relation to design, sample size, patient characteristics, and the intervention used. Subsequently, we evaluate the effect of the intervention on the primary outcome measures of the studies, divided into two main categories (i.e., cardiac and patient-centered). For the patient-centered outcomes, we focus on QoL, anxiety and depression, given that they were the outcome measures most frequently used across studies.

***Table 1.*** *Overview of studies on psychosocial interventions in ICD patients*

| **Authors**[reference] | **Sample size** $N_{int}$ | $N_{con}$ | **Study design** | **Intervention** | **Duration** | **Comparison intervention** | **Endpoint(s) therapy** |
|---|---|---|---|---|---|---|---|
| Badger et al. (1989)[30] | 6 | 6 | Comparative study | Support group | 2 months | Usual care | QoL |
| Carlsson et al. (2002)[22] | 10 | 10 | RCT | Education | Not reported | Usual care | QoL |
| Chevalier et al. (2006)[23] | 35 | 35 | RCT | CBT | 3 months | Usual care | Shocks, HRV, QoL, anxiety, depression, defibrillator tolerance |
| Dougherty et al. (2004, 2005)[24, 32] | 84 | 84 | RCT | Telephone support | 2 months | Usual care | Shocks, QoL, anxiety, depression, health care use, ICD-related knowledge |
| Fitchet et al. (2003)[25] | 8 | 8 | RCT | CCR | 3 months | Usual care | Ventricular arrhythmias and shocks, exercise test, anxiety, depression |
| Frizelle et al. (2004)[26] | 12 | 10 | RCT | CCR | 3 months | Usual care | Shocks, ATP episodes, QoL, exercise test, anxiety, depression, ICD-related concerns, perceived health status |
| Kohn et al. (2000)[27] | 25 | 24 | RCT | CBT | 5 months | Usual care | Shocks, anxiety, depression, psychosocial adjustment |
| Molchany et al. (1994)[31] | 11 | 5 | Comparative study | Support group | Not reported | Usual care | QoL, anxiety |
| Sneed et al. (1997)[28] | 17 | 17 | RCT | Telephone support, counseling, support group | 4 months | Usual care | Mood states, psychosocial adjustment |

CBT = cognitive behavioral therapy; CCR = comprehensive cardiac rehabilitation; HRV = heart rate variability; $N_{con}$ = number of patients in control group; $N_{int}$ = number of patients in intervention group; RCT = randomized controlled trial; QoL = quality of life

**Description of included studies**

*Design*

The majority of studies (7/9) used a randomized controlled trial (RCT) design[22-28], with two of these studies employing an RCT with a case-crossover design[25,26]. The RCT is considered the gold standard in medicine and the most powerful design in terms of providing the strongest evidence for the efficacy of a given intervention[29]. In two studies, an observational design was employed[30, 31].

In several studies, the participant rate was low, with 26% of eligible patients participating in the Frizelle et al. study[26], 35% in the Chevalier et al. study[23], and 47% in the Fitchet et al. study[25], although in the latter study a random sample of 16 patients was drawn from those who agreed to participate ($n$ = 34). Molchany and colleagues included a convenience sample of ICD patients and their significant other and did not report the initial number of patients and significant others approached[31]. In some[24-26], but not all studies[23] with a low participant rate, responders and nonresponders were compared on baseline characteristics to rule out systematic differences. Such a comparison is important, in particular in studies with a low response rate, as systematic differences between responders and nonresponders jeopardize the external validity of the study.

In four studies, patients were included during hospitalization for ICD implantation, with three studies including prior to implantation[22, 27, 28] and one study at the time of discharge from hospital[24]. One study included patients who had their ICD implanted prior to or during the study[23]. The other four studies recruited patients who had their ICD implantation for some time. In these studies, the mean time since implantation was 8-12.5 months[30] and 20 months[25]. One study did not provide information on the time since implantation[26] and one study only reported the range (i.e., 5-24 months)[31].

The follow-up periods for evaluating the endpoints varied widely between studies from 1[22] to 12 months[23, 32].

*Sample size*

Sample sizes varied considerably across studies, ranging for the total sample from 12-168, and from 6-84 in the intervention group and 5-84 in the control group[22-28, 30, 31]. Generally, sample sizes were small, with ≤ 35 patients in the intervention and usual care groups, respectively, in all but one study[24].

*Patient characteristics*

The majority of patients were men[22-25, 27, 30, 31], with two studies not providing information on sex[26,28]. The mean age was between 57 and 66 years[22-28], with a range of 28-83 years[22, 25, 27, 30, 31]. When reported, mean left ventricular ejection fraction varied from 30-44%[23-25, 29, 30]. Only four studies provided information on the reason for ICD implantation, including coronary artery disease etiology[22-25, 32].

*Interventions*

The interventions employed across studies were heterogeneous, although the majority of studies used a multifactorial approach. Four studies included a cognitive behavioral component[23, 25-27], with cognitive behavioral therapy (CBT) being the mainstay of treatment. Using a CBT framework, anxiety, apprehensions, avoidance behavior, fear of shocks, and distorted cognitions were targeted, with stress management and relaxation therapy often forming adjunctive therapies[23, 25, 26]. In two studies, patients also engaged in aerobic exercise, as part of a comprehensive cardiac rehabilitation program[25, 26].

Group or individual counseling comprised the key component in the other five studies[22, 24, 28, 30, 31], with counseling most frequently being provided by a specialized nurse. The main objective of the counseling was to provide support to patients, educate patients about the ICD and their illness, and to enhance their coping styles.

The duration of the intervention varied from 2 to 5 months across studies[23-28, 30, 32], with the average length being 3 months. In two studies, the duration was not reported[22, 31]. Usual care comprised the control condition for all studies**,** although the exact constellation of, for example, visits to the cardiologist, ICD nurse, and general practitioner was often not reported.

**Effect of intervention**

*On cardiac outcomes*

*Shocks.* Shocks comprised one of the outcome measures in 5/9 studies[23-27]. In none of the studies did the intervention lead to a statistically significant reduction in the rate of shocks compared with usual care[23-27], although reductions were found[23]. This null finding may in part be attributed to the relatively short follow-up periods, ranging from 1-12 months. In the study by Dougherty and colleagues, evaluating the effect of the intervention on shocks at several time points (i.e., 1, 3, 6, and 12 months post-implantation), there were no statistically significant differences between the intervention and usual care groups at any of the time points[24, 32]. Kohn and colleagues found similar results at 9-months follow-up, although when stratifying by number of shocks using a threshold of ≥ 1 shock, there was a trend for more shocks in the intervention versus usual care group (61% versus 33%, $p = .07$)[27]. A further subgroup analysis revealed, however, that of patients who received ≥ 1 shock, usual care patients ($n = 6$) had significantly higher symptom levels of anxiety and depression compared with patients in the intervention group ($n = 10$). This suggests that the intervention per se had no direct effect on shocks but buffered the effect of shocks on distress[27]. In a subgroup analysis of patients without antiarrhythmic drugs, Chevalier and colleagues found a reduced risk of shocks in the CBT group ($n = 19$) versus usual care ($n = 20$) at 3 months but not at 12 months[23]. It is important to emphasize, however, that the subgroup analyses performed in the latter two studies were based on small numbers with only 16 and 39 patients, respectively.

*Heart rate variability and exercise capacity*. Other physiological and cardiac outcome measures used were heart rate variability and exercise capacity. Chevalier and colleagues report an improved sympathovagal balance in patients treated with CBT, with daytime pNN 50 and nocturnal SDNN increasing significantly in the CBT group compared to usual care[23]. The two cardiac rehabilitation trials both found an improvement in exercise capacity in the intervention group. In the study by Fitchet and colleagues, mean exercise time increased with 16% (9m55sec versus 11m11sec, $p = .001$) in patients receiving the 12-week rehabilitation program, whereas the mean exercise time did not differ

significantly in the usual care group pre- and post-test[25]. In the study by Frizelle and colleagues, significant increases were found in the level of difficulty ($p$ = .05) and the total distance walked ($p$ = .01) in the rehabilitation group compared to usual care[26]. No significant differences were found in heart rate change and patient-rated breathlessness.

*On patient-centered outcomes*

*Quality of life*. Of all studies, six studies focused on QoL as an endpoint[22-24, 26, 30, 31, 32]. Frizelle and colleagues found an improvement in emotional, physical, social, and global QoL in patients receiving rehabilitation compared with usual care[26]. Badger and colleagues found a trend toward improvement in role functioning and psychological adjustment in the treatment group, but differences in mean pre- and post-scores were not statistically significant[30]. Of note, there was a trend in the opposite direction for the usual care group, with these patients experiencing deterioration in adjustment over time. Carlsson and colleagues provided information on change scores within the intervention and usual care group, respectively, but did not compare the effect of the intervention on QoL relative to that in the usual care group[22]. None of the other studies found any effect of the intervention on QoL compared with usual care[23, 24, 31, 32].

*Anxiety*. Anxiety was employed as an outcome in the majority of studies (i.e., 7/9), with most[23, 27, 32] but not all studies[28, 31] finding that the intervention reduced levels of anxiety. In the study by Chevalier and colleagues, where CBT was the mainstay of treatment, the intervention group experienced significantly less anxiety than usual care at 3 ($p$ = .04) and 12 months ($p$ = .03)[23]. Kohn and colleagues, also using CBT as the mainstay of treatment, reported equal levels of state as well as trait anxiety in the intervention and usual care group at baseline, but they found lower levels of trait anxiety in the intervention group compared with usual care ($p$ = .013) at 9-months follow-up, but no difference on state-anxiety[27]. However, this study only compared differences in anxiety between groups cross-sectionally, that is at baseline and at 9 months follow-up, but not the potential impact of the intervention on changes of anxiety over time[27]. In fact, when examining changes in anxiety over time both state and trait anxiety were reduced in the intervention

group between baseline and follow-up, whereas the usual care group experienced reductions in state anxiety only, but an increase in trait anxiety.

Similarly, cardiac rehabilitation was found to reduce levels of anxiety. Fitchet and colleagues found a significant decrease in anxiety in the rehabilitation group ($p < .001$), whereas the usual care group experienced more feelings of anxiety after 12 weeks ($p = .028$)[25]. The second study on cardiac rehabilitation yielded similar results, with significant differences in change of anxiety scores between the rehabilitation and control group ($p = .012$)[26]. The results of Dougherty and colleagues were mixed, with a significant reduction in anxiety over a 12-month period in the intervention group compared with usual care[32], although there were no significant differences between groups at 1 and 3 months[24].

Dougherty and colleagues also looked at the proportion of patients scoring in the range of severe anxiety, using a cut-off ≥ 40 on the State-Trait Anxiety Inventory[24, 32]. At baseline, 40% of the patients in the intervention group scored within this range, with it being reduced to 20%, 21%, and 18% at 3-, 6-, and 12-months follow-up. By contrast, fewer patients in the usual care group reported severe anxiety at baseline, namely 29%, with prevalence rates of 27%, 19%, and 23% at 3-, 6-, and 12-months follow-up. A post-hoc analysis showed that the change in number of cases with severe anxiety in the intervention group was reduced by 55% compared with 21% in the control condition over the 12-month period. Fears and ICD-related concerns, which likely comprise the basis of anxiety in ICD patients, were also reduced in the intervention compared with the usual care group[24, 26, 32].

*Depression*. Of studies on depression[23-28, 32], 2/6 found a significant reduction in the burden of depression in the intervention group compared with usual care[25, 26]. The choice of intervention used in the two positive studies was comprehensive cardiac rehabilitation. In the study by Fitchet and colleagues, mean depression scores decreased from 9.9 pre- to 6.7 post-rehabilitation ($p < .001$), whereas mean scores in the control group rose from 7.6 to 9.5 ($p = .074$)[25]. In the study by Frizelle and colleagues, mean depression scores were also reduced between pre- and post-rehabilitation from 3.05 ±3.07

to 1.73 ±1.90 ($p$ = .003)[26]. Although Kohn and colleagues report a lower mean depression score in the CBT compared to the usual care group (6.9 ±5.9 versus 15.0 ±13.0, $p$ = .037) at 9-months follow-up, this difference cannot necessarily be attributed to the intervention due to lack of baseline assessment of depression[27]. Dougherty and colleagues found no significant differences between groups on depressive symptoms[24, 32]. However, using a cut-off ≥ 16 on the Center for Epidemiologic Studies Depression Scale (CES-D), they found that 26% of patients in the intervention group compared with 19% in the usual care group experienced depressed mood at baseline; at 3 months, prevalences were similar, with 18% versus 19%. Nevertheless, a post-hoc comparison showed a reduction in the number of patients with depressive symptomatology in the intervention group by 31% versus 0% in the usual care group over the 3-month period. Unfortunately, in contrast to anxiety, the authors only reported depression prevalence rates for baseline and 3 months.

**Effect sizes for changes in anxiety**

Given that the majority of studies were based on relatively small sample sizes and hence at risk of being underpowered, which limits the chance of finding statistically significant differences if present, we evaluated the clinical significance of the intervention compared with usual care, using Cohen's effect size index[33]. An effect size of 0.20 is considered small, 0.50 moderate, and ≥ 0.80 large. We chose to evaluate the effect of the intervention using anxiety as the outcome measure, since anxiety was the endpoint most frequently used across studies. In addition, in ICD patients symptoms of anxiety are more prevalent than depression[6, 12], making it an important patient-centered outcome in this distinct patient group[34]. Effect sizes were calculated for the difference in anxiety between baseline and the last follow-up reported in the study.

Effect sizes and the measures used to assess anxiety are shown in Table 2. For three studies, it was not possible to calculate effect sizes for the impact of the intervention on changes in anxiety either because anxiety was not assessed[22, 30] or due to means and standard deviations not being reported for the groups at baseline[28]. In the two studies using an RCT with a case-crossover design, means and standard deviations were not reported separately for the groups but only for the total group (i.e., when all patients had

been subjected to the intervention)[25, 26]. Generally, the impact of the intervention on reductions in anxiety had a small[24, 26, 31, 32] to large effect[23, 25, 27], as indicated by Cohen's effect size index, ranging from 0.14 to 1.79[31, 25]. In studies where it was possible to compare the effect size for the intervention versus usual care, the intervention was superior to usual care in terms of reducing anxiety at follow-up in 3 out of 4 studies[23, 27, 32]. Of note, in the study by Chevalier and colleagues, the usual care group had a large negative effect size, indicating that patients receiving no intervention deteriorated substantially during follow-up[23].

***Table 2.*** *Effect sizes for impact of intervention versus usual care on changes in anxiety*

| **Authors**[reference] | **Follow-up period** | **Effect size* Intervention** | **Effect size* Usual care** | **Anxiety measure** |
|---|---|---|---|---|
| Badger et al. (1989)[30] | 2 months | - | - | - |
| Carlsson et al. (2002)[22] | 1 month | - | - | - |
| Chevalier et al. (2006)[23] | 12 months | 0.72 | -0.84 | HAM-A |
| Dougherty et al. (2004, 2005)[24, 32] | 12 months | 0.38 | 0.15 | STAI-S |
| Fitchet et al. (2003)[25] ** | 6 months | 1.79 | - | HADS |
| Frizelle et al. (2004)[26] ** | 3 months | 0.34 | - | HADS |
| Kohn et al. (2000)[27] | 9 months | 0.89 | 0.30 | STAI-S |
| Molchany et al. (1994)[31] | 6 months | 0.14 | 0.20 | STAI-S |
| Sneed et al. (1997)[28] | 4 months | - | - | POMS |

* Based on $mean_1 - mean_2$ / pooled standard deviation,
** Pre- and post-treatment scores were not reported separately for the intervention and usual care groups, but only for the total group (i.e., when all patients including the waiting group had undergone the intervention)
HADS = Hospital Anxiety and Depression Scale; HAM-A = Hamilton Anxiety Scale; POMS = Profile of Mood States; STAI-S = State-Trait Anxiety Inventory (state scale)

**DISCUSSION**

Based on the current review, the evidence for a benefit of psychological intervention in ICD patients is most convincing for symptoms of anxiety and exercise capacity, with intervention leading to a significant reduction in anxiety and improvement in exercise capacity. By contrast, there is little evidence to suggest that the interventions studied to date have had a notable impact on depressive symptoms, QoL, heart rate variability, and shocks. These findings, however, should be viewed in the context of the small number of studies, the very small sample sizes, and the variability in their methodological quality.

Generally, there is a paucity of large-scale, well-designed psychological intervention studies in ICD patients. Nevertheless, when calculating effect sizes to indicate the clinical impact of the intervention on reductions in anxiety, current evidence indicates that this pursuit is worthwhile and that patients may benefit substantially, with large effect sizes found in three trials[23, 25, 27]. In turn, a reduction in anxiety levels is likely to have beneficial effects on secondary outcomes, such as avoidance behavior, returning to work, sexual activity, physical activity, and QoL[6, 8].

In order to expand our knowledge of the most optimal intervention to offer ICD patients, it is paramount that future trials include sufficiently large samples to have adequate power to test the efficacy of a given intervention. This has also been suggested by others[6]. In addition, it is important to provide an intervention that appeals to patient needs and concerns and is logistically feasible for them to attend, as the response rate was low and the attrition rate high in a number of studies[23, 25, 26]. In this regard, a web-based intervention may be worth considering, as it is accessible and can reach large groups of patients as well as safeguard patients' anonymity, in turn providing an interesting alternative to those patients who need help but are less inclined to see a psychologist[35].

On the basis of the current review, we would recommend that CBT and exercise training form the mainstays of treatment, as these components were included in those trials showing the largest effect[23, 25, 27]. Others have also advocated the inclusion of CBT[6], primarily since CBT may be the most effective means by which to deal with ICD related concerns and fears that are highly prevalent in ICD patients[11, 26], and which may eventually lead to manifest clinical anxiety, including panic disorder[7]. In this regard, education about the ICD in order to avoid misconceptions and minimize ICD related

concerns should form part of any intervention[11, 26, 36], with adjunctive pharmacotherapy being necessary in subgroups of patients to curb emotional distress[7]. The available evidence also suggests that health policy makers are justified in supporting coverage for psychosocial and exercise interventions for ICD patients to reduce anxiety and improve functioning. However, future trials should evaluate the influence of the intervention on health-care utilization and the cost-effectiveness of the intervention in addition to the potential moderating influence of factors, such as ICD indication, cardiac resynchronization therapy, disease etiology and severity, on the effectiveness of the intervention.

The preferred research design for future studies should be an RCT, which is the most powerful study design to test the efficacy of an intervention[29]. We also recommend the inclusion of multiple assessments of the outcome measures under study, spanning both psychological (e.g., anxiety) and physiological markers (e.g., cortisol) whenever possible, in order to evaluate changes over time and investigate whether the effect of a given intervention will remain stable and not just have short-term effects. The longest follow-up reported in studies included in the current review was 12 months[23, 24, 32]. Attention should also be given to the choice of instruments used to evaluate the effect of the intervention. Several instruments routinely used in psychosomatic research are not sensitive to tap treatment-related changes[37]. ICD disease-specific instruments have also been established, including measures of “ICD patient acceptance”, “shock anxiety”, “ICD worries”, and “ICD concerns” that allow for more precise interventional targets[11, 38-40]. Importantly, the instruments used to assess anxiety in the majority of studies in the current review have been shown to be sufficiently sensitive to measure an effect following intervention, if present.

In future interventions, it may also be important to include personality traits, such as Type D personality, given its potential moderating effect on outcome. Type-D is an emerging risk factor in cardiovascular disease[41] that has also been associated with increased anxiety and depressive symptoms in ICD patients, irrespective of shocks[12]. Positive affect comprises another important potentially moderating factor that has been associated with better mental health and social functioning in ICD patients[42]. Given that patients may not necessarily identify themselves by negative emotions alone, focus on

increasing positive emotions rather than only reducing negative emotions may also enhance the compliance and commitment of patients to the intervention. Finally, when reporting on future RCTs in the context of ICD patients, the CONSORT (Consolidated Standards of Reporting Trials) statement should be adhered to[43]. Briefly, the CONSORT statement includes a 22-item checklist and a flow diagram for reporting RCTs. There is preliminary evidence that the quality of the reporting of RCTs improves with compliance with these guidelines[44]. In addition, using this statement would enhance the interpretation of RCTs and facilitate the conductance of future meta-analyses.

The results of this review should be interpreted with some caution, given that we only included studies published in English peer-reviewed journals. This could have led to a potential selection bias. In addition, the number of studies was limited, with the review based on only nine studies. The heterogeneity of studies, including the relative small sample sizes, made comparisons across studies difficult. Although we calculated and compared effect sizes for reductions in anxiety in the intervention and usual care group, respectively, with the aim of alleviating the problem of small sample sizes and reduced power, the use of small sample sizes increases the risk of having a selected group of patients.

In conclusion, preliminary evidence from small-scale intervention trials suggests that psychological intervention is worthwhile in ICD patients, in particular with a view to reducing anxiety and concerns about the ICD. Nevertheless, large-scale, well-designed psychological intervention trials are warranted to substantiate these findings, with a multifactorial approach using a cognitive behavioral component and exercise training likely to be the most successful. These intervention trials are necessary in order to provide the most optimal care for the increasing number of patients who receive an ICD now and in the future[19].

***ACKNOWLEDGEMENTS***

*This research was supported with a VENI grant (451-05-001) to Dr. SS Pedersen from the Netherlands Organization for Scientific Research (NWO), The Hague, The Netherlands.*

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*PART III*

# The Role of Partners in ICD Treatment

*Chapter 10*

# Increased Emotional Distress in Type D Cardiac Patients without a Partner

**Van den Broek KC, Martens EJ, Nyklíček I, Van der Voort PH, Pedersen SS. Increased emotional distress in Type D cardiac patients without a partner. J Psychosom Res 2007;63:41-9.**

**ABSTRACT**

**Objective** The distressed (Type D) personality is an emerging risk factor in coronary artery disease that has been associated with adverse prognosis, impaired health status, and emotional distress. Little is known about factors that may influence the impact of Type D personality on health outcomes. Therefore, the aim of this study was to determine the combined effect of Type D and not having a partner on symptoms of anxiety and depression.

**Methods** Patients (*N* = 554) hospitalized for acute myocardial infarction or implantable cardioverter defibrillator implantation completed the Type D Scale (DS14) during hospitalization and the State-Trait Anxiety Inventory and Beck Depression Inventory at 2 months follow-up.

**Results** Stratifying by personality and partner status showed that Type D patients without a partner had a higher risk of both anxiety (OR = 8.27; 95%CI 2.50-27.32) and depressive symptoms (OR = 6.74; 95%CI 2.19-20.76) followed by Type D patients with a partner (OR = 3.73; 95%CI 2.16-6.45 and OR = 3.81; 95%CI 2.08-6.99, respectively) and non-Type D patients without a partner (OR = 2.04; 95%CI 1.05-3.96 and OR = 3.03; 95%CI 1.46-6.31, respectively) compared to non-Type D patients with a partner, adjusting for demographic and clinical baseline characteristics, indicating a dose-response relationship.

**Conclusion** Lack of a partner further exacerbated the risk of symptoms of anxiety and depression in the already distressed Type D patients. In clinical practice, it is important to identify Type D patients without a partner and carefully monitor them, as they may be less likely to alter health-related behaviors due to their increased levels of distress.

## INTRODUCTION

There is increasing emphasis on patient-centered outcomes in cardiovascular disease (CVD), such as quality of life and emotional distress[1]. Knowledge of the determinants of these outcomes is also important in order to facilitate identification of high-risk patients in clinical practice[1]. The distressed (Type D) personality may be an important determinant of individual differences in outcomes, as this personality disposition has been associated with an increased risk of adverse prognosis[2-5], impaired quality of life and health status[6, 7], exhaustion and fatigue[8], and a wide range of emotional distress, including anxiety[9], depressive symptoms[9, 10], and post-traumatic stress disorder[11]. Type D has been shown to be a risk factor for adverse health outcomes across different types of CVD, including peripheral arterial disease[6], coronary artery disease[12], chronic heart failure[10], arrhythmias[9], and heart transplantation[13, 14]. The risk associated with Type D in relation to clinical outcome is on par with established biomedical risk factors, such as left ventricular dysfunction[3, 4, 15].

Type D personality is characterized by the two stable personality traits negative affectivity (the tendency to experience negative emotions across time and situations)[16] and social inhibition (the tendency to inhibit the expression of emotions and behaviors in social interactions to avoid disapproval by others)[17]. The prevalence of Type D ranges from 24%-34% in patients with coronary artery disease[3, 4] and arrhythmias[9] to 33-53% in patients with hypertension[18], peripheral arterial disease[6], and chronic heart failure[10, 19].

Little is known about factors that may influence the impact of Type D personality on prognosis, quality of life, and emotional distress. Knowledge of these factors is important for optimizing risk stratification in clinical practice, and may also point to targets for intervention. There are several pathways that may link Type D to adverse health outcomes, including physiological and behavioral pathways. As for physiological pathways, they may comprise inflammation[19, 20], blood pressure reactivity to stress[21], and hyperactivity of the hypothalamic-pituitary-adrenal axis, including increased levels of cortisol[21, 22]. Potential behavioral pathways comprise health-related behaviors, including failure to change risk factors, such as smoking, and poor treatment adherence[3, 23]. In addition, because Type D patients inhibit behavior in social interactions, it is likely that

communication with doctors is impaired, which may also hinder effective treatment[24]. However, to date, these potential mechanisms have not been examined in Type D patients.

A potentially important behavioral factor influencing the relationship between Type D and health outcomes is social support. Since social support has been shown to buffer the effects of stress on both well-being[25] and cardiovascular function[26, 27], lack of support may enhance the adverse effects of Type D personality on health outcomes, including emotional distress. By analogy, since Type D patients have been shown to have fewer social ties and to experience less social support than non-Type D patients[3], Type D patients who have a fulfilling relationship with a partner may be at less risk for adverse health outcomes than patients without a partner.

Therefore, the aim of this study was to determine the combined effect of Type D personality and not having a partner on symptoms of anxiety and depression across different CVD treatment groups, that is, in patients with acute myocardial infarction (MI) or patients who received an implantable cardioverter defibrillator (ICD). An additional advantage of pooling data was to enhance the statistical power of the study, which has also been advocated by others[28].

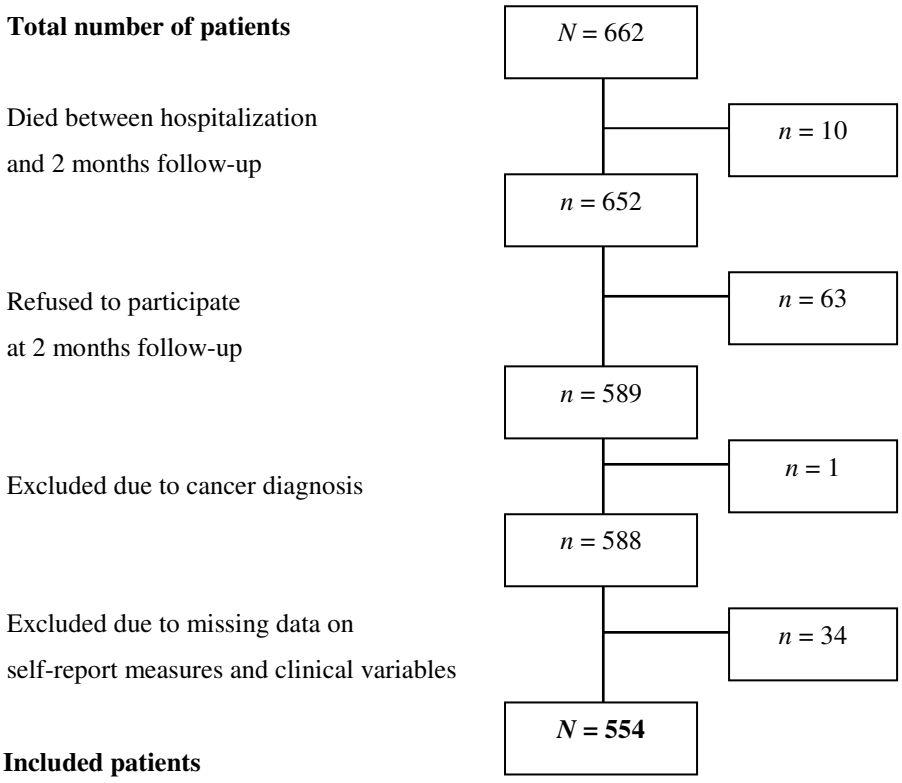
## METHODS

### Patient population and design

Patients hospitalized for acute MI or ICD implantation between May 2003 and December 2005 were included from five hospitals in the Netherlands (Catharina Hospital, Eindhoven; Amphia Hospital, Breda; St. Elisabeth Hospital, Tilburg; TweeSteden Hospital, Tilburg; and St. Anna Hospital, Geldrop). Inclusion criteria were hospitalization for acute MI ($n$ = 452) or ICD implantation ($n$ = 210). Exclusion criteria were significant cognitive impairments (e.g., dementia) and severe life-threatening comorbidities (e.g., cancer). Criteria for diagnosis of acute MI were troponin I levels that are more than twice the upper limit, typical ischemic symptoms (e.g., chest pain) lasting for more than 10 minutes, and ECG evidence of ST segment elevation or new pathological Q waves. ICDs were implanted for primary or secondary prevention of ventricular arrhythmias, according to accepted criteria[29].

Patients completed self-report measures on Type D personality at baseline as well as measures on anxiety and depressive symptoms at 2 months follow-up. The 2-month follow-up period was adopted due to logistic reasons. Two months after acute MI or ICD implantation, patients visited the outpatient clinic for a routine control. To minimize patient burden, we combined our study with these visits to the hospital. Demographic and clinical variables were obtained from the medical records. Of the original 662 patients, 554 patients were included in the final analyses (i.e., 390 MI patients and 164 ICD patients; see Figure 1).

***Figure 1.*** *Flowchart of patient selection*




The 108 patients who were excluded comprised 62 MI patients and 46 ICD patients. Excluded patients differed significantly from included patients regarding Type D/no partner (9.2% versus 3.6%, $\chi^2(1) = 6.01$, $p = .014$), female sex (28.0% versus 18.2%,

$\chi^2(1) = 5.43$, $p = .020$), history of ischemic heart disease (47.9% versus 34.1%, $\chi^2(1) = 6.52$, $p = .011$), treatment (ICD implantation) (43.0% versus 29.6%, $\chi^2(1) = 7.42$, $p = .006$), diabetes (23.2% versus 13.2%, $\chi^2(1) = 6.35$, $p = .012$), use of anticoagulants (62.8% versus 75.9%, $\chi^2(1) = 7.14$, $p = .008$), and use of psychotropics (25.2% versus 13.6%, $\chi^2(1) = 9.35$, $p = .002$).

The study was approved by the ethics committees of the participating hospitals. The study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent.

**Measures**

*Demographic and clinical characteristics*

Demographic variables included partner status (i.e., not having a partner), gender, age, and educational level. Clinical variables included comorbidity (arthritis, renal insufficiency or chronic obstructive pulmonary disease), history of ischemic heart disease (previous MI, percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery), multivessel disease and left ventricular ejection fraction (for MI patients), ICD indication and history of shocks (for ICD patients), diabetes mellitus, smoking (self-report), cardiac medication (β-blockers, anticoagulants, statins, and aspirin), and psychotropic medication (self-report).

*Personality*

The 14-item Type D Scale (DS14) was used to assess Type D personality[18]. Items are answered on a 5-point Likert scale from 0 to 4. The scale consists of two 7-item subscales: negative affectivity (e.g., "I often feel unhappy") and social inhibition (e.g., "I am a closed person"). Only patients scoring high on both subscales according to a standardized cut-off score ≥ 10 are categorized as Type D[18]. The DS14 is a valid and reliable scale with Cronbach's α of 0.88 and 0.86 and a test-retest reliability over a 3-month period with $r = 0.72$ and 0.82 for the two subscales, respectively[18]. It is important to note that in addition to negative affectivity, social inhibition is crucial in defining Type D personality, as it is the interaction of negative affectivity and social inhibition, and not

the single traits, that is related to cardiac prognosis, independent of concurrent symptoms of anxiety and depression[30].

*Symptoms of anxiety and depression*

The State-Trait Anxiety Inventory (STAI) was used to assess symptoms of anxiety[31]. The STAI is a self-report measure consisting of two 20-item scales developed to measure the level of general state and trait anxiety[31]. In the current study, we only used the state measure, as the objective was to assess the current presence of anxiety symptoms at two months follow-up, rather than anxiety as a stable trait. Each item is rated on a 4-point Likert scale from 1 to 4. We used the cut-off ≥ 39, which represents clinical levels of anxiety[31]. The STAI has been demonstrated to have adequate validity and reliability, with a Cronbach's α of 0.92[32]. Elevated scores on the STAI have been associated with poor prognosis in patients with CVD[33].

The Beck Depression Inventory (BDI) is a 21-item self-report measure developed to assess the presence and severity of depressive symptoms[34]. Each item is rated on a Guttmann scale from 0 to 3. The BDI is a reliable and validated measure of depressive symptomatology[35, 36], with a Cronbach's α of 0.81 in non-psychiatric samples[35], and the most frequently used self-report measure of depressive symptomatology in cardiac patients. We used the standardized cut-off ≥ 10, indicative of at least mild to moderate symptoms of depression, which has also been associated with poor prognosis in patients with CVD[37-39]. In addition, this cut-off has good sensitivity and specificity to screen for major depression, that is, 81.8% and 78.7%, respectively[40].

Scores on anxiety and depression measures were dichotomized in order to enhance clinical interpretability, which is also advocated by others[41].

**Statistical Analysis**

To examine differences in baseline characteristics stratified by personality type (Type D versus non-Type D) and partner status (partner versus single), we used the Chi-square test (Fisher's Exact Test when appropriate) for nominal variables and analysis of variance (ANOVA) for continuous variables. In the ANOVA, we used Tukey's test for post hoc

comparisons. The impact of Type D personality and partner status on symptoms of anxiety and depression was examined by means of logistic regression analysis with non-Type D/partner as the reference category. In multivariable analysis, we adjusted for sex, age, educational level, smoking status, cardiac history, treatment (MI versus ICD implantation), days between MI or ICD implantation and completion of baseline questionnaires, comorbidity, diabetes, dyslipidemia, hypertension, beta-blockers, aspirin, anticoagulants, statins, and psychotropic medication. A $p$-value < .05 was considered to be statistically significant. Odds ratios (OR) with 95% confidence intervals are reported. All statistical analyses were performed using SPSS 12.0.1 for Windows.

## RESULTS

### Patient characteristics

No significant differences between ICD patients and MI patients were found for either Type D personality or partner status, although Type D personality was slightly more prevalent in ICD patients than in MI patients (27% versus 20%, $\chi^2(3) = 3.40$, $p = .07$). In the total patient group, 121 patients (22%) were classified as Type D and 89 patients (16%) had no partner. Partner status did not differ in Type D versus non-Type D patients (17% versus 16%, $\chi^2(1) = 0.25$, $p = .88$).

Patient characteristics stratified by personality and partner status are presented in Table 1. The groups differed significantly with respect to female sex (14%, 28%, 19%, and 55%; $\chi^2(3) = 25.97$, $p < .0001$) and current use of psychotropic medication (9%, 13%, 22%, and 35%; $\chi^2(3) = 20.85$, $p < .0001$). Type D patients without a partner were more likely to be female, to have had an invasive treatment for MI, and to use psychotropic medication compared with the other three groups. No other significant differences were found between groups on baseline characteristics.

In the ICD group, 7 patients received a shock, but this number did not differ significantly between groups (Fisher's Exact Test = 1.12, $p = .76$). Likewise, no significant differences were found for secondary indication for ICD implantation ($\chi^2(3) = 2.72$, $p = .44$). In MI patients, multivessel disease ($\chi^2(3) = 5.59$, $p = .13$) and left ventricular ejection fraction ($F$ (3,305) = 0.83, $p = .48$) did not differ significantly between

groups, whereas invasive treatment did ($\chi^2(3) = 11.37$, $p = .01$). However, because invasive treatment and the other four group-specific indices were not significantly related to anxiety and depression (all $p$-values > .10), they were omitted from further analyses.

***Table 1.*** *Patient characteristics stratified by Type D personality and partner status*[1]

| | **Non-Type D/partner** (***n*** **= 364)** | **Non-Type D / no partner** (***n*** **= 69)** | **Type D /partner** (***n*** **= 101)** | **Type D /no partner** (***n*** **= 20)** | ***p*** |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| **Female** | **14** | **28** | **19** | **55** | **<.0001** |
| Age, mean (SD) | 61 (10) | 61 (14) | 60 (11) | 60 (11) | .91 |
| Low education[2] | 43 | 50 | 53 | 70 | .06 |
| **Clinical variables** | | | | | |
| History of ischemic heart disease[3] | 33 | 33 | 39 | 40 | .65 |
| Treatment[4] | 71 | 78 | 61 | 75 | .10 |
| Days[5], mean (SD) | 7 (9) | 9 (8) | 8 (10) | 10 (12) | .44 |
| Comorbidity[6] | 20 | 18 | 22 | 25 | .86 |
| Diabetes | 13 | 19 | 10 | 10 | .46 |
| Dyslipidemia | 39 | 40 | 39 | 25 | .65 |
| Hypertension | 39 | 43 | 33 | 35 | .64 |
| Current smoking | 29 | 40 | 36 | 45 | .17 |
| **Invasive treatment MI[7]** | **65** | **41** | **61** | **67** | **.01** |
| Multi-Vessel Disease[8] | 42 | 32 | 26 | 47 | .13 |
| LVEF[9], mean (SD) | 52 (13) | 50 (13) | 52 (13) | 55 (12) | .48 |
| Shocks[10] | 5 | 7 | 3 | 0 | .76 |
| Secondary indication for ICD implantation[10] | 65 | 53 | 54 | 40 | .44 |
| **Medication** | | | | | |
| Beta-blockers | 85 | 84 | 86 | 85 | .99 |
| Aspirin | 67 | 78 | 69 | 60 | .32 |
| Anti-coagulants | 78 | 68 | 72 | 75 | .28 |
| Statins | 85 | 81 | 88 | 75 | .42 |
| **Psychotropics** | **9** | **13** | **22** | **35** | **<.0001** |

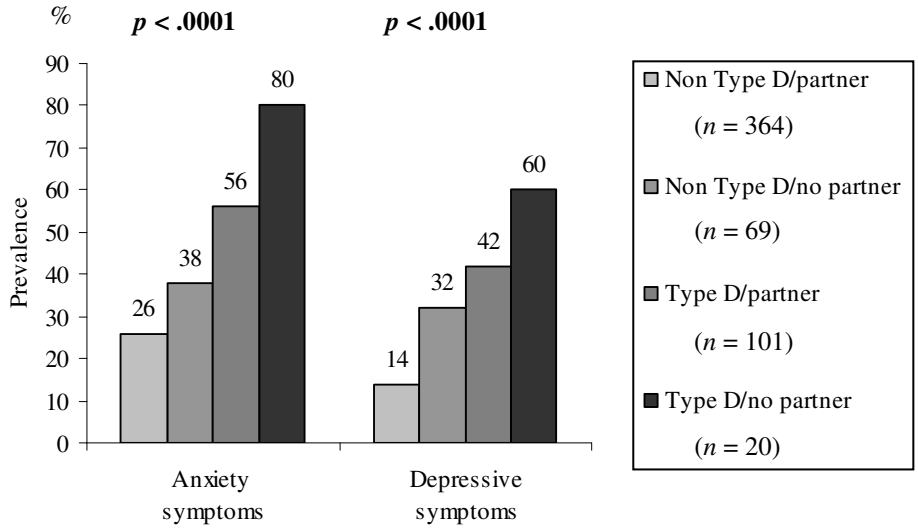
[1]Data are presented as percentages ($\chi^2$ test), unless specified as mean (SD) (ANOVA); [2]No education completed, first level (primary school), or secondary level (first phase); [3]Previous MI, PCI, CABG; [4]MI versus ICD implantation, MI = reference category; [5]Days between MI or ICD implantation and completion of baseline questionnaire; [6]Lung, renal, or rheumatic disease; [7]MI patients ($n$ = 389); [8]MI patients ($n$ = 318); [9]LVEF = left ventricular ejection fraction ($n$ = 309 MI patients); [10]ICD patients ($n$ = 164)

**Group differences on anxiety and depressive symptoms**

Both Type D personality and partner status had main effects on anxiety (OR = 4.01; 95%CI 2.63-6.11 and OR = 1.88; 95%CI 1.19-2.97, respectively) and depressive symptoms (OR = 3.91; 95%CI 2.53-6.05 and OR = 2.44; 95%CI 1.50-3.96, respectively) in unadjusted analyses.

When stratifying by personality type and partner status, statistically significant differences were found between the four groups on anxiety ($\chi^2(3) = 52.92$, $p < .0001$) and depression scores ($\chi^2(3) = 53.67$, $p < .0001$) (Figure 2). Type D patients without a partner had the highest prevalence of symptoms of anxiety and depression compared to the other three groups.

***Figure 2.*** *Prevalence of anxiety and depressive symptoms at 2 months stratified by Type D personality and partner status (Chi-square test was used)*



**Univariable predictors of anxiety and depressive symptoms**

In univariable logistic regression analyses, non-Type D/no partner (OR = 1.76; 95%CI 1.03-3.03), Type D/partner (OR = 3.78; 95%CI 2.39-5.97), and particularly Type D/no partner (OR = 11.66; 95%CI 3.80-35.75) had an increased risk of anxiety at 2 months follow-up compared with non-Type D/partner patients (Table 2, left). Other significant predictors were female gender, low education, comorbidity, and the use of psychotropic medication.

Similarly, non-Type D/no partner (OR = 2.81; 95%CI 1.56-5.04), Type D/partner (OR = 4.27; 95%CI 2.61-6.99), and Type D/no partner patients (OR = 9.00; 95%CI 3.51-23.08) had an increased risk of depressive symptoms compared to non-Type D/partner patients (Table 2, right). Female gender, current smoking, comorbidity, and psychotropic medication were also significantly related to an increased risk of depressive symptoms in univariable logistic regression analysis. For both anxiety and depressive symptoms, Type D/no partner patients had the highest risk followed by Type D/partner, and non-Type D/no partner patients.

When analyzing the data separately for the two treatment groups, the results remained the same, with non-Type D/partner having the lowest risk and Type D/no partner having the highest risk.

**Multivariable predictors of anxiety and depressive symptoms**

In multivariable analysis, non-Type D/no partner (OR = 2.04; 95% CI 1.05-3.96), Type D/partner (OR = 3.73; 95%CI 2.16-6.45), and Type D/no partner (OR = 8.27; 95%CI 2.50-27.32) remained significant predictors of anxiety symptoms, adjusting for all other variables (Table 3, left). Other independent variables related to anxiety symptoms were female gender, low education, and use of psychotropic medication.

Similar results were found for depressive symptoms, where non-Type D/no partner (OR = 3.03; 95% CI 1.46-6.31), Type D/partner (OR = 3.81; 95%CI 2.08-6.99), and Type D/no partner (OR = 6.74; 95%CI 2.19-20.76) remained as significant predictors, adjusting for all other variables (Table 3, right). Other independent variables associated with depressive symptoms were female gender, treatment, comorbidity, use of aspirin, and psychotropic medication. For both anxiety and depressive symptoms, there was a dose-

response relationship, with the presence of both risk factors (Type D and no partner) incurring the highest risk.

***Table 2.*** *Univariable predictors of anxiety and depressive symptoms*[1]

| | Anxiety symptoms | | | Depressive symptoms | | |
|---|---|---|---|---|---|---|
| | **OR** | **95% CI** | ***p*** | **OR** | **95% CI** | ***p*** |
| **Groups** | | | | | | |
| Non TD/partner | 1.00 | - | **-** | 1.00 | - | **-** |
| **Non TD/no partner** | **1.76** | **1.03-3.03** | **.04** | **2.81** | **1.56-5.04** | **.001** |
| **TD/partner** | **3.78** | **2.39-5.97** | **<.0001** | **4.27** | **2.61-6.99** | **<.0001** |
| **TD/no partner** | **11.66** | **3.80-35.75** | **<.0001** | **9.00** | **3.51-23.08** | **<.0001** |
| **Demographics** | | | | | | |
| **Female** | **2.15** | **1.39-3.33** | **.001** | **2.30** | **1.44-3.66** | **<.0001** |
| Age | 1.00 | 0.98-1.02 | .99 | 1.01 | 0.99-1.02 | .59 |
| **Low education**[2] | **2.12** | **1.48-3.02** | **<.0001** | 1.36 | 0.92-2.03 | .13 |
| **Clinical variables** | | | | | | |
| History of ischemic heart disease[3] | 1.24 | 0.85-1.80 | .26 | 1.32 | 0.87-2.00 | .19 |
| Treatment[4] | 0.76 | 0.52-1.11 | .16 | 1.00 | 0.65-1.53 | .98 |
| Days[5] | 1.01 | 1.00-1.03 | .13 | 1.00 | 0.98-1.02 | .88 |
| **Comorbidity**[6] | **1.72** | **1.11-2.66** | **.01** | **2.19** | **1.38-3.48** | **.001** |
| Diabetes | 1.46 | 0.87-2.43 | .15 | 1.25 | 0.71-2.12 | .44 |
| Dyslipidemia | 1.25 | 0.86-1.83 | .25 | 1.52 | 1.00-2.31 | .05 |
| Hypertension | 0.94 | 0.64-1.36 | .74 | 1.05 | 0.69-1.60 | .84 |
| **Current smoking** | 1.38 | 0.95-1.99 | .09 | **1.61** | **1.07-2.42** | **.02** |
| **Medication** | | | | | | |
| Beta-blockers | 1.18 | 0.71-1.96 | .52 | 1.08 | 0.61-1.91 | .79 |
| Aspirin | 0.89 | 0.61-1.30 | .55 | 0.72 | 0.47-1.10 | .13 |
| Anticoagulants | 0.88 | 0.88-1.33 | .55 | 0.72 | 0.46-1.13 | .15 |
| Statins | 1.26 | 0.76-2.10 | .37 | 1.08 | 0.61-1.91 | .79 |
| **Psychotropics** | **4.89** | **2.87-8.34** | **<.0001** | **5.40** | **3.21-9.10** | **<.0001** |

[1] Logistic regression analysis; [2] No education completed, first level (primary school), or secondary school (first phase); [3] Previous MI, PCI, CABG; [4] MI versus ICD implantation, MI = reference category; [5] Days between MI or ICD implantation and completion of baseline questionnaire; [6] Lung, renal or rheumatic disease

***Table 3.*** *Multivariable predictors of anxiety and depressive symptoms*[1]

| | Anxiety symptoms | | | Depressive symptoms | | |
|---|---|---|---|---|---|---|
| | **OR** | **95%CI** | ***p*** | **OR** | **95%CI** | ***p*** |
| **Groups** | | | | | | |
| Non TD/partner | 1.00 | - | **-** | 1.00 | - | **-** |
| **Non TD/no partner** | **2.04** | **1.05-3.96** | **.04** | **3.03** | **1.46-6.31** | **.003** |
| **TD/partner** | **3.73** | **2.16-6.45** | **<.0001** | **3.81** | **2.08-6.99** | **<.0001** |
| **TD/no partner** | **8.27** | **2.50-27.32** | **.001** | **6.74** | **2.19-20.76** | **.001** |
| **Demographics** | | | | | | |
| **Female** | **1.79** | **1.01-3.17** | **.05** | **1.92** | **1.02-3.62** | **.05** |
| Age | 0.99 | 0.97-1.02 | .61 | 1.00 | 0.97-1.02 | .85 |
| **Low education**[2] | **1.79** | **1.14-2.81** | **.01** | 0.97 | 0.58-1.65 | .92 |
| **Clinical variables** | | | | | | |
| History of ischemic heart disease[3] | 0.88 | 0.47-1.63 | .68 | 1.75 | 0.87-3.53 | .12 |
| **Treatment**[4] | 0.62 | 0.31-1.25 | .18 | **2.50** | **1.13-5.53** | **.02** |
| Days[5] | 1.01 | 0.99-1.03 | .26 | 0.99 | 0.97-1.02 | .60 |
| **Comorbidity**[6] | 1.57 | 0.90-2.74 | .12 | **1.96** | **1.06-3.60** | **.03** |
| Diabetes | 1.51 | 0.82-2.79 | .19 | 1.34 | 0.65-2.73 | .43 |
| Dyslipidemia | 1.21 | 0.75-1.95 | .44 | 1.58 | 0.91-2.74 | .10 |
| Hypertension | 0.91 | 0.57-1.47 | .70 | 0.90 | 0.52-1.56 | .70 |
| Current smoking | 1.57 | 0.95-2.60 | .08 | 1.72 | 0.98-3.02 | .06 |
| **Medication** | | | | | | |
| Beta-blockers | 1.23 | 0.67-2.28 | .51 | 1.13 | 0.56-2.28 | .74 |
| **Aspirin** | 1.10 | 0.61-1.98 | .76 | **0.46** | **0.23-0.90** | **.02** |
| Anticoagulants | 1.11 | 0.64-1.92 | .72 | 0.61 | 0.33-1.15 | .13 |
| Statins | 1.57 | 0.76-3.24 | .22 | 1.30 | 0.56-3.01 | .55 |
| **Psychotropics** | **3.06** | **1.64-5.70** | **<.0001** | **4.54** | **2.40-8.57** | **<.0001** |

[1] Logistic regression analysis; [2] No education completed, first level (primary school), or secondary school (first phase); [3] Previous MI, PCI, CABG; [4] MI versus ICD implantation, MI = reference category; [5] Days between MI or ICD implantation and completion of baseline questionnaire; [6] Lung, renal or rheumatic disease

## DISCUSSION

This is the first study to examine the combined effect of Type D personality and not having a partner on emotional distress in cardiac patients. Stratifying by personality and partner status showed that non-Type D patients without partner had a twofold increased risk of both anxiety and depressive symptoms followed by Type D patients with partner

with a threefold risk and, most importantly, Type D patients without partner having a six- to eightfold risk compared to non-Type D patients with partner, adjusting for demographic and clinical baseline characteristics. This shows that there was a dose-response relationship between the two risk factors (Type D personality and having no partner) and emotional distress, with Type D patients without a partner having the highest risk. It is important to note that the effect of the two risk factors on emotional distress was consistent across treatment group (i.e., MI versus ICD).

Previous research has demonstrated that Type D personality is a *cardiotoxic* factor that is associated not only with adverse prognosis[2-5] and impaired health status[6-8] but also with increased levels of emotional distress[9-11]. It is important to include indices of emotional distress, such as symptoms of anxiety and depression, as outcome measures since these symptoms are associated with adverse prognosis[42], impaired health-related quality of life[43], increased health care consumption[42, 44] and reduced compliance[45, 46].

Traditionally, depression but not anxiety has been studied as an important psychosocial risk factor for adverse outcomes in CVD, despite the co-occurrence of anxiety and depression[42, 47, 48]. Recent studies have demonstrated the detrimental effect of anxiety for adverse outcomes in CVD over and above the effect of depression[42, 47, 48]. Our results also show that anxiety may be an important person-centered outcome; the dose-response relationship of the combination of Type D personality and having no partner was found for both depressive and anxiety symptoms. In this context, it is important to note that Type D personality is not equivalent to anxiety or depressive symptoms. This was verified in a recent prospective study of patients treated with PCI who were all anxious at 6 months[49]. Another study of PCI patients showed that Type D personality predicted adverse prognosis above and beyond symptoms of anxiety and depression, which was due to the combined effect of high negative affectivity and social inhibition and not to the main effects of anxiety and depressive symptoms[30].

As shown in the current study, not all Type D patients experience similar levels of risk, suggesting that within the group of Type D patients, there is some heterogeneity. This heterogeneity is also supported in a recent study of PCI patients, showing that Type D patients with diabetes were at increased risk of onset of depressive symptoms at 12 months when compared to patients with a Type D personality or diabetes alone[50].

Although our findings indicate the importance of having a partner, the results also suggest that partner status does not completely buffer the effects of Type D on distress since Type D patients with a partner still had a significantly higher risk compared to non-Type D patients with or without a partner. In a recent study of ICD patients, Type D personality was also shown to have a larger impact on distress than shocks[9], emphasizing the importance of personality as an independent determinant of distress. In the present study, lack of a partner showed a further elevated risk of emotional distress in the already distressed Type D patients.

It is important to note that in the current study, disease severity was not related to emotional distress at 2 months follow-up, indicating that emotional distress is not just a consequence of disease severity, which is in line with some[51, 52] but not all[53] studies.

In view of our results, in clinical practice, it is important to screen for and identify patients with a Type D personality, particularly those Type D patients who do not have a partner. Type D personality has been associated with adverse prognosis[2-5], and other studies have shown that patients without a partner are less compliant[54, 55], less physically active[56], and at increased risk of CVD mortality[57, 58]. Cardiologists and nurses should therefore carefully monitor Type D patients without a partner, as they may be less likely to adhere to medication, participate in cardiac rehabilitation, and attend regular check-ups. In this context, nurses could serve as an important source of support. In addition, these patients may benefit from psychosocial intervention in order to prevent the development of anxiety and depressive symptoms, as these symptoms are associated not only with reduced compliance[44, 45] and impaired health-related quality of life[42] but also with worse prognosis[33].

This study has some limitations. First, the number of patients in the Type D/no partner group was relatively small, which may have led to reduced power. Therefore, replication of these results is warranted in future studies. Nevertheless, we still found significant and consistent results across patient groups and psychological symptomatology. Second, the 2-month follow-up period was relatively short. Future studies need to replicate our findings using a longer follow-up period**.** Third, we had no information on the psychological and physical status of the partner or on marital quality or marital satisfaction. Marital status may have an impact on quality of life. Nevertheless, we

were able to show that not having a partner was associated with increased risk of anxiety and depressive symptoms in both non-Type D and Type D patients. Fourth, we had no information on behavioral risk factors and compliance with medical regiments, which may serve as confounders. Fifth, excluded patients differed from included patients with respect to several demographic and clinical indices, which may result in limited generalizability of the findings. However, since excluded patients appeared to be more ill, the adverse effect of Type D personality and having no partner found in this study is more likely to be an underestimation rather than an overestimation. Finally, the two pooled cardiac patient groups differed on indices of disease severity. However, disease severity was not associated with either the independent or outcome variables.

Despite these limitations, this study also has several strengths. This is the first study to examine partner status as a potentially important factor in the link between Type D personality and anxiety and depressive symptoms. In addition, results are based on a heterogeneous patient group with acute MI or ICD implantation, showing that results are generalizable across CVD patient groups.

In conclusion, these results show that there was a dose-response relationship between the two risk factors (Type D personality and having no partner) in relation to anxiety and depressive symptoms, with Type D patients without a partner having the highest risk 2 months after hospitalization for acute MI or ICD implantation. Given the fact that this is the first study to show that lack of a partner in patients with a Type D personality is associated with a particularly high risk of emotional distress, future studies that replicate these findings are warranted. In clinical practice, it is important to screen for Type D personality to monitor Type D patients without a partner particularly carefully. These patients may be less likely to comply with medication, take part in cardiac rehabilitation, and change health-related behaviors that are detrimental to their health due to their increased levels of emotional distress.

***ACKNOWLEDGEMENTS***

*This research was supported by a VENI grant (451-05-001) to Dr. S.S. Pedersen from the Netherlands Organization for Scientific Research (NWO), The Hague, The Netherlands.*

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*Chapter 11*

# Anxiety in Partners of Implantable Defibrillator Patients

**Van den Broek KC, Nyklíček I, Alings M, Van der Voort PH, Denollet J. Anxiety in partners of implantable defibrillator patients. *Submitted for publication*.**

**ABSTRACT**

**Background** Little is known about the psychological consequences of implantable cardioverter defibrillator (ICD) implantation for partners of patients. The objective of this study was to examine anxiety in partners of ICD patients.

**Methods** At baseline, partners ($N$ = 182) completed measures on personality, that is, the Type D scale (DS14) and Anxiety Sensitivity Index (ASI). Two months following ICD implantation, general anxiety (STAI-state) and posttraumatic stress symptoms (PTSS) were assessed. The patient variables ICD indication and occurrence of shocks were deduced from medical records.

**Results** Mean levels of general anxiety were equal ($p$ = 0.42) among partners (37.6±11.4) and patients (36.7±10.9). Similarly, the proportion of partners (41%) and patients (40%) experiencing clinically relevant levels of general anxiety was also equal ($p$ = 1.0). Multivariable linear regression analysis showed that Type D personality ($\beta$ = .25, $p$ = .001) and anxiety sensitivity ($\beta$ = .35, $p$ < .0001) were significant predictors of general anxiety in partners, independent of gender, age, shocks, and ICD indication. Regarding PTSS in partners, anxiety sensitivity ($\beta$ = .48, $p$ < .0001) and age ($\beta$ = -.15, $p$ = .041) were independent predictors, whereas Type D was not ($\beta$ = .11, $p$ = .12).

**Conclusion** These findings emphasize the clinical significance of anxiety in partners of ICD patients. In clinical practice, following the implantation of an ICD in patients, it may be important to identify partners of ICD patients with a Type D personality and anxiety sensitivity.

## INTRODUCTION

The implantable cardioverter defibrillator (ICD) is important in the treatment of life-threatening arrhythmias, in patients who have already experienced a cardiac arrest (i.e., secondary prevention), and in patients with severe left ventricular dysfunction without documented cardiac arrest, ventricular fibrillation, or ventricular tachycardia (i.e., primary prevention)[1]. ICDs can terminate ventricular arrhythmias by antitachycardia pacing (overdrive pacing), or shocks, which constitute the most aggressive treatment[2].

A major issue has been the psychological adaptation after ICD implantation in patients. Psychological problems, such as anxiety[3-7], posttraumatic stress symptoms (PTSS)[8], and depression[3, 4] are frequently experienced by patients in the months or even years after ICD implantation. ICD shocks may enhance these levels, although studies report inconsistent results[9-11]. In contrast, indication for ICD implantation may not influence anxiety[3, 12] or health-related quality of life[12-14] in the months post-implantation.

Psychological distress may also be experienced by partners of ICD patients, but this issue has received little attention in the literature, even though some studies have reported that anxiety levels in partners are as high as levels in ICD patients[15, 26] or even higher[10, 17]. To our knowledge, the prevalence of PTSS following ICD implantation has never been studied in partners of ICD patients. In addition, the role of shocks for mood status in partners remains unclear[15, 17, 18].

Personality may play an important role in the psychological adjustment after ICD implantation in both patients and partners. In their cross-sectional study, Pedersen et al.[10] found that Type D personality was independently related to anxiety in patients as well as partners. Type D personality refers to the combination of two personality traits, that is, negative affectivity (the tendency to experience negative emotions across time and situations) and social inhibition (the tendency to inhibit the expression of emotions due to fears of how others will react)[19]. Type D personality has been associated with an increased risk for morbidity and mortality[20] as well as increased feelings of anxiety[10, 20] in patients with coronary heart disease.

Anxiety sensitivity may also play a role in the experience of anxiety. Anxiety sensitivity is a personality trait that refers to the fears of anxiety-related sensations based on beliefs that these sensations have harmful consequences[21]. For example, persons with

high anxiety sensitivity may believe that heart palpitations indicate a heart attack, whereas those with low anxiety sensitivity experience these sensations as unpleasant but non-threatening. Such a misinterpretation of sensations in people high in anxiety sensitivity may lead to a vicious cycle, where higher levels of anxiety may cause further anxiety-related sensations that may be misinterpreted again, et cetera.

The aims of this study were 1) to determine the prevalence of general anxiety and posttraumatic symptoms in partners of ICD patients after ICD implantation and 2) to determine the influence of personality on general anxiety and posttraumatic symptoms in partners of ICD patients, taking into account the possible effects of gender, age, and ICD indication as well as shocks experienced by the patient.

## METHODS

### Study population and design

Patients having had an ICD implanted in two large Dutch referral hospitals between September 2005 and July 2007 as well as their partners were asked to participate in an ongoing longitudinal study on psychological reaction to ICD implantation. Inclusion criteria for patients comprised implantation with an ICD and age between 18 and 80 years. Subjects were excluded in case of inability to read and understand Dutch. Partners could only participate when they were living together with the patient and the patient had already agreed to participate in the study. No further criteria were formulated for the partners. The study was approved by the Medical Ethic Committees of the participating hospitals. The study was conducted in accordance with the Helsinki Declaration, and all subjects provided written informed consent.

### Demographic and clinical variables

Demographic variables included gender and age of the partner, since previous studies have shown that women[22] and younger respondents[23, 24] are more likely to experience anxiety, compared to men and older respondents, respectively. Age was dichotomized using the median score, which was 61. Clinical variables comprised ICD indication (primary versus secondary prevention) and shocks (0 versus ≥1 shocks). ICD indication was included, because the relationship between ICD indication and psychological

adaptation in partners has not been studied to our knowledge. Previous research regarding the experience of ICD shocks in relation to anxiety in partners yielded inconsistent results[15, 17, 18].

**Personality**

Measures of personality of the partner were completed at baseline, which was between 0 and 3 weeks following ICD implantation.

*Anxiety sensitivity*

The 16 item Anxiety Sensitivity Index (ASI)[25] was used to measure anxiety sensitivity, which refers to sensitivity and fear of anxiety symptoms[25]. Items are rated on a five-point Likert scale from *0-very little* to *4-very much*. Total scores are obtained by summing the scores on the 16 items, that is, total scores range from 0 to 64, with higher scores reflecting greater sensitivity and fear of anxiety symptoms. The reliability of the ASI among partners was good, with Cronbach's $\alpha = 0.90$. To determine effect sizes of anxiety sensitivity, the ASI was dichotomized. Since no standardized cut-offs have been described for the ASI, we used the upper quartile score (i.e., 14) to define patients with increased anxiety sensitivity.

*Type D personality*

Type D personality was measured using the 14-item Type D personality Scale (DS14)[19]. The DS14 consists of two 7-item subscales: negative affectivity (e.g., "I often feel unhappy") and social inhibition (e.g., "I am a 'closed' person"). Items are answered on a five-point Likert scale ranging from *0-false* to *4-true*. Total scores on both subscales range from 0 to 28. Patients scoring high on both subscales, that is, equal to or above 10, are classified as Type D. Internal consistency is high, with Cronbach's α values of 0.88 for negative affectivity and 0.86 for social inhibition[19]. A recent study has shown that Type D personality is a stable taxonomy over an 18-month period in patients who had experienced a myocardial infarction[26].

**Anxiety**

Both anxiety outcomes were completed by the partner at 2 months following ICD implantation.

*General anxiety*

The 20-item state-version of the State-Trait Anxiety Inventory (STAI; form Dutch Y-1)[27] was used to assess the current presence of general symptoms of state anxiety. State anxiety refers to a transient emotional status, characterized by feelings of apprehension (i.e., worries and concerns) and tension as well as increased activity of the autonomic nervous system. Items are scored on a 4-point Likert scale from *1-not al all* to *4-very much so*. Scores range from 20, that is, low level of state-anxiety to 80, that is, high level of state-anxiety. The STAI has been demonstrated to have adequate validity and reliability, with Cronbach's α ranging from 0.87 to 0.92[27]. To indicate clinically elevated levels of general anxiety, the cut-off ≥ 40 was used. In patients, this cut-off was previously used in studies involving the ICD[9] and myocardial infarction[28] population.

*PTSS*

The Posttraumatic Stress Diagnostic Scale (PDS) was first described by Foa[29, 30] and was translated into Dutch according to standard practice for the purpose of the current study. The PDS was designed to correspond to DSM-IV diagnostic criteria for PTSD. The Dutch PDS comprises 17 items that correspond to the 17 DSM-IV symptoms of PTSD, which can be clustered in the three symptom groups: reexperiencing (i.e., "Having bad dreams of nightmares about the ICD of your partner", avoidance (i.e., "Trying to avoid activities, people, or places that remind you of the ICD of your partner"), and arousal (i.e., "Being jumpy or easily startled (for example, when someone walks up behind you")). The frequency of each symptom in the past month is rated on a 4-point Likert scale, ranging from *0-not at all or only one time* to *3-five or more times a week/almost always*. The Dutch version of the PDS also contains questions on the level of impairment in functioning as well as on feeling helpless or terrified, but these questions were not used in this study. In our study, the ICD of the patient was referred to as the traumatic event, since the ICD is implanted to prevent sudden cardiac death. Foa[29] reported good internal

consistency, with Cronbach's α = 0.92 for the 17 symptom items. Our study confirmed this consistency, with Cronbach's α = 0.91. The validity of the PDS has also been shown to good[30].

**Statistical analysis**

The Chi-square test (Fisher's Exact Test when appropriate) was used to compare discrete variables, Student's *t*-test for independent samples to compare groups on continuous variables, and the paired-samples *t*-test to compare means of continuous variables. The nonparametric McNemar test was used to compare two percentages. A correlation coefficient was used to determine the association between levels of anxiety of partners and patients. Cross tabulation was applied to determine if the proportion of patients with increased levels of anxiety was different between partners with increased levels of anxiety and partners without increased levels. A biseral correlation coefficient was computed to determine the association between a discrete variable and a continuous variable. A series of univariate and multivariable linear regression analyses were performed to examine determinants of general anxiety and PTSS. A priori, we decided to include anxiety sensitivity, Type D personality, gender, age, secondary prevention, and the experience of shocks in multivariable analyses. To test the mediational effect of anxiety sensitivity, we performed a Sobel test, which directly tests the significance of a mediated effect, in contrast with causal step methods (e.g., the Baron and Kenny approach). However, a major drawback of the Sobel test is its assumption that the distribution of the mediational effects is normal[31]. Therefore, we additionally used a bootstrapping approach, by taking 5,000 samples from the data. This approach makes no assumptions about the shape of the distributions of the variables or the sampling distribution of the statistic[31]. The point estimate of the indirect effect is the mean computed over the 5,000 samples. The 95% confidence interval is computed and when this interval does not include zero, the indirect effect is significantly different from zero. Sobel tests and bootstrapping were performed with an SPSS macro by Preacher and Hayes[31] (http://www.comm.ohio-state.edu/ahayes/sobel.htm). All other statistical analyses were performed using SPSS 14.0 for Windows. A *p*-value < .05 was considered to be statistically significant.

## RESULTS

### Partner characteristics

Of the 268 patients who agreed to participate, 225 (84%) had a partner, of whom 199 (88%) agreed to participate in the study. At two months follow-up, 1 (0.5%) patient had died, 10 (4%) patients and partners refused to complete the follow-up questionnaires, and 6 (3%) partners had missing data on questionnaires, resulting in a final sample of 182 (81%) partners. Included partners did not differ significantly from excluded partners on any of the baseline characteristics.

Demographic, clinical, and personality characteristics of the 182 included partners are shown in Table 1, as well as the mean scores and prevalences of general anxiety and PTSS. In our study, data on general anxiety in patients two months following ICD implantation were available. Partners (37.6±11.4) and patients (36.7±10.9) reported similar levels of general anxiety ($t$ = 0.80, $p$ = .42) and the proportion of partners (41%) and patients (40%) experiencing increased levels of general anxiety was also similar ($p$ = 1.0), indicating that anxiety is not only important in ICD patients, but also in their partners. The correlation coefficient between anxiety levels of the partners and patients was 0.26 ($p$ < .0001), indicating that higher anxiety levels in the partner may be associated with higher anxiety levels in the patient. In contrast, the proportion of patients with increased levels of general anxiety was not significantly different in partners with increased levels of anxiety (47%) versus partners without increased anxiety scores (35%; $p$ = .11).

Type D personality was significantly related to anxiety sensitivity, with Type D partners scoring higher on anxiety sensitivity than non Type D partners (17.0±12.6 versus 9.0±7.6, $t$ = -4.19 $p$ < .0001). Similarly, significantly more Type D partners reported increased feelings of anxiety sensitivity compared to non Type Ds (42% versus 21%, $p$ = .005). However, the biseral correlation coefficient between Type D personality and anxiety sensitivity was 0.49, indicating no multicollinearity and permitting these variables to be included simultaneously in the regression model.

***Table 1.*** *Partner characteristics (N = 182)*

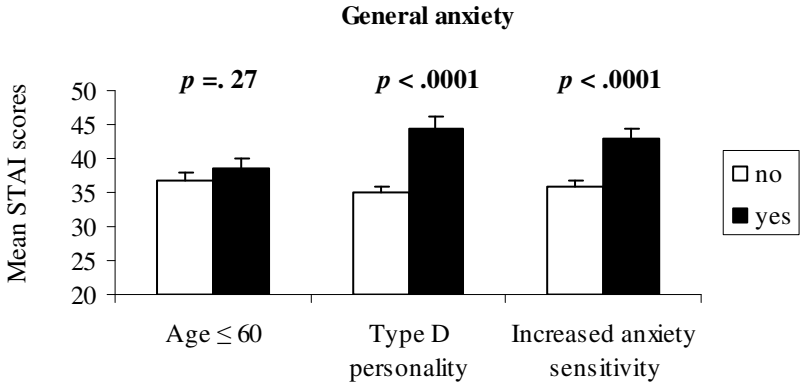
| | % (*N*) | Mean (SD) | Range |
|---|---|---|---|
| **Demographics** | | | |
| Female | 82 (150) | | |
| Age | | 60.2 (9.3) | 28-80 |
| **Clinical variables patient** | | | |
| Secondary prevention | 29 (53) | | |
| ≥ 1 shock since implantation | 5 (9) | | |
| **Personality** | | | |
| Type D personality | 28 (50) | | |
| Anxiety sensitivity score | | 11.2 (9.9) | 0-54 |
| Increased anxiety sensitivity[1] | 27 (49) | | |
| **Anxiety** | | | |
| General anxiety | | 37.6 (11.4) | 20-74 |
| Increased general anxiety[2] | 41 (75) | | |
| Posttraumatic symptoms | | 5.4 (7.5) | 0-36 |

[1] Anxiety Sensitivity Index ≥ 14, [2] State-Trait Anxiety Inventory ≥ 40

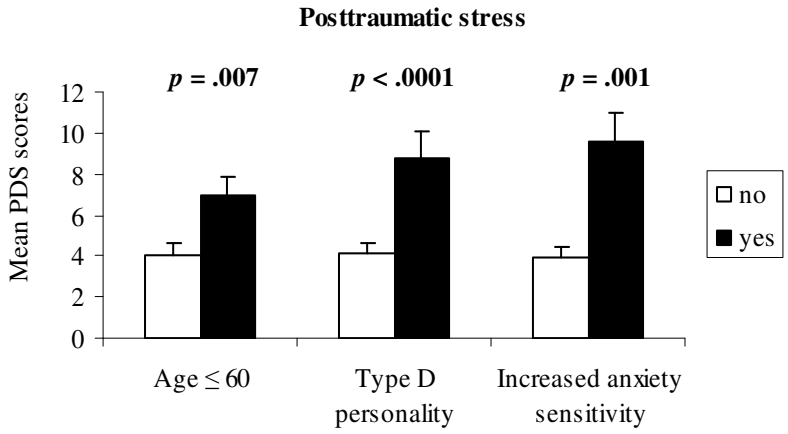
**General anxiety and PTSS**

*T*-tests for independent samples revealed that partners with a Type D personality, elevated levels of anxiety sensitivity, or younger age experienced significantly more general symptoms of anxiety and posttraumatic stress, compared to partners without these characteristics (Figure 1). Univariable linear regression analyses yielded the same results. Effect sizes, computed by Cohen's *d*, were large for Type D personality and anxiety sensitivity, and small to moderate for shocks regarding general anxiety as well as PTSS (Figure 2). Age had a small effect on general anxiety and a moderate effect on PTSS. Secondary prevention only had a small effect on PTSS.

***Figure 1.*** *Mean scores on general anxiety and PTSS among partners of ICD patients at two months follow-up, stratified by age, Type D personality, and anxiety sensitivity*

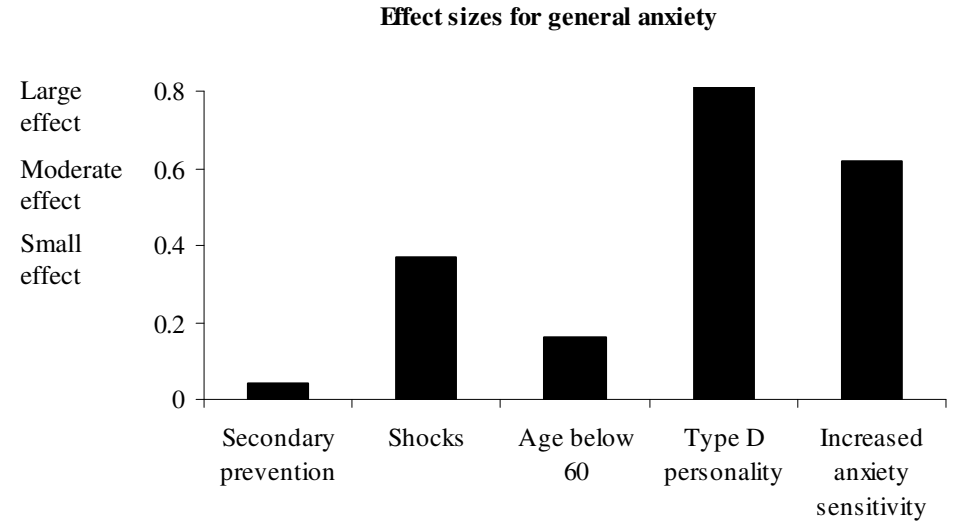


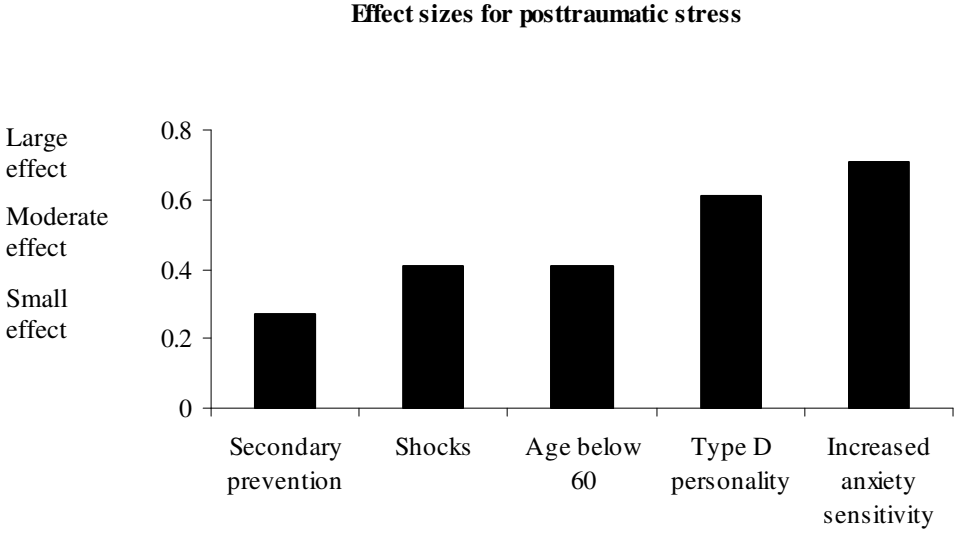

STAI = State-Trait Anxiety Inventory




PDS = Posttraumatic Stress Diagnostic Scale

***Figure 2.*** *Effect size estimates indicating the magnitude of the effect of ICD indication, shocks, age, Type D personality, and increased anxiety sensitivity*



Results of multivariable linear regression analyses are shown in Table 2. Anxiety sensitivity and Type D personality remained the only significant and independent predictors of general symptoms of anxiety. Regarding PTSS, anxiety sensitivity as well as age were significant and independent predictors, with younger partners experiencing more PTSS.

Simultaneous entering of anxiety sensitivity and Type D personality in the multivariable analysis resulted in a nonsignificant contribution of Type D personality to PTSS. Therefore, anxiety sensitivity may have mediated this relationship. Both Sobel tests ($z = 4.28$, $p < .0001$) and the bootstrapping method (95% confidence interval 1.24-5.20) confirmed this hypothesis, indicating that anxiety sensitivity may act as a mediator in the relationship between Type D personality and PTSS.

***Table 2.*** *Multivariate predictors of general anxiety and posttraumatic stress symptoms in partners of ICD patients two months following ICD implantation*

| | **General anxiety symptoms** | | **Posttraumatic stress symptoms** | |
|---|---|---|---|---|
| | ***ß*** | ***p*** | ***ß*** | ***p*** |
| **Anxiety sensitivity** | **.35** | **<.0001** | **.48** | **<.0001** |
| **Type D personality** | **.25** | **.001** | .11 | .12 |
| Female gender | .06 | .38 | .08 | .22 |
| **Age** | -.01 | .92 | **-.13** | **.041** |
| Secondary prevention[1] | .02 | .77 | .09 | .14 |
| Shocks[1] | .09 | .20 | .09 | .17 |

[1] Patients' medical characteristics

## DISCUSSION

This study suggests that anxiety levels are equally high in ICD patients and their partners, indicating that anxiety is a major issue not only in ICD patients, but also in their partners. Partners with increased anxiety sensitivity and Type D personality were at increased risk for experiencing general anxiety two months following ICD implantation. Posttraumatic stress in partners was predicted by anxiety sensitivity and younger age. Type D

personality was not directly related to PTSS, but evidence was found for an indirect association, in which anxiety sensitivity mediated the relation between Type D personality and PTSS.

Our finding that partners may experience similar levels of anxiety as compared to patients corroborates results of previous research[10, 15-17]. However, previous studies included small samples[16-18] or applied a cross-sectional design with a wide interval range between ICD implantation and completion of questionnaires[10, 15]. In the present study, 182 partners completed measurements on anxiety at two months following ICD implantation. One third of the partners experienced clinically elevated levels of general anxiety two months following ICD implantation, indicating that anxiety is an important issue in partners of ICD patients. Therefore, research and clinical practice should not only focus on psychological distress in ICD patients, but also in their partners.

To our knowledge, no previous studies have investigated PTSS in partners of ICD patients. Even studies on PTSS in patients are scarce and comprise merely case-studies[8]. The paucity of studies may be due to a lack of adequate measurements to assess PTSS specifically after ICD implantation in both patients and their partners. The PDS was used in this study and showed good reliability. Therefore, future research may incorporate this questionnaire.

Only a few studies have focused on the identification of partners at high risk for anxiety, let alone PTSS. Pedersen and collegues[10] reported that Type D personality was associated with an eightfold increased risk of anxiety in partners, which is in line with our results. Partners of patients who had experienced a shock did not experience more general anxiety or PTSS as compared to partners of patients who did not experience a shock. Therefore, we may conclude that the experience of a shock is not a risk marker for anxiety in partners. However, this result should be interpreted with caution, since only 9 patients experienced a shock. Moreover, a number of studies have found that shocks were associated with increased levels of anxiety and other forms of psychological distress in family members, including partners[17, 18]. Only De Groot et al.[15] reported no association between shocks and mood. However, as mentioned earlier, these studies differ in their methods and suffer from serious flaws. Overall, future studies are warranted on risk markers for anxiety in partners of ICD patients.

The major limitations of our study comprise the short-term follow-up period of only two months and concomitant low number of shocks experienced by patients. Therefore, the power to detect effects of shocks for anxiety was rather low. Furthermore, personality and anxiety outcomes were measured with self-report questionnaires only. Another limitation concerns the generalizability of the results, since 7% of the patients had missing data or refused to complete the questionnaires and were subsequently omitted from analyses. However, these patients did not differ from patients included in the analyses. Nevertheless, the results clearly showed that anxiety is an important issue in partners of ICD patients and also that partners with Type D personality and anxiety sensitivity are at increased risk.

In clinical practice, it is important to identify high risk patients, but also high risk partners. In particular, attention should be focused on partners who are high in anxiety sensitivity and have a Type D personality. This may be realized by the use of the easy to administer 16-item ASI and DS14. The DS14 has well-established cut-off scores, but further research is required on the critical cut-off point to determine enhanced anxiety sensitivity. Next, these high-risk partners should receive adequate psychological support, but no randomized controlled trials have focused on the treatment of Type D personality or anxiety sensitivity, to our knowledge. Hence, future research should focus on the treatment options for these personality traits. Interventions for Type D persons may aim at coping differently with negative emotions, whereas for persons with enhanced anxiety sensitivity it may be important to focus on the meaning of anxiety-related sensations.

In sum, anxiety is a major issue not only in ICD patients, but also in their partners. Partners with a Type D personality or enhanced anxiety sensitivity are at increased risk to experience anxiety and posttraumatic stress symptoms. In clinical practice, these partners at risk should be identified and receive adequate support.

***ACKNOWLEDGEMENTS***

*This study was supported by the Netherlands Organization for Scientific Research, The Hague, The Netherlands with a VICI grant (453-04-004) to Dr. Johan Denollet. We would like to thank Eefje Postelmans for inclusion of patients into the study in the Amphia Hospital.*

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*Chapter 12*

# Selection Bias in Implantable Defibrillator Patients with a Type D Personality

**Van den Broek KC, Nyklíček I, Denollet J. Selection bias in implantable defibrillator patients with a Type D personality.** ***Submitted for publication.***

**ABSTRACT**

**Background** We examined whether partner research may affect participation rates of implantable cardioverter defibrillator (ICD) patients with a Type D personality (joint presence of negative affectivity and social inhibition).

**Methods** 507 patients (80.5% men, mean age = 62.7±10.1 years) who underwent ICD implantation between May 2003 and November 2007 were included. In September 2005, a substudy on partners of ICD patients was added ($N$ = 276 patients). The DS14 was used to assess Type D personality.

**Results** The proportion Type D patients after the start of the partner substudy was significantly lower as compared to the proportion before the start of this substudy (18.8% versus 29.1%; $p$ = .007). Multivariable regression analysis showed that patients who participated after the start of the partner substudy were less likely to have a Type D personality (OR = 0.48; 95%CI 0.30-0.78; $p$ = .003) and biventricular ICD ($p$ =. 003), and more likely to have primary prevention ($p$ = .0001) and comorbidities ($p$ = .023), adjusting for age, gender, education, and etiology. In the partner substudy, nonparticipation was more prevalent among partners of Type D patients as compared to partners of non-Type D patients (20.4% versus 10.1%; $p$ = .044). Multivariable regression analysis showed that partner nonparticipation was associated with female gender of patients (OR = 2.92; 95%CI 1.30-3.45; $p$ = .010) and marginally significant with Type D personality of the patient (OR = 2.13; 95%CI 0.91-4.99; $p$ = .083), but not with age and education.

**Conclusion** The addition of a partner substudy was related to a decreased proportion of participants with a Type D personality. Nonparticipation was more prevalent among partners of Type D patients. These issues should be taken into account when planning studies with partners of cardiac patients.

## INTRODUCTION

The psychological impact of cardiac disease and treatment on patients has been studied widely, but relatively little attention has been paid to the psychological effects of disease and treatment on the partners of cardiac patients[1-3]. More specifically, research on partners of implantable cardioverter defibrillator (ICD) patients is lacking[1]. However, the number of studies on partners of cardiac patients is increasing, and in this regard, it is important to examine the influence of conducting a partner study on participation rates.

In general, study participants may systematically differ from nonparticipants. This threat to the generalizability of study results is called 'selection bias' and constitutes a major issue in research using volunteers as study participants[4]. Nonparticipation or nonresponse exists in different forms and each form may be related to different characteristics[5-6]. For instance, potential participants who immediately refuse participation may differ from participants who refuse continuation of the study[5]. These groups may also be different from participants who omit items during the survey[6]. Another form of selection bias may result from the addition of a substudy (for instance, on partners of patients), but to our knowledge, this has not been examined to date.

There are no established risk factors for nonparticipation[7]. Some medical studies found nonparticipants or nonconsenters to be more often female[8-10], older[8], or less healthy[11, 12], while other studies found nonparticipants to be younger[10, 12]. Personality characteristics may also play an important role in the distinction between participants and nonparticipants. A recent study has shown that participants were significantly lower in neuroticism and higher in conscientiousness, extraversion, and agreeableness as compared to nonparticipants[5]. In line with the findings regarding neuroticism and extraversion, Type D personality may also be related to nonparticipation. Type D personality comprises two stable personality traits, that is negative affectivity (i.e., the tendency to experience negative emotions across time and situations) and social inhibition (i.e., the tendency to inhibit self-expression in order to avoid negative reactions from others)[13]. Type Ds are rather reserved in nature, which may augment the probability of refusal to participate compared to the non Type D patient, especially when the partner is also approached for study participation.

The construct of Type D personality has been developed in the cardiovascular field. Previous studies in different cardiac populations have shown that Type D patients are at increased risk for morbidity and mortality[14]. A potential association between Type D personality and nonparticipation may have important consequences for the outcomes of such studies, because research has shown that nonparticipants may be less healthy than participants[5, 11, 12]. For these reasons, it is important to examine the impact of having Type D personality on participation rates.

The aim of this study was twofold. First, to examine whether the addition of a partner substudy was associated with participation rates of ICD patients with a Type D personality. Second, to examine whether Type D personality of patients was associated with participation rates of partners in the partner substudy.

## METHODS

### Patient population

Patients, aged 18-80 years, who underwent ICD implantation in the Catharina Hospital, Eindhoven, The Netherlands and the Amphia Hospital, Breda, The Netherlands between May 2003 and November 2007, were included in a study on personality, anxiety, and person-centered and medical outcomes in ICD patients. Patients were excluded in case of significant cognitive impairments (e.g., dementia), severe life-threatening comorbidities (e.g., cancer), or inability to read and understand Dutch.

### Partner substudy

In September 2005, a substudy on psychological effects of ICD implantation for partners of ICD patients was added. Partners were asked to participate when they were living together with the patient and when the patient had already agreed to participate in the study. No further criteria were formulated for the partners. When the patient agreed to participate in the study, he/she was asked whether he/she had a partner. Next, the partner substudy was explained to the patient, and he/she was asked to hand over the study material to the partner, including a form which outlined the study, the informed consent form, and the questionnaire.

The later addition of the partner substudy provided us with the opportunity to test differences between patients who were included before the start of the substudy and patients who were included after the start of the substudy. In addition, differences could be examined between patients whose partner participated in the substudy and patients whose partner refused to participate.

Both the main study and the partner substudy were approved by the Medical Ethics Committees of the participating hospitals, and were conducted in accordance with the Helsinki Declaration. All patients and partners provided written informed consent.

**Demographic variables**

The demographic patient variables age, gender, and education were included, with low education referring to less than 7 years of education. In addition, clinical patient variables were incorporated, including type of ICD (1 or 2 chamber ICD versus biventricular ICD), ICD indication (primary versus secondary prevention), etiology (ischemic cardiomyopathy versus nonischemic cardiomyopathy), and comorbidity (rheumatic, lung, or kidney disease, or diabetes).

**Personality**

Between 0 and 3 weeks following ICD implantation, patients completed the 14-item Type D Scale (DS14) to measure Type D personality[13]. The DS14 consists of the 7-item subscales negative affectivity (e.g., "I often feel unhappy") and social inhibition (e.g., "I am a 'closed' person"). Items are answered on a five-point Likert scale ranging from *0-false* to *4-true*. Total scores on both subscales range from 0 to 28. Patients scoring high on both subscales; i.e., equal to or above the standardized cut off score 10, are classified as Type D[13]. These cut-off points have shown to be reliable in discriminating Type Ds from non Type Ds[15]. Internal consistency is high with Cronbach's α values of 0.88 for negative affectivity and 0.86 for social inhibition[13]. The temporal stability of Type D personality has also been confirmed[13, 16].

**Statistical analyses**

First, differences in clinical and personality characteristics between patients included after the start of the partner substudy and those included before the start of this substudy were examined by means of Chi-square tests and independent *t*-tests. Next, another series of Chi-square tests and independent *t*-tests were performed to investigate differences between patients whose partner agreed to participate and patients whose partner declined participation. Subsequently, logistic regression analysis was performed to determine independent associations of Type D personality and demographic and clinical variables with the cohort of patients who were included after the start of the partner substudy. A logistic regression analysis was also applied to determine independent associations between Type D personality and demographic variables and the cohort of patients whose partner did not participate. Clinical variables were not included in these additional analyses. All statistical analyses were performed using SPSS 14.0 for Windows. A *p*-value < .05 was considered to be statistically significant.

**RESULTS**

**Patient and partner characteristics**

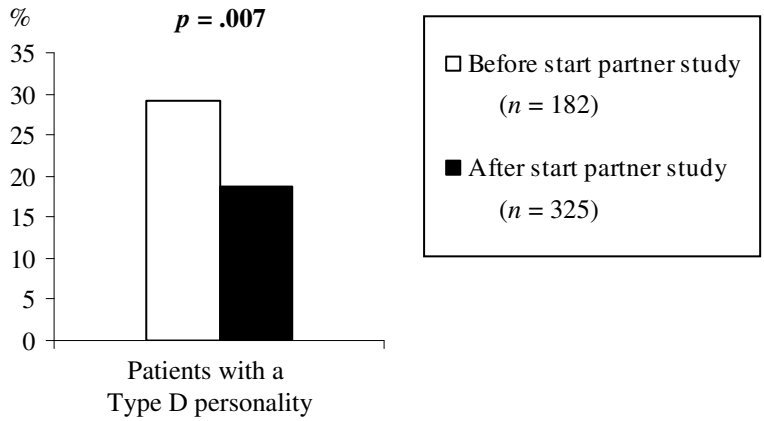
Of the 513 patients who agreed to participate in the study, 6 patients had to be excluded due to missing data on Type D personality ($n$ = 4) or smoking ($n$ = 2), resulting in a final sample of 507 ICD patients. Of these patients, 22.5% was classified as Type D ($n$ = 114), 80.5% was male ($n$ = 408), 23.3% had less than 7 years of education ($n$ = 118), 60.0% had a primary indication ($n$ = 304), 72.4% had ischemic cardiomyopathy ($n$ = 367), 32.1% had a biventricular ICD ($n$ =163), and 36.7% was suffering from comorbidities ($n$ = 186). The mean age of these patients was 62.7 years (SD = 10.1, range 24-79).

Of these 507 patients, 325 patients (64.1%) were included after the start of the partner substudy. About 15% of these patients did not have a partner ($n$ = 49), resulting in a potential sample of 276 partners, of whom 243 (88.0%) participated and 33 (12.0%) did not participate. The mean age in this sample of 243 partners was 60.3 years (SD = 9.4) and 45 partners (18.4%) were male.

**Patient participation following start partner substudy**

First, differences between patients included before ($n$ = 182) and after ($n$ = 325) the partner substudy were investigated. The proportion of Type D patients included after the start of the partner substudy was significantly lower compared to the proportion before the start of this substudy (18.8% versus 29.1%, $p$ = .007), suggesting a decreased participation rate of Type D patients following the addition of the partner substudy (Figure 1). Furthermore, patients included after addition of the partner substudy were slightly older ($p$ = .047) and more often had primary prevention ($p$ < .0001) and comorbidities ($p$ = .024) as compared to patients included before the start of the substudy (Table 1).

***Figure 1.*** *Percentage of patients with a Type D personality before and after the start of the partner substudy*




Multivariable logistic regression analysis showed that patients who were included during the partner substudy were less likely to have a Type D personality (OR = 0.48) as compared to the proportion of Type Ds before the start of the substudy, when controlling for other variables (Table 2). This indicates that the reduction in the proportion of Type D patients after the start of the partner substudy was not a function of other patient characteristics. Patient participation after the start of the partner substudy was also independently associated with primary prevention (OR = 6.13) and comorbidities (OR = 1.66), and inversely with having a biventricular ICD (OR = 0.47). Age, gender, education, and etiology were not significant in this model.

***Table 1.*** *Characteristics of patients included before and after the start of the partner substudy (N = 507)*

| Patient variables | Before start substudy (*n* = 182) % (*n*) | After start substudy (*n* = 325) % (*n*) | *p** |
|---|---|---|---|
| **Demographic variables** | | | |
| **Age (mean±SD)** | **M=61.5±10.9** | **M=63.4±9.6** | **.047** |
| Female gender | 16.5% (30) | 21.2% (69) | .20 |
| Low education | 23.1% (42) | 23.4% (76) | .94 |
| **Clinical variables** | | | |
| **Primary prevention** | **36.8% (67)** | **72.9% (237)** | **.0001** |
| Ischemic cardiomyopathy | 75.3% (137) | 70.8% (230) | .28 |
| Biventricular ICD | 30.8% (56) | 32.9% (107) | .62 |
| **Comorbidity** | **30.2% (55)** | **40.3% (131)** | **.024** |

* Univariate analysis (Chi-square tests and independent *t*-tests)

***Table 2.*** *Characteristics of patients included after the start of the partner substudy (N = 507)*

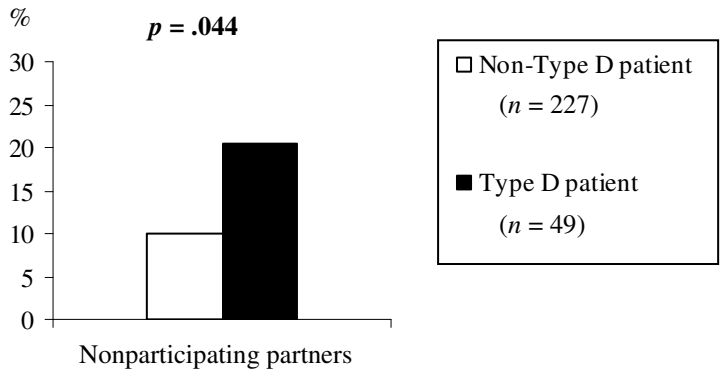
| Patient variables | Multivariable logistic regression analysis* OR | 95% CI | *p* |
|---|---|---|---|
| **Personality** | | | |
| **Type D personality** | **0.48** | **0.30-0.78** | **.003** |
| **Demographic variables** | | | |
| Age (mean±SD) | 1.02 | 1.00-1.04 | .081 |
| Female gender | 1.43 | 0.83-2.45 | .20 |
| Low education | 1.04 | 0.64-1.70 | .88 |
| **Clinical variables** | | | |
| **Primary prevention** | **6.13** | **3.93-9.55** | **.0001** |
| Ischemic cardiomyopathy | 0.63 | 0.38-1.02 | .060 |
| **Biventricular ICD** | **0.47** | **0.29-0.77** | **.003** |
| **Comorbidity** | **1.66** | **1.07-2.56** | **.023** |

* Patients included after the start of the partner substudy coded as 1.

**Partner nonparticipation in the substudy**

Selection bias was also investigated in partners who participated in the study ($n$ = 243) versus partners who did not participate in the study ($n$ = 33). Chi-square analysis showed that nonparticipation was more prevalent among partners of Type D patients as compared to partners of non-Type D patients (20.4% versus 10.1%; $p$ = .044) (Figure 2). In addition, 9.4% of the partners did not participate when the patient was male versus 22.6% when the patient was female ($p$ = .008).

***Figure 2.*** *Percentage nonparticipating partners as a function of Type D personality of the patient*




Multivariable logistic regression analysis (Table 3) showed that female gender of the patient was the only variable which was independently associated with a 2.9 fold risk of nonparticipation of partners. In addition, there was a trend for Type D personality of the patient (OR = 2.13) to be associated with nonparticipation of the partner. Age and education of the patient were not significantly related to partner nonparticipation.

***Table 3.*** *Participating versus nonparticipating partners as a function of patient characteristics (n = 276).*

| | **Participating partners (*n* = 243)** | **Nonparticipating partners (*n* = 33)** | **Multivariable logistic regression analysis*** | | |
|---|---|---|---|---|---|
| **Patient variables** | **% (n)** | **% (n)** | **OR** | **95% CI** | ***p*** |
| **Personality patient** | | | | | |
| **Type D personality** | **16.0% (39)** | **30.3% (10)** | **2.13** | **0.91-5.00** | **.083** |
| **Demographic variables** | | | | | |
| Age; mean±SD | M=63.0±9.0 | M=64.3±10.5 | 1.03 | 0.99-1.07 | .20 |
| **Female gender** | **16.9% (41)** | **36.4% (12)** | **2.92** | **1.29-6.61** | **.010** |
| Low education | 21.4% (52) | 24.2% (8) | 0.89 | 0.36-2.21 | .81 |

* Nonparticipation of partner coded as 1.

## DISCUSSION

This study investigated the associations of Type D personality and demographic and clinical variables of ICD patients (i) with their participation rate in research either involving or not involving additional participation of their partners, and (ii) associations of Type D personality and demographic variables of the patient with nonparticipation rates of their partners. We found that patients who participated following the start of the partner substudy were significantly less likely to have a Type D personality and biventricular ICD, and significantly more likely to have primary prevention and comorbidities. Partner nonparticipation was more prevalent among partners of female patients and tended to be more prevalent in partners of Type D patients. Hence, the addition of a substudy on partners of ICD patients has caused selection bias related to the personality of the patients in two different ways.

We can only speculate why the prevalence of Type D personality significantly decreased after the addition of a substudy on partners. Type D patients are closed persons and want to keep people at a distance, in combination with a tendency to experience high negative affect[13]. It may be speculated that because of this combination, they are more reluctant to cooperate in a study which may trigger their partner to encourage the patient

to disclose their negative feelings. Since the patients' cooperation was also needed in asking the partner to participate, this also may have influenced participation rates of their partners.

In this study, the Type D personality played an important role in selection bias. Participants and nonparticipants may also differ on a number of characteristics related to personality traits, including their psychological and physical health; that is, participants may be more psychologically adapted (e.g., lower in neuroticism and higher in conscientiousness) and may therefore be healthier than nonparticipants[5]. In patients with coronary heart disease, Type D personality has been associated with clinical outcomes, such as an increased risk for morbidity and mortality[14]. As a consequence, selection bias may result in an underrepresentation of Type D patients and therefore an overrepresentation of healthy participants. The power to detect differences between Type D patients and non Type D patients will also be decreased. These effects imply potentially important consequences for study results.

ICD indication is being incorporated in most studies on ICD patients. In recent years, guidelines for ICD implantation have been expanded, particularly regarding primary prevention[17]. Therefore, the significant effect of primary prevention for patients included after the partner substudy was expected. We had no specific prospects regarding etiology, having a biventricular ICD, or comorbidities, but these characteristics were all (marginally) significantly related to inclusion after the start of the partner substudy.

Some of the demographic covariables were also significantly associated with study participation. Differences were found regarding age, with patients included after the substudy being slightly older. However, this small difference (mean age 63.4 versus 61.5) may not have clinical relevance. In addition, male partners more often did not participate as compared to female partners, which contradicts results of previous studies[8-10], but is important to take into account when performing substudies involving partners of (ICD) patients.

The results of this study should be interpreted with caution. No data were available on patients who were invited to participate but declined. This group may contain a high percentage of Type D patients, but this prevalence is hard to determine, since Medical Ethics Committees will not easily approve a proposition to provide patients, who declined

participation immediately, with a questionnaire. Nevertheless, the present study reveals important information on the association of Type D personality with participation rates, when adding a partner substudy to the main study. Given that a better comprehension of the interpersonal context of Type D patients is important[18], the results of the current study should be taken into account in future studies.

In conclusion, in the ICD population, the addition of a partner substudy was related to a decreased proportion of participating patients with a Type D personality. Also, nonparticipation of partners was more prevalent among partners of Type D patients as compared to partners of non Type D patients. These effects should be considered when planning a partner substudy. In general, it is important for researchers to consider possible bias by introducing new elements to the main study that may affect participation rates.

***ACKNOWLEDGEMENTS***

*This study was supported by the Netherlands Organization for Scientific Research, The Hague, The Netherlands with a VICI grant (453-04-004) to Dr. Johan Denollet.*

*We would like to thank Eefje Postelmans for inclusion of the patients into the study and Martha van den Berg (MSc), Vivianne Sterk, Jolien Diekhorst (MSc), Marjan Traa, and Marie-Anne Mittelhaeuser for help with data management.*

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*Chapter 13*

# General Discussion and Summary

The present thesis describes ongoing prospective research in patients with an implantable cardioverter defibrillator (ICD) and their partners. ICD implantation constitutes the main treatment of choice in patients with life-threatening arrhythmias as well as in patients at increased risk for these arrhythmias[1]. Although ICDs do not prevent ventricular arrhythmias, their aim is to prevent sudden cardiac death due to ventricular arrhythmia. Most patients adapt well to the ICD, but a subgroup experiences psychological problems, including anxiety[2]. Identification of patients with anxiety is important as this adverse emotional state may be related to unfavorable outcomes[3], including ventricular arrhythmias, although results are inconclusive[4-6]. Furthermore, anxiety levels in partners may be as high as in ICD patients themselves, although only a few studies have investigated this issue.

The objectives of this thesis were to examine vulnerability factors for anxiety in ICD patients and to examine the role of anxiety for patient-centered and clinical outcomes. In addition, anxiety in partners of ICD patients was investigated. ICD patients and their partners completed questionnaires on psychological variables at the time of implantation, and 2, 12, and 18 months post-implantation. In this chapter, the main findings of this thesis are summarized and discussed. Limitations and strengths of the research as well as implications for clinical practice and research are also discussed.

## VULNERABILITY FACTORS FOR ANXIETY IN ICD TREATMENT

The first part of this thesis presented studies on vulnerability factors for anxiety in ICD patients. Findings on both short-term (including 2 months post-implantation) and longer-term (12 months post-implantation) follow-up are discussed.

*Chapter 2* showed that clinically relevant levels of self-reported anxiety were present in 46% of patients at baseline and in 36% of patients at 2 months post-implantation, although mean levels of self-reported anxiety were equal at both time points. These prevalences are in the range of prevalences reported in previous research[2, 7]. Despite similar levels at baseline, shocked patients exhibited higher levels of self-reported anxiety at follow-up as compared to non-shocked patients. Type D personality and anxiety sensitivity were the only vulnerability factors for self-reported anxiety and interviewer-rated anxiety, adjusting for shocks, gender, age, marital status, education, ICD indication,

etiology, and comorbidity. Regarding Type D personality, the present findings are in line with those from previous research, as one cross-sectional study found an association between Type D and anxiety[8] and another study reported a large effect size of Type D personality for anxiety[9]. Regarding anxiety sensitivity, two previous studies did not find a clear relationship with anxiety in ICD patients[10, 11]. Although Lemon et al.[11] reported a significant relationship at the time of implantation, anxiety sensitivity was not related to changes of anxiety. This may be due to a power problem as only 21 patients completed the follow-up assessments. The nonsignificant results in the study by Hegel et al.[10] may either also be due to limited power (range of *N* 21-38), or to the use of the trait-version of the STAI instead of state version or the longer time since ICD implantation (mean of 4.2 years). Thus, our study is the first to report an independent predictive effect of both Type D personality and anxiety sensitivity for anxiety in ICD patients. The nonsignificant effect of shocks for anxiety may be due to limited power but may also reflect the actual relationship, since other studies also demonstrated that shocks were unrelated to anxiety[12, 13]. However, as there are also prospective studies which reported an effect of shocks on anxiety[9, 14, 15] and an adverse effect of ≥ 5 shocks, but not of < 5 shocks, on emotional states[16], future studies on this relationship are warranted[17]. Our study shows that ICD indication was unrelated to anxiety, which is in line with previous studies[9, 18, 19].

*Chapter 3* focused on ICD recall because of potential malfunctioning of particular ICDs as a determinant of anxiety. Although mean levels of anxiety did not differ between baseline and extra device evaluation, a significantly higher proportion of patients experienced highly increased levels of anxiety after additional device evaluation (24.2%) as compared to the time of ICD implantation (6.1%). Hence, ICD recall may also be a vulnerability factor for anxiety. This is in line with an older study which demonstrated that ICD recall negatively affected confidence in the ICD[20]. In addition, a vignette study showed that patients would be concerned about ICD recall, regardless of the brand that was recalled[21]. In contrast, Cuculi et al.[22] reported that distress levels in patients with ICD recall were not increased, as mean distress levels of these patients were within the normal range and a control group of ICD patients with unaffected devices reported similar levels. However, this study did not investigate the proportion of patients with highly increased distress levels.

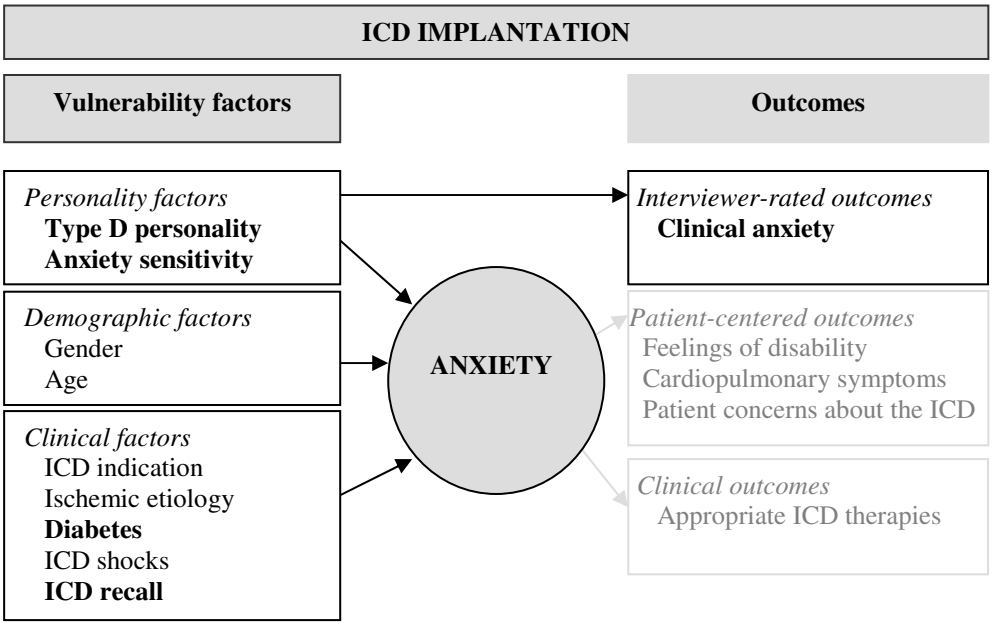
*Chapter 4* presented a large prospective study on chronic anxiety, which showed that over 50% of patients who experienced increased anxiety levels at the time of implantation were still anxious after 12 months of follow-up. Type D personality and diabetes were identified as vulnerability factors, as Type D personality was associated with a 2.8-fold risk to experience chronic anxiety and diabetes with a 4.6-fold risk, independent of various demographic and clinical variables. Although prior research in ICD patients showed that diabetes was unrelated to anxiety[9], a study in heart failure patients showed that comorbid diabetes and angina were related to anxiety[23]. Diabetes may generally be associated with distress[24], including anxiety[25]; we have no explanation for the inconsistent results. The finding of Type D personality corroborates the results of the short-term study reported in *Chapter 2*. Similarly, shocks and ICD indication were not related to chronic anxiety, which also expands the findings of *Chapter 2*. Anxiety sensitivity could not be included in this study as this construct was not assessed in the MIDAS study[26], which was part of this particular investigation.

While previous studies examined changes in mean distress scores, *Chapter 5* focused on trajectories of anxiety and depressive symptoms in the first year following ICD implantation. Four trajectories were found for both anxiety and depressive symptoms, with very low (8%), low (53%), mildly (35%), and severely (4%) anxious groups and correspondingly labeled depressive groups (respectively, 38%, 37%, 17%, and 8%). Trajectories were relatively stable, although particularly depressive trajectories showed some initial within-class change. A decline of symptom levels after ICD implantation is in line with other studies[27, 28], but our results also support previous studies showing a stable course of symptoms from one month to five years post-implantation[7, 13, 18]. This study also demonstrated that anxiety is more prevalent in ICD patients as compared to depression, which was also reported in the review by Sears et al.[2] Finally, comparable to previous chapters, Type D personality and anxiety sensitivity were the most prominent predictors of trajectories, while ICD indication and appropriate ICD therapies were unrelated to trajectories.

Overall, the findings of the first part of this thesis are graphically shown in Figure 1, with significant associations being presented in bold face. This part emphasizes the prevalence and chronicity of anxiety in ICD patients. ICD indication, etiology, and

ICD shocks were all unrelated to anxiety, but patients with ICD recall and diabetes were at increased risk to experience anxiety. In terms of psychological risk factors, both Type D personality and anxiety sensitivity were independently associated with increased anxiety in ICD patients.

***Figure 1.*** *Vulnerability for anxiety in ICD treatment (bold face = significant)*




**THE ROLE OF ANXIETY IN THE OUTCOME OF ICD TREATMENT**

Considering the high prevalence of anxiety, it is essential to evaluate the influence of anxiety on patient-centered and clinical outcomes in ICD patients. Previous studies found that anxiety in ICD patients is related to low treatment satisfaction[29], impaired quality of life[30, 31], and higher pain intensity of ICD shocks[32]. Moreover, anxious patients may also be at increased risk to experience ventricular arrhythmias, although these findings are inconclusive[5, 6]. Therefore, part II of this thesis focused on empirical studies examining the role of anxiety for outcomes in ICD patients. In addition, treatment of anxiety is also important. Hence, we conducted a systematic review of studies investigating interventions for anxiety and other psychological problems in ICD patients.

*Chapter 6* examined the role of general anxiety versus disease-specific anxiety for patient-centered outcomes. The shared variance between these anxiety dimensions ranged from 5% tot 12%, suggesting uniqueness of dimensions. Anxiety dimensions were differentially associated with outcomes: patient concerns about the ICD and feelings of disability were associated with general as well as disease-specific anxiety. However, clinical anxiety was predicted by general anxiety only and cardiopulmonary symptomatology by disease-specific anxiety only. These results demonstrate a differential but also independent predictive value of general and disease-specific anxiety, which has not been investigated before. In addition, shocks and comorbidity were related to feelings of disability, and shocks were also associated with patient concerns about the ICD, while comorbidity was also related to cardiopulmonary symptomatology. Shocks have been related to patient concerns about the ICD in some[14, 33] but not all[34, 35] studies. Results may depend on the instrument used for measuring ICD concerns. Education, working status, smoking, etiology, and use of psychotropic medication were unrelated to the outcomes.

The following two chapters center on psychological predictors of ventricular arrhythmias for which appropriate ICD therapies (ATPs or shocks) were delivered. *Chapter 7* reported three endpoints, including occurrence of ≥ 1 ventricular arrhythmia(s) with appropriate therapies, ≥ 5 ventricular arrhythmias with appropriate therapies, and ≥1 shocks. While ICD indication (secondary prevention) was associated with a 2.5-fold risk of arrhythmia for all three endpoints, increased anxiety (2.3-fold risk) and ischemic etiology predicted the occurrence of ≥ 5 ventricular arrhythmias. Previous research also reported a relationship between anxiety and appropriate ICD therapies[6]. However, this particular study reported a relationship between anxiety and ≥ 1 appropriate therapies whereas in our study anxiety was only related to ≥ 5 appropriate therapies but not to ≥ 1 appropriate therapies. Another study also found that anxiety was not related to ≥ 1 shocks[5], which was supported by our results. In sum, anxiety may be related to life-threatening arrhythmias, but future research is warranted to clarify inconsistent findings.

*Chapter 8* compared the importance of anxiety, depressive symptoms, Type D personality, and their interaction effects for ventricular arrhythmias with appropriate ICD therapies. This is the first study that examined the independent predictive value of several psychological variables at the same time. Only the combined presence of increased

anxiety and Type D personality was significantly related to appropriate ICD therapies. Anxiety by Type D personality was associated with a 2.3-fold independent risk for arrhythmias and secondary prevention with a 2.1-fold risk, adjusting for gender, age, and etiology. Given the inconsistent results of previous studies regarding anxiety and ventricular arrhythmias[5, 6], these results are very important, as they suggest that the combined presence of anxiety and Type D personality may be detrimental rather than the presence of anxiety alone. In addition, these results may give more insight into the relationship between Type D personality and morbidity and mortality[36], at least for a subgroup of Type D patients.

Given the high prevalence of anxiety and other psychological problems in ICD patients, studies have examined psychological interventions in ICD patients. *Chapter 9* provides a systematic review of these studies. Most studies were small-scale randomized controlled intervention trials. Evidence from these trials suggests anxiety may best be treated by a multi-factorial approach using a cognitive behavioral component together with exercise training. In contrast, the results were inconclusive to present recommendations for interventions regarding depressive symptoms and quality of life.

***Figure 2.*** *Outcomes in ICD treatment (bold face = significant)*

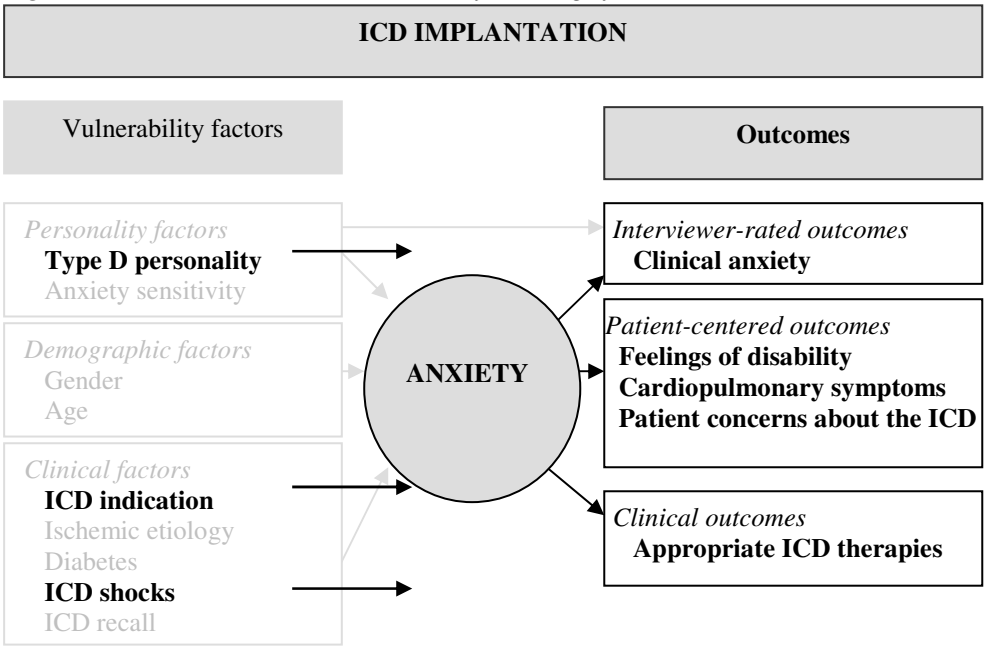


Figure 2 schematically shows the results of the second part of this thesis. Anxiety alone and in combination with a Type D personality was associated with appropriate ICD therapies, independent of ICD indication. In addition, general anxiety and disease-specific anxiety were differentially related to patient-centered outcomes and interviewer-rated anxiety. Shocks and comorbidity were also associated with some of these outcomes. Our review of psychological intervention studies suggests that patients with anxiety may be well treated with a combination of cognitive-behavioral therapy and exercise training.

**THE ROLE OF PARTNERS IN ICD TREATMENT**

Previous parts of this thesis focused on anxiety in ICD patients, but attention should also be given to anxiety in partners, because partners may be at least as anxious as ICD patients themselves[8, 28, 37, 38]. In addition, as lack of social support may be related to increased emotional distress[39], not having a partner may also be associated with distress, especially in Type D patients who have fewer social ties and experience less social support as compared to non-Type Ds[40, 41]. Moreover, Type D personality is associated with adverse outcomes[36], but not all Type D patients are at increased risk.

*Chapter 10* examined the role of partner status and Type D personality for psychological distress in a pooled sample of ICD patients and myocardial infarction patients. This short-term follow-up study showed that Type D patients without a partner had a 6- to 8-fold risk to experience increased levels of anxiety and depressive symptoms as compared to non-Type D patients with a partner, followed by a 3-fold risk for Type D patients with a partner and a 2- to 3-fold risk for non-Type D patients without a partner. Since this pattern of results was obtained in both patient groups, we concluded that not having a partner may negatively affect emotional distress levels in ICD patients with a Type D personality.

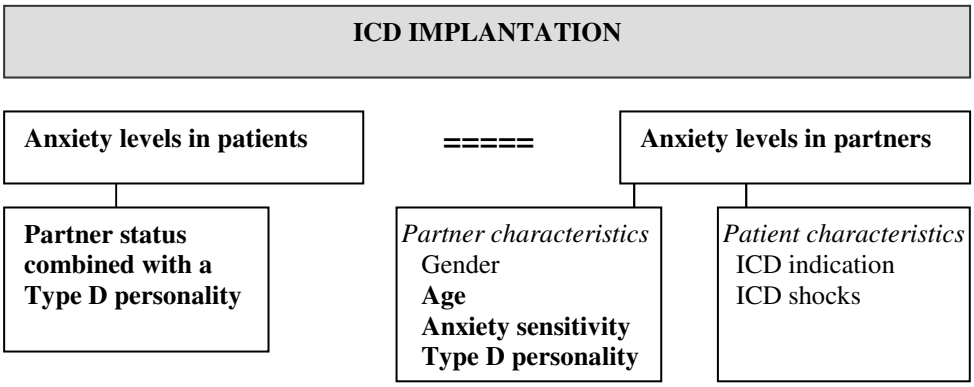
*Chapter 11* showed that ICD patients and partners reported equal levels of anxiety symptoms and also that the proportion of patients and partners experiencing increased levels of anxiety was similar, which confirms findings of previous small-scale or cross-sectional studies[8, 28, 37, 38]. Comparable with the patient studies presented in this thesis, Type D personality and anxiety sensitivity of the partner were vulnerability factors of anxiety and posttraumatic stress symptoms (PTSS) in partners, and ICD indication and

shocks experienced by the patient were not. In addition, anxiety sensitivity acted as a mediator in the relationship between Type D personality and PTSS in partners.

*Chapter 12* reported that the proportion of Type D patients was significantly lower after the start of the partner substudy as compared to before the start of the substudy. In addition, during the partner substudy, nonparticipation of partners was more prevalent among partners of Type D patients as compared to partners of non-Type D patients. Hence, the addition of a partner substudy may affect participations rates of both patients with a Type D personality and their partners, which in turn may influence generalizability of results. We speculated that the partner substudy may trigger partners to encourage the patient to disclose their negative feelings, which may be unpleasant for the Type D patient and may result in nonparticipation.

The results regarding research involving partners is schematically presented in Figure 3. Distress levels of patients were influenced by partner status, with Type D patients without a partner having the highest risk to experience emotional distress. In addition, partners of ICD patients experience as least as much anxiety as ICD patients themselves. Anxiety levels in partners were not related to ICD indication and shocks. However, partners with a Type D personality or anxiety sensitivity were at increased risk to experience anxiety. Importantly, starting a substudy in partners of ICD patients may lead to nonparticipation of Type D patients and their partners, which may influence generalizability of results.

***Figure 3.*** *Results of the studies involving partners of ICD patients (bold face = significant)*



## LIMITATIONS AND STRENGTHS OF THE PRESENT THESIS

The present research has a number of limitations. First, no information was available on nonresponse rate, i.e., the proportion of patients who were invited to participate but declined. However, attrition rate was consequently reported as were differences between patients in- versus excluded from analyses. Although some studies reported no differences (*Chapter 4* and *7*), other studies reported that excluded patients more often had a Type D personality, no partner, and increased anxiety as compared to included patients (*Chapter 2, 5, 6, 8,* and *10*), which may have limited the generalizability of results. Second, baseline questionnaires were completed between 0 and 3 weeks post-implantation, which means that baseline levels of distress do not reflect pre-implantation levels. However, personality assessment may not be influenced by the time of completion of questionnaires. Third, the power to find an association between shocks and outcomes may have been limited because of a low incidence of shocks, especially in the short-term follow-up studies. Fourth, the study in *Chapter 3* involved a small sample. Fifth, we had no information on participation in cardiac rehabilitation and use of psychopharmaca. These factors may have influenced anxiety levels. Sixth, addition of the partner substudy may have influenced patient participation which in turn may have affected results and generalizability. Finally, it was not possible to investigate clinical factors including ejection fraction and functional class because these data were missing for many patients.

Nevertheless, this thesis reports the results of a large prospective long-term multi-center study focusing on anxiety in ICD patients and their partners. Both self-reported anxiety and interviewer-rated anxiety were investigated. These prospective studies are the first to show that Type D personality and anxiety sensitivity independently predict anxiety. In addition, several psychological factors were simultaneously investigated in relation to ventricular arrhythmias. Finally, this is one of the few prospective studies on distress in partners of ICD patients.

## IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

The studies presented in this thesis generate a number of implications for clinical practice as well as recommendations for future research.

Chronic anxiety in the first year post-implantation may be present in a quarter of patients (*Chapter 4*). Similarly, after a small initial decline, levels of anxiety and depression tended to be relatively stable within the first year post-implantation (*Chapter 5*). Future studies need to a) replicate these findings, with inclusion of more time points as well as pre-implantation levels of anxiety, and b) investigate the prognostic value of trajectories. Given the probable triggering effect of anxiety and depression on ventricular arrhythmias[4, 6], early identification of ICD patients at risk for emotional distress is important. Identification of anxiety and depression may already be realized at the time of implantation, as these levels seem to represent the level of anxiety during the first year post-implantation. The state version of the STAI may be used as a screening tool for anxiety, because the STAI is an adequate measure of general anxiety and is easy to administer. To screen for depression, we used the Beck Depression Inventory, which is also an easy to administer questionnaire although it comprises 21 items.

General anxiety and disease-specific anxiety were differentially predictive for patient-centered outcomes in ICD patients (*Chapter 6*). Future research may examine the possible differential effect towards clinical endpoints, including ventricular arrhythmias and mortality. To measure disease-specific anxiety, we recommend the use of two short 5-item scales deduced from the Cardiac Anxiety Questionnaire, measuring fear and worry about heart sensations and cardioprotective avoidance of activities that could bring on symptoms (*Chapter 6*). However, these scales need to be validated first and cut-off values indicating increased levels of disease-specific anxiety need to be determined.

The results of the present thesis indicate that some (ICD recall, shocks and diabetes) but not all (ICD indication and etiology) clinical factors may be related to anxiety in ICD patients. As ICD recall may lead to increased anxiety (*Chapter 2*), psychological support for patients with ICD recall is warranted. Next, shocks were related to self-reported anxiety (*Chapter 2*), feelings of disability, and patient concerns about the ICD (*Chapter 6*), but not to interviewer-rated anxiety (*Chapter 2* and *6*), chronic anxiety (*Chapter 4*), trajectories of anxiety (*Chapter 5*), and anxiety or PTSS in partners of

patients (*Chapter 11*). Importantly, limited power was a problem in some of these studies. However, prior research also contains inconsistencies regarding the role of shocks for emotional distress, including anxiety[17], with some[9, 14, 15] but not all[12, 13] studies demonstrating a relationship between shocks and anxiety. A final point regarding shocks refers to the number of shocks. The CIDS trail reported that having had ≥ 5 shocks was associated with a poorer quality of life, but ≥ 1 shocks was not[16]. Our study did not have sufficient power to study the effect of having had ≥ 5 shocks on patient-centered outcomes, but future research may investigate this issue.

Regarding diabetes, we found a relationship with chronic anxiety in ICD patients (*Chapter 4*). Diabetes has also been linked to depression and anxiety in other cardiac populations[23, 42], but other studies found no relationship between diabetes and distress[9]. Therefore, more research is needed on the role of diabetes for emotional distress in ICD patients. Regarding ICD indication, our results indicated no relationship with anxiety in patients and partners (*Chapter 2, 4, 5,* and *11*), which is in line with all previous studies on this topic[9, 18, 19]. However, comparable to the point mentioned for shocks, the relationship between ICD indication and distress may be influenced by other factors that have been related to distress, including personality factors. Future research is needed to explore this issue.

A non-cardiac factor that may play an important role in the relationship between shocks and patient-centered outcomes is personality. Future research needs to examine further whether Type D personality and anxiety sensitivity influence the effect of shocks on emotional distress. Regarding vulnerability factors for anxiety, future research should not only investigate clinical factors but also personality dispositions, as our studies showed that Type D personality and anxiety sensitivity may predispose patients for increased levels of anxiety (*Chapter 2, 4,* and *5*). As these personality traits were often independently associated with anxiety, they may have a differential influence on anxiety. In addition, the combined presence of Type D personality and increased anxiety predicted life-threatening arrhythmias (*Chapter 8*). In clinical practice, it may be timely to standardize screening for Type D personality, and possibly also for anxiety sensitivity. Especially Type D patients without a partner should be closely monitored. In addition, partners may also be screened for Type D personality and anxiety sensitivity, as these

were predictors of anxiety in partners (*Chapter 11*). In clinical practice, screening may be performed by ICD nurses or other health-care professionals. The 14-item Type D Scale and 16-item Anxiety Sensitivity Index reflect short, adequate, and easy to administer questionnaires to screen for Type D personality and anxiety sensitivity. The DS14 also has established cut-off values to classify a person as Type D[43], but the ASI needs further evaluation regarding cut-off values to indicate clinically relevant levels. In addition, some physical symptoms in ICD patients may reflect an actual threat for survival and several items of the ASI may therefore measure realistic concerns[11].

The role of psychological factors as precipitants of life-threatening arrhythmias should be further explored. These studies may incorporate various emotions besides anxiety, as depression, anger, fatigue, vigor, and confusion have also been linked to ventricular arrhythmias[4-6]. In addition, the predictive value of personality characteristics such as Type D personality, but also anxiety sensitivity, may be further investigated. Importantly, ejection fraction and functional class should be included in this research, as these factors are associated with arrhythmias[44-46]. Due to missing values, these factors could not be included in our research. A final recommendation for future research in this regard concerns the investigation of physiological mechanisms that may account for the relationship between psychological factors and life-threatening arrhythmias.

As partner levels of anxiety were as high as levels in patients (*Chapter 11*), future research should also focus on anxiety in partners of ICD patients. PTSS should also be included in partner research; our study was the first to investigate these symptoms in partners. However, even in patients, only a few studies have focused on PTSS, and these were mostly case-studies[47]. Our results suggest that ICD indication and shocks are not related to distress in partners, but future studies are warranted. Another essential topic of future research is the influence of partner characteristics and distress on patient well-being. However, research involving both ICD patients and their partners should take into account the possible negative effect of the partner study on participation rates, especially among Type D patients and their partners.

Finally, the research presented in this thesis necessitates psychological intervention in ICD patients, as anxiety and depression levels may remain high in a subgroup of ICD patients. In addition, anxiety, Type Personality, and anxiety sensitivity were associated

with adverse outcomes. According to the review presented in *Chapter 9*, treatment of anxiety may comprise cognitive behavioral therapy combined with exercise training. Cognitive behavioral therapy may address anxiety, apprehensions, avoidance behavior, fear of shocks, and distorted cognitions. Stress management training and relaxation therapy may also be applied, as most of the cognitive behavioral interventions studies included these trainings as adjunct therapies. In addition, as patients with disease-specific anxiety want to avoid physical exercise[48], these patients may also benefit from exercise training. Management of depressive patients may be realized by comprehensive cardiac rehabilitation, because our review of psychological interventions demonstrated this to be effective.

Interventions for patients with a Type D personality or anxiety sensitivity have not been systematically investigated in trials. Sher[49] has proposed a number of interventions which may reduce distress in Type D patients and improve the ability to socialize. Suggested interventions included cognitive behavioral therapy, social skills training, interpersonal psychotherapy, and progressive muscle relaxation. The following considerations may also be implemented in intervention. Although changing personality itself may be very difficult, behaviors arising from the personality trait may be targeted. For instance, Type D patients perform fewer health-related behaviors[41] and inadequate consultation behavior[50] as compared to non-Type D patients. Therefore, interventions may address self-management and self-care abilities of the Type D patient. In addition, the socially inhibited Type D patients may benefit from a supportive and stimulating social network. Hence, interventions should focus on consolidation of the social network. Furthermore, since Type D patients experience a number of negative emotions, another target of intervention may comprise coping abilities for these emotions.

Interventions for anxiety sensitivity may also embrace cognitive behavioral therapy, including education and arousal reduction, cognitive-restructuring techniques, and exposure to the somatic sensations which are feared by the patients[51]. Interoceptive exposure may be accomplished by means of exercise. A recent study showed that both high-intensity exercise and low-intensity exercise were successful in reducing anxiety sensitivity levels, although high-intensity exercise was associated with more rapid reductions in anxiety sensitivity levels[52].

**CONCLUDING REMARKS**

Anxiety represents a major issue in ICD patients, as anxiety levels in a quarter of patients tended to be chronic. ICD indication, etiology, and shocks appear less important for anxiety, although results regarding shocks were inconsistent. Personality factors, including Type D personality and anxiety sensitivity, were related to anxiety and should be incorporated in future studies on vulnerability factors for anxiety. Future research may also investigate whether inter-individual differences exist regarding the impact of clinical factors on patient-centered outcomes, as this impact may be influenced by personality traits or other psychological factors. Anxiety alone and in combination with a Type D personality was associated with the occurrence of ventricular arrhythmias in ICD patients. However, these findings should be replicated in future studies, and importantly, mechanisms of this relationship should be studied. Our review on psychological interventions indicated that anxiety in ICD patients may be treated with cognitive-behavioral therapy and exercise training, although larger studies are needed.

Anxiety levels in partners of ICD patients were as high as in patients themselves, but were not influenced by disease etiology or ICD indication. However, partners with a Type D personality or anxiety sensitivity were at increased risk to experience anxiety levels. Although this calls for more research in partners of patients, our results also showed that a substudy in partners may be associated with nonparticipation rates of Type D patients and their partners. Future research has to take this issue into account.

Overall, the results of this thesis suggest that psychological factors are important in ICD treatment. A subgroup of patients as well as partners experiences increased levels of anxiety, which may trigger ventricular arrhythmias in ICD patients.

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*Chapter 14*

# Nederlandse Samenvatting en Discussie (Summary and Discussion in Dutch)

## EEN IMPLANTEERBARE DEFIBRILLATOR

Ongeveer 50% van de overlijdens door een cardiovasculaire ziekte wordt veroorzaakt door een plotse hartdood[1]. Plotse hartdood is in de meeste gevallen (85%) het gevolg van ventriculaire hartritmestoornissen[2]. Patiënten die dergelijke levensbedreigende ritmestoornissen hebben ervaren (secundaire preventie) of die een verhoogd risico hebben op deze ritmestoornissen (primaire preventie) worden behandeld met een implanteerbare cardioverter defibrillator (ICD)[3]. De ICD kan de ritmestoornissen niet voorkomen, maar wel beëindigen door middel van een schok, cardioversie, of antitachycardia pacing (ATP)[4]. Tijdens ATP geeft de ICD korte elektrische impulsen aan het hart die 10-20% sneller gaan dan de ritmestoornis. Door de complexe technologie van de ICD wordt de betrouwbaarheid soms betwijfeld, waardoor patiënten met deze ICDs opgeroepen moeten worden voor extra controle (ICD-recall).

## PSYCHOLOGISCHE GEVOLGEN VAN ICD IMPLANTATIE

Veel patiënten ervaren geen psychologische problemen na ICD-implantatie. Er is echter een subgroep patiënten die wel psychologische problemen vertonen na de ICD-implantatie. Deze patiënten ervaren angst, depressie en een verminderde kwaliteit van leven en ze vertonen vaak vermijdingsgedragingen[5-7]. Vooral angst is een belangrijk probleem binnen de ICD-populatie. Studie schatten de prevalentie van klinische angst op 13% tot 38% bij ICD-patiënten en van klinische depressie op 10% tot 15%[7].

Aanpassingsproblemen kunnen voortkomen uit verschillende bronnen, zoals de reanimatie, de diagnose van een levensbedreigende ziekte, en de onvoorspelbaarheid van de ritmestoornissen, maar ook de ICD-implantatie zelf kan een rol spelen[8]. Uit eerdere onderzoeken is gebleken dat de reden voor het krijgen van de ICD (primaire versus secundaire preventie) geen invloed heeft op angstniveaus[9, 10]. Bevindingen over de relatie tussen schokken en angst zijn daarentegen tegenstrijdig[9, 11, 12]. Aanpassingsproblemen zouden ook veroorzaakt kunnen worden door het terugroepen van ICDs die mogelijk niet goed functioneren[13].

Angst bij ICD-patiënten kan ook veroorzaakt worden door kwetsbaarheidfactoren die niet direct gerelateerd zijn aan de ICD zelf, zoals bijvoorbeeld leeftijd (≤ 50 jaar), geslacht (vrouw) en psychologische problemen in het verleden[9, 14]. Er zijn echter weinig

studies die de invloed van persoonlijkheidsfactoren, zoals Type D persoonlijkheid[15, 16] en angstgevoeligheid[17], op angst hebben onderzocht.

## PSYCHOLOGISCHE FACTOREN EN RISICO OP VENTRICULAIRE RITMESTOORNISSEN BIJ ICD-PATIËNTEN

Het is belangrijk om risicofactoren voor ventriculaire ritmestoornissen te onderzoeken, omdat a) ICDs de ritmestoornissen niet kunnen voorkomen, b) de laatste jaren steeds meer ICDs worden geïmplanteerd vanwege uitbreiding van de preventie redenen, c) ICD-schokken kunnen leiden tot psychologische problemen en d) ICDs niet 100% effectief zijn in het beëindigen van ventriculaire ritmestoornissen. Onderzoeken hebben aangetoond dat klinische factoren, zoals een verlaagde pompfunctie[18] en functionele klasse[19], risicofactoren zijn voor ventriculaire ritmestoornissen, maar er is nog weinig bekend over de rol van psychologische factoren. Eerdere studies hebben een samenhang gevonden tussen depressie[20], angst (maar niet depressie en woede)[21] en woede (maar niet angst en depressie)[22] en ventriculaire ritmestoornissen. Een andere studie heeft aangetoond dat ICD-patiënten met angst en woede als persoonlijkheidskenmerken een hogere kans hebben op ICD-schokken die uitgelokt waren door respectievelijk angst of woede[23].

## DE ROL VAN DE PARTNER BIJ BEHANDELING MET EEN ICD

Patiënten die geen partner hebben zijn mogelijk meer kwetsbaar voor angst in vergelijking met patiënten die wel een partner hebben. Vooral bij Type D patiënten, die toch al minder sociale steun ervaren[14, 24], kan het al dan niet hebben van een partner een rol spelen ten aanzien van negatieve emoties. Daarnaast kunnen partners van ICD-patiënten ook angst ervaren. De reanimatie van de patiënt en de kans op nieuwe levensbedreigende hartritmestoornissen kunnen leiden tot negatieve emoties bij partners. Ondanks studies die aangetoond hebben dat angstniveaus bij partners en patiënten mogelijk even hoog zijn[7], hebben nog weinig onderzoeken zich gericht op partners van ICD-patiënten.

## DOEL VAN DIT PROEFSCHRIFT

Dit proefschrift richt zich voornamelijk op angst bij ICD-patiënten, omdat a) angst meer voorkomt bij ICD-patiënten in vergelijking met depressie[25], b) angst veroorzaakt kan

worden door factoren rondom de behandeling met een ICD, zoals reanimatie en de onvoorspelbaarheid van ritmestoornissen, en c) angst gerelateerd lijkt te zijn aan verschillende negatieve uitkomsten. In dit proefschrift verwijst angst voornamelijk naar algemene symptomen van toestandsangst. Dit is een voorbijgaande emotionele toestand, die gekenmerkt wordt door bezorgdheid en spanning, maar ook door fysiologische arousal. Naast algemene angst wordt ook aandacht besteed aan ziektespecifieke angst en klinische angst gemeten met een interview.

Dit proefschrift rapporteert de bevindingen van een voortdurend onderzoek bij ICD-patiënten, waarbij we het volgende wilden onderzoeken 1) kwetsbaarheidfactoren voor angst bij ICD-patiënten, 2) de rol van angst voor uitkomsten inclusief ritmestoornissen en 3) angst bij partners van ICD-patiënten. De patiënten en hun partners werden geworven in het Catharina Ziekenhuis (Eindhoven) en het Amphia Ziekenhuis (Breda).

## SAMENVATTING VAN DE BELANGRIJKSTE RESULTATEN VAN DIT PROEFSCHRIFT

### Deel I Kwetsbaarheidfactoren voor angst bij ICD-patiënten

In het eerste deel van dit proefschrift is gerapporteerd dat tijdens de implantatieperiode ongeveer 50% van de ICD-patiënten verhoogde angstniveaus ervaart (*Hoofdstuk 2* en *4*). Bij de helft van deze patiënten is het verhoogde angstniveau 1 jaar na de implantatie nog steeds aanwezig, wat betekent dat bij een kwart van de ICD-patiënten verhoogde angstniveaus chronisch aanwezig zijn (*Hoofdstuk 4*). Ook in een andere studie werd gevonden dat angstniveaus, na een initiële daling, relatief stabiel bleven (*Hoofdstuk 5*). ICD-indicatie, schokken en vaatlijden waren niet gerelateerd aan de angstniveaus (*Hoofdstuk 2, 4* en *5*). Daarentegen hadden patiënten met een ICD-recall of diabetes wel een verhoogde kans op angst (*Hoofdstuk 3* en *4*). Voor wat betreft psychologische factoren hadden de patiënten met een Type D persoonlijkheid of angstgevoeligheid een significant verhoogde kans om angst te ervaren (*Hoofdstuk 2, 3* en *5*).

De gevonden prevalentie van angst komt overeen met eerdere onderzoeken[7, 26]. Toekomstig onderzoek moet de stabiliteit van angst bevestigen, maar kan zich ook richten

op de prognostische waarde van deze stabiele angstniveaus. Desalniettemin lijkt het belangrijk om patiënten met angst tijdig te identificeren.

Onze bevindingen omtrent ICD-indicatie komen overeen met resultaten van eerdere onderzoeken[5, 9, 10, 27, 28], namelijk dat ICD-indicatie geen invloed heeft op angst, depressie en kwaliteit van leven. Dat schokken niet onafhankelijk gerelateerd waren aan angstniveaus zou de werkelijke relatie kunnen weergeven omdat sommige eerdere onderzoeken ook geen relatie gevonden hadden[11, 29]. Niettemin zijn er ook onderzoeken die wel een verband hadden aangetoond[30, 31] of die vonden dat met name het ervaren van ≥ 5 schokken een negatieve invloed heeft[32]. Toekomstig onderzoek is daarom nodig, waarbij het belangrijk is om de invloed van schokken en psychologische factoren gelijktijdig te onderzoeken[12].

Vergelijkbaar met onze studies, hadden eerdere onderzoeken binnen de ICD-populatie ook een verband aangetoond tussen Type D persoonlijkheid en angst[9, 14]. Daarentegen hadden onderzoeken gericht op angstgevoeligheid bij ICD-patiënten geen relatie met angst aangetoond, maar dat zou het gevolg kunnen zijn van lage power in deze studies[15, 16].

**Deel II De rol van angst voor uitkomsten**

Het tweede deel van dit proefschrift beschrijft dat angst, zowel op zichzelf (*Hoofdstuk 7*) als in combinatie met Type D persoonlijkheid (*Hoofdstuk 8*), gerelateerd is aan het optreden van levensbedreigende ritmestoornissen. Verder werd aangetoond dat algemene en ziektespecifieke angst op een verschillende manier gerelateerd waren aan uitkomsten, zoals invaliditeitsbeleving en zorgen van de patiënt omtrent de ICD (*Hoofdstuk 6*). Schokken en co-morbiditeit waren ook aan bepaalde uitkomsten gerelateerd. Tenslotte werd uit het review geconcludeerd dat behandeling van angst het beste verwezenlijkt kan worden met cognitieve-gedragstherapie in combinatie met beweging (*Hoofdstuk 9*).

Resultaten uit eerdere onderzoeken naar het verband tussen angst en levensbedreigende hartritmestoornissen waren inconsistent[20, 21]. Volgens onze resultaten zou juist de gecombineerde aanwezigheid van angst en Type D persoonlijkheid ook belangrijk kunnen zijn. Meer onderzoek is nodig om de relatie tussen angst en ritmestoornissen te verhelderen.

Algemene en ziektespecifieke angst waren verschillend voorspellend voor bepaalde uitkomsten. Toekomstige studies zouden kunnen onderzoeken of dit ook geldt ten aanzien van klinische uitkomsten zoals ritmestoornissen en overlijden.

**Deel III De rol van partners bij behandeling met een ICD**

Het derde deel van dit proefschrift beschrijft onderzoeken met betrekking tot partners van ICD-patiënten. Met name bij Type D patiënten is partnerstatus belangrijk omdat Type Ds zonder partner de grootste kans hadden op verhoogde angst- en depressieniveaus in vergelijking met de andere patiënten (*Hoofdstuk 10*). Verder werd aangetoond dat angst bij partners even hoog is als bij patiënten (*Hoofdstuk 11*). Net als bij patiënten, werden de angstniveaus van de partner niet beïnvloed door ICD-indicatie of -schokken. Partners met een Type D persoonlijkheid of angstgevoeligheid hadden wel een verhoogde kans om angst te ervaren. Tenslotte werd duidelijk dat het uitvoeren van een substudie bij partners van ICD-patiënten een negatieve invloed heeft op deelname aan de studie (*Hoofdstuk 12*). Na het opstarten van de partner substudie bleek het deel patiënten met een Type D persoonlijkheid namelijk veel lager te zijn in vergelijking met het deel Type D patiënten vóór de start van de substudie. Ook werd gevonden dat deelname van partners van Type D patiënten veel lager was in vergelijking met de deelname van partners van niet Type D patiënten.

Uit het eerste deel van dit proefschrift bleek dat patiënten met een Type D persoonlijkheid een verhoogde kans hebben op angst en uit dit derde deel blijkt dat met name de Type D patiënten zonder partner een verhoogde kans hebben op angst. Omdat het tweede deel ook had aangetoond dat angstige Type D personen een verhoogde kans hebben op ritmestoornissen, lijkt het erg belangrijk om in de klinische praktijk te screenen voor Type D persoonlijkheid bij patiënten.

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# Dankwoord (Acknowledgements)

Dit proefschrift is tot stand gekomen dankzij de ideeën, het werk, de hulp en de steun van een heleboel mensen, die ik graag wil bedanken in dit woord (in een redelijk willekeurige volgorde).

Mijn enthousiasme voor onderzoek is ontstaan tijdens mijn afstudeeronderzoek in Antwerpen onder supervisie van Johan Denollet, mijn promotor. Johan, hiervoor wil ik je bedanken, maar nog meer voor jouw vertrouwen in mij en dat je mij hebt aangenomen op het ICD-project, ondanks mijn uitstapje van drie jaar zonder enige wetenschappelijke activiteit. Jouw goede begeleiding met een verantwoorde (?) dosis humor tijdens de gesprekken werkt erg stimulerend, ondanks de (niet altijd even hartelijk ontvangen) suggesties om op een andere manier naar de data te kijken. Ik ben vereerd dat ik de komende jaren deel mag blijven uitmaken van jouw onderzoeksgroep.

Ivan Nyklíček, co-promotor, jou wil ik natuurlijk ook bedanken voor de goede begeleiding, de opbouwende kritiek en de tijd die je te pas en onpas voor me hebt vrijgemaakt (als dagelijkse begeleider van dit promotie-onderzoek heb ik volgens mij goed gebruik gemaakt van jouw openstaande deur). Van jou heb ik geleerd om te relativeren en stil te staan bij het 'waarom' (waarom zou dit een voorspeller zou van dat, etc).

Albert Meijer, co-promotor, voor jouw inhoudelijke uitleg over cardiologische onderwerpen, kritische opmerkingen, suggesties voor verder onderzoek en voor alle andere hulp ben ik je dankbaar. Hopelijk wordt de samenwerking in de toekomst voortgezet.

Mijn collega's van de UvT wil ik graag bedanken voor de aangename werkomgeving, prettige sfeer en gezellige lunches (Floor bedankt voor je stiptheid, ga zo door). In het bijzonder wil ik een aantal (ex)collega's bedanken: Ilona, voor het uitwerken en opzetten van de studie; Liesje en Viola, voor onderzoeksadviezen en gezelligheid in kamer P612; Susanne, Liesje, Robert, en Alien, voor hulp en gezelligheid op congressen; Nina, voor je uitleg, onder andere het over gebruik van computerprogramma's; Robert, voor uitleg over statistische toetsen; Kim, voor de vlotte samenwerking bij de parenting

papers; Angelique, voor jouw adviezen als recent gepromoveerde collega; Mariette, voor paraatheid en assistentie; en Susanne, voor deelname in de commissie, maar zeker ook voor de prettige samenwerking (ik hoop op een vruchtbare ICD toekomst). Ook Ton Heinen en Hans Dieteren wil ik graag bedanken voor hun behulpzaamheid.

Medewerking van de ziekenhuizen is erg belangrijk, daarom wil ik graag de mensen bedanken van het Catharina Ziekenhuis en het Amphia Ziekenhuis die bij dit project betrokken waren, en in het bijzonder de volgende personen. (Catharina Ziekenhuis:) Pepijn, bedankt voor je enthousiaste en nauwe betrokkenheid bij dit project en voor alles wat je me geleerd hebt en nog steeds leert over ICDs en wat daar mee te maken heeft. Collega's van de afdeling Cardiologie R&D van het Catharina Ziekenhuis, in het bijzonder Antoinette, bedankt voor jullie hulp en hartelijkheid. Het medisch archief, in het bijzonder Lizet, bedankt voor de bereidwilligheid om statussen keer op keer klaar te leggen. (Amphia Ziekenhuis:) John Bartels, bedankt voor je interesse in het onderzoek en de introductie van het onderzoek in het Amphia Ziekenhuis. Speciale dank aan het ICD-team van het Amphia ziekenhuis, in het bijzonder Marco, bedankt voor jouw belangstelling voor dit onderzoek, hulp bij het opzetten, uitleg over cardiologische onderwerpen en kritische opmerkingen; en Eefje en Hidde, bedankt voor jullie inzet bij de inclusie van patienten.

Onmisbaar voor dit type onderzoek is de medewerking van patiënten. Daarom wil ik hen hartelijk bedanken voor hun tijd waarin ze vier keer binnen anderhalf jaar een omvangrijk vragenlijstenboekje hebben ingevuld en ook (in de eerste jaren van de studie) bereid waren om twee keer een interview te ondergaan.

De dataverzameling van dit project was omvangrijk, daarom dank aan de studenten die in de afgelopen jaren voor hun masterthesis (Jolien Diekhorst, Mike de Vet), onderzoeksstage (Esther Muskens) of vrijwillig (Martha van den Berg, Vivianne Sterk, Marjan Traa, Marie-Anne Mittelhaeuser) hebben bijgedragen aan de datamanagement.

I would like to thank all members of the defense committee for their valuable time to read and judge this thesis and discuss the results next September: Dr. A.M.W. Alings, Dr. M.M. Burg, Prof.dr. G.L.M. van Heck, Prof.dr. K.H. Ladwig, Dr. S.S. Pedersen, and Dr. D.A.M.J. Theuns.

Nanda, Judith en Miriam, met jullie als paranimfen moet ik de weken tot 19 september en De dag goed door kunnen komen. Bedankt voor jullie vriendschap en voor jullie hulp en steun bij alle voorbereidingen en op De dag.

Naast de paranimfen wil ik natuurlijk ook andere vrienden bedanken, voor (vrouwen) film- en TVserie-avondjes, tennispartijtjes en andere sportactiviteiten, vakanties, etentjes en gezelligheid, of voor dat ze er gewoon waren voor ontspanning.

Mijn (schoon) familie wil ik bedanken voor hun vertrouwen in mij en voor de stimulatie en steun om het beste uit jezelf te halen en het hoogst haalbare te bereiken. Mijn ouders wil ik speciaal bedanken voor de kansen die ze mij gegeven hebben en mijn schoonouders voor de gezellige etentjes (niet in het minste van de donderdagen).

Caspar, voor jou de laatste bijzondere woorden in dit dankwoord. Zonder jouw liefde, vertrouwen, steun, hulp, en flexibiliteit was ik nooit zo ver gekomen als ik nu ben. Ook jouw relativeringsvermogen en stabiliteit zijn voor mij onmisbaar. De afgelopen jaren heb ik met spanning toegeleefd naar De dag, dus hopelijk begint na 19 september een tijd van ontspanning.

Krista van den Broek,
Tilburg, juni 2008

# Publication List

***Papers included in thesis***

**1. Van den Broek KC**, Denollet J, Nyklícek I, van der Voort PH. Psychological reaction to potential malfunctioning of implantable defibrillators. Pacing Clin Electrophysiol 2006;29:953-6.

**2. Van den Broek KC**, Martens EJ, Nyklícek I, van der Voort PH, Pedersen SS. Increased emotional distress in type-D cardiac patients without a partner. J Psychosom Res 2007;63:41-9.

**3.** Pedersen SS, **Van den Broek KC**, Sears SF. Psychological intervention following implantation of an implantable defibrillator: a review and future recommendations. Pacing Clin Electrophysiol 2007;30:1546-54.

**4. Van den Broek KC**, Nyklíček I, Van der Voort P, Alings M, Denollet J. Shocks, personality, and anxiety in patients with an implantable defibrillator. Pacing Clin Electrophysiol, *in press*.

**5. Van den Broek KC**, Nyklíček I, Denollet J. Anxiety predicts poor perceived health in patients with an implantable defibrillator. Psychosomatics, *in press*.

***Other papers***

**1.** Denollet J, Smolderen KG, **Van den Broek KC**, Pedersen SS. The 10-item Remembered Relationship with Parents ($RRP^{10}$) scale: two-factor model and association with adult depressive symptoms. J Affect Disord 2007;100:179-89.

**2. Van den Broek KC**, Smolderen KG, Pedersen SS, Denollet J. Type D personality mediates the relationship between remembered parenting and perceived health. Psychosomatics, *in press*.

**3.** Pedersen SS, **Van den Broek KC**. ICD shocks and their adverse impact on patient-centered outcomes: Fact or Fiction? J Am Coll Cardiol, *in press*.

**4.** Smith ORF, **Van den Broek KC**, Renkens M, Denollet J. Fatigue levels in stroke patients as compared to end-stage heart failure patients: Application of the Fatigue Assessment Scale. J Am Geriatrics Society, *in press*.

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Krista van den Broek was born on April 17th, 1978 in Zundert, the Netherlands. She completed her pre-university education at the Mencia de Mendoza Lyceum in Breda, the Netherlands, in 1996. From 1996 to 2001, she studied psychology at Tilburg University, with a specialization in clinical health psychology. Her research internship was conducted at the Cardiac Rehabilitation Center of the University Hospital of Antwerp, Belgium. From 2001 to 2004 she worked as a budget consultant for several Debt and Budget Advisory Units. In 2004, she returned to Tilburg University to start her PhD research on psychological factors in implantable defibrillator treatment. She published several papers in *Pacing and Clinical Electrophysiology*. In addition, she presented her research at international conferences, including the *International Conference on the (Non)Expression of Emotions in Health and Disease* in Tilburg, the Netherlands, and the *Annual Scientific Meetings of the American Psychosomatic Society*, for example, in Baltimore, MD, USA, where she won an APS scholar award. Currently, she is working as a postdoctoral researcher at the Center of Research on Psychology in Somatic diseases (C*o*RPS), Tilburg University, the Netherlands.