Towards a comprehensive understanding of patients with an implantable cardioverter-defibrillator

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A biopsychosocial approach

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A BIOPSYCHOSOCIAL APPROACH

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PARANIMFEN

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General introduction and outline of the dissertation

1

Sudden cardiac death

Sudden cardiac death (SCD) refers to an unexpected natural death due to a cardiac cause that is usually attributed to a very fast heart rhythm caused by an electrical disturbance of the heart.[1] Ventricular tachycardia (VT) refers to an accelerated rhythm of >100 beats per minute in the heart's ventricles. VT often results in a reduced pump function of the heart, which causes symptoms such as dizziness, lightheadedness, and heart beat sensations that feel like pounding.[2] VT can deteriorate into ventricular fibrillation (VF), with quick, chaotic electrical impulses causing the ventricles to contract in an asynchronous manner. This leads to insufficient blood flow to vital organs and to sudden cardiac arrest, and eventually to SCD if left untreated (**Figure 1**). SCD may occur in individuals with or without preexisting cardiovascular disease, although many have a previous cardiac history, and may have experienced an acute myocardial infarction (MI), a cardiac arrest or suffer from severe heart failure.[2]

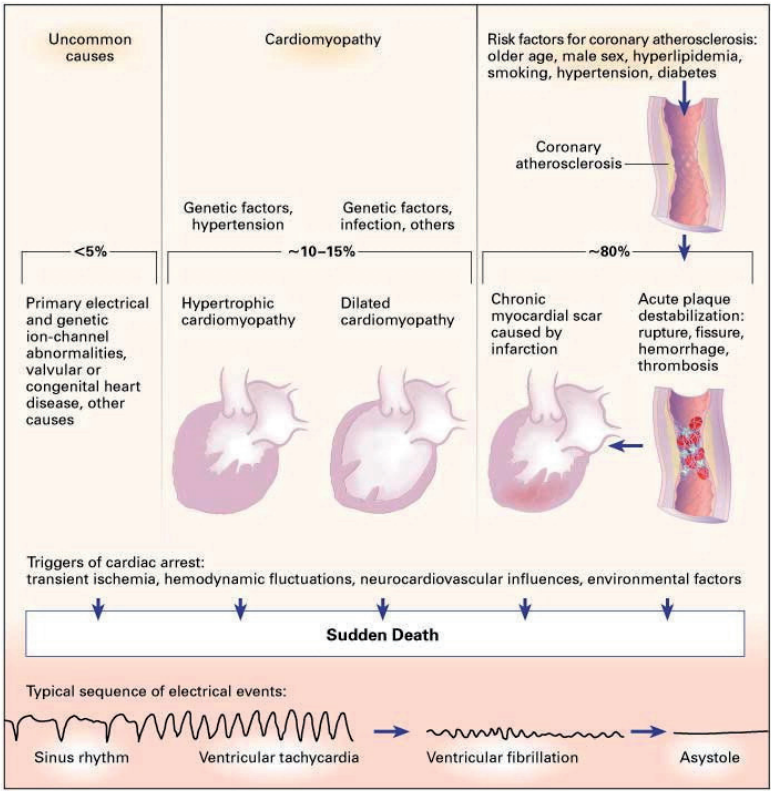

Figure 1. Pathophysiology and epidemiology of sudden death from cardiac causes
Reproduced with permission from Huikuri HV, Castellanos A & Myerburg RJ. Sudden death due to cardiac arrhythmias. New England Journal of Medicine 2001;345(20):1473-1482.

The incidence of SCD varies between countries and depends on the definition used, but recent prospective studies have shown worldwide annual incidences ranging from 50-100 per 100.000 in the general population.[3-5] Due to improved primary and secondary prevention, the mortality risk due to coronary heart disease (CHD) has declined considerably during the past decades,[6,7] while mortality rates due to SCD remain high.[8,9] Still more than 50% of all CHD deaths are caused by SCD, and SCD accounts for 15-20% of all deaths, which emphasizes the importance of adequate measures to prevent SCD.[1]

The implantable cardioverter-defibrillator – a continuously evolving field

In the late 1960s, the development of the implantable cardioverter-defibrillator (ICD) was pioneered by Michel Mirowski, as he was frustrated by lack of available treatment options for a close friend who had been admitted to hospital with recurrent VTs. He envisaged the implantation of a continuous guard of the cardiac rhythm that could deliver defibrillation in the event of VT/VF. After building and refining experimental models during the 1970s, the first human cardiac electronic device was implanted in 1980 in a patient who had suffered two previous cardiac arrests.[10,11] While the ICD at first was limited to patients with documented cardiac arrest due to VF and was only implanted in a small number of centers, the United States Food and Drug Administration (FDA) approved the use of commercial devices in 1985.[10] This was the start of a revolutionary treatment for the prevention of SCD that has continued to evolve.

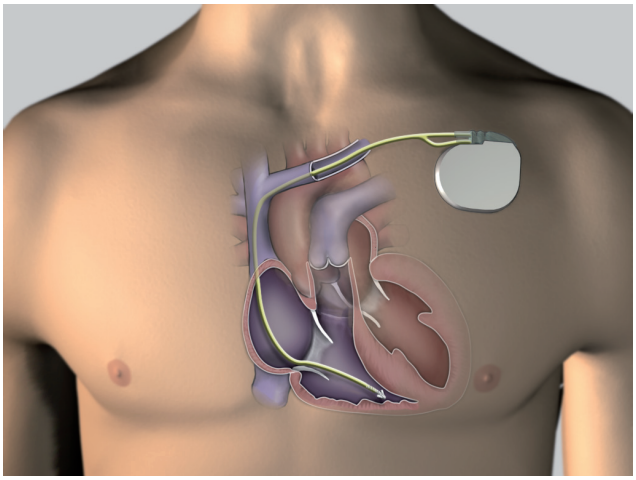

Figure 2. The transvenous implantable cardioverter-defibrillator[12]

The ICD is an electronic device that is implanted right under the skin in the pectoral area, where it continuously monitors the heart rhythm **(Figure 2)**. Detection of VTs is based on information derived from the high-voltage defibrillation lead placed in the right ventricle. Therapies for VTs are delivered by this lead as well. In case of a potentially life-threatening tachyarrhythmia, the ICD can offer three types of treatment: antitachycardia pacing (ATP), cardioversion (a low energy shock), or

defibrillation (a high energy shock up to 800 volts). VTs are usually treated by means of ATP, with cardioversion as back-up therapy in case of non-successful ATP. VF on the contrary, is generally directly treated with defibrillation.[10]

In addition to tachyarrhythmia treatment, a small number of patients are estimated to need additional bradycardia pacing (i.e. rhythm control when the heart beats too slow).[13] In patients suffering from chronic heart failure (CHF), a debilitating disease characterized by symptoms of tiredness, shortness of breath and peripheral and/or lung edema due to structural or functional abnormality of the heart, an ICD with additional resynchronizing capacities (the cardiac resynchronization therapy device or CRT-D) may be indicated.[14] CHF affects cardiac conduction pathways in approximately 30% of the cases, by causing a delayed depolarization of the ventricles.[15] This can lead to disruption of the regular and simultaneous innervation of the ventricles, which may further deteriorate the already impaired ejection fraction of patients with CHF.[16] CRT facilitates synchronous innervation by simultaneously pacing both ventricles via at least two leads: one in the right ventricle and one inserted through the coronary sinus to pace the left ventricle.

Due to the potentially disabling complications that can result from transvenous leads, an entirely subcutaneous ICD system (S-ICD, **Figure 3**) has recently been developed, which is unlikely to be the last development in this continuously evolving field.[17]

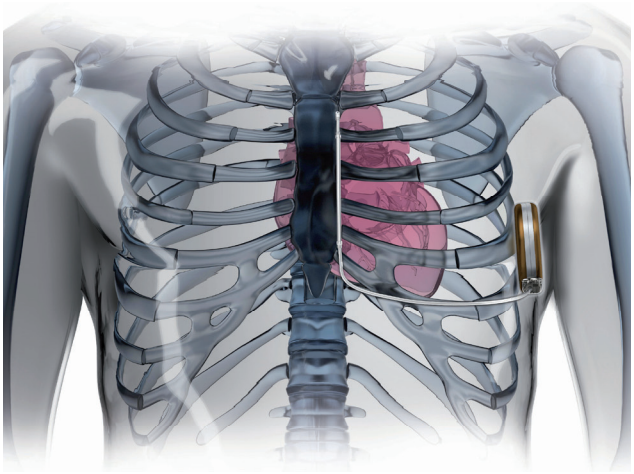

Figure 3. The subcutaneous implantable cardioverter-defibrillator

Initially, the ICD was only indicated as a secondary prevention measure in patients who had experienced a sudden cardiac arrest. A meta-analysis of three large scale secondary prevention trials (the Antiarrhythmics Versus Implantable Defibrillator (AVID) trial, the Cardiac Arrest Study Hamburg (CASH) and the Canadian Implantable Defibrillator Study (CIDS)) has shown that the ICD is superior in reducing the risk of mortality, with a relative risk reduction of 28% as compared to antiarrhythmic

drugs. This improved prognosis was almost entirely attributed to a 50% risk reduction in arrhythmic death.[18] Throughout the years, however, the indications for ICD therapy have expanded to include also primary prevention of SCD. Patients with a primary prevention prophylaxis have not previously experienced a sudden cardiac arrest or suffered from symptomatic VTs, but are considered at higher risk due to depressed left ventricular function based on ischemic or non-ischemic cardiomyopathy. Recently, genetic disorders, such as long QT syndrome or Brugada syndrome, have also been included as an indication for a primary prophylactic ICD. The beneficial effect of ICD implantation for primary prevention in the reduction of all-cause mortality has been demonstrated in several randomized clinical trials (i.e. the Multicenter Automatic Defibrillator Implantation Trial (MADIT) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)).[19,20] Several meta-analyses confirmed the reduction in all-cause mortality by ICD implantation compared to optimal medical treatment, with mortality reductions up to 26% in patients at high risk of SCD.[21-24]

Medical challenges for patients with an ICD

Despite the evident benefits of the ICD in terms of prevention of SCD, ICD patients may face several challenges in the phase around implantation and later on. Procedure- and device-related complications occur both on the short- and long-term, including pocket infections, hematomas, lead dislodgement and lead fractures.[25,26] Patients experiencing a lead complication are at risk for electrical storm, i.e. multiple recurrences of ventricular arrhythmias over a short period of time. In addition, ICD hardware malfunction could lead to inappropriate sensing, with resultant inappropriate shocks.[25] Next to the challenges of the ICD itself, the underlying heart disease may have a considerable impact on patients, with for example reduced ejection fraction negatively impacting on daily functioning. Moreover, a substantial number of ICD patients has experienced a previous cardiac event, such as myocardial infarction or sudden cardiac arrest, and are currently suffering from CHF and other comorbid conditions such as hypertension, peripheral arterial disease, diabetes, renal failure and respiratory disease.[27] Thus, complications,[28] underlying heart disease and non-cardiac comorbidities[27] all pose patients at increased risk of morbidity and mortality.

Psychological functioning of patients with an ICD

After implantation, ICD patients are faced not only with medical challenges, but also have to overcome both the stress of possibly having experienced a life-threatening arrhythmia (in case of a secondary prevention indication) and get used to the presence of the ICD as well.[29] Although the majority of patients with an ICD adjusts well to living with the ICD,[29,30] emotional distress is not uncommon, with a recent review indicating that approximately one in five (i.e. 20%) patients experience emotional distress that might affect not only their daily functioning but may also increase the risk of morbidity and mortality despite state-of-the-art treatment with an ICD.[31,32] This prevalence is similar to the prevalence of emotional distress in other cardiac populations[31] and somewhat higher than the prevalence of emotional distress in the general population.[33] Because of the unpredictable course of arrhythmias and the uncontrollability of shocks, anxiety plays a leading role in ICD patients, with prevalence rates ranging from 13-87% for anxiety, versus 5-41%

reported for depression.[29,31,34,35] Most likely related to the occurrence of shocks post implantation, posttraumatic stress symptoms occur in approximately 10-20% of patients (versus a prevalence of 8% in the general population).[36-38] Notably, patients who experience a sudden cardiac arrest outside the hospital setting report an even higher prevalence of posttraumatic stress.[39]

Several medical and patient factors have been associated with emotional distress and patient well-being in the arrhythmia literature. Among the patient factors, these include personality, pre implantation distress, coping and social support.[38,40-42] Among the medical factors, the occurrence of shocks is often mentioned as primary culprit of emotional distress and poor quality of life,[43-45] although the influence of shocks may depend on the interval between the shock and when distress was assessed.[46] Patients' perceptions of the ICD and shocks vary considerably, with some patients describing the ICD as a live-saving device, while a smaller group indicates that they would rather be without the defibrillator and take their chances with a potentially lethal arrhythmia. There is also variability in patients' pain perception of shocks, although 80% of patients rate the shock-associated pain as 3 or higher on a 1 to 5 scale.[47] Besides shocks, the underlying heart disease, in particular symptomatic heart failure, influences the well-being of patients, possibly playing a more prominent role than the ICD itself and the occurrence of shocks.[48,49] With ICD patients often using multiple medications to control their heart disease, it is important to investigate the relation between cardiac medication use and emotional distress. With respect to the use of beta-blockers and statins, results within the general cardiac population are mixed, with some studies reporting a positive association between beta-blocker[50] and statin use[51] and the presence of emotional distress, while other studies do not find such a relationship[52-54] or even report a protective effect.[55-57] Importantly, evidence in patients with an ICD is lacking. Furthermore, as mentioned previously, ICD patients often suffer from multiple comorbid conditions, which may hamper their daily functioning and influence psychological well-being. Unfortunately, evidence on the impact of comorbidities on emotional distress in ICD patients is absent. In sum, gaps in knowledge exist on the relation between medical factors, including complications around and post implantation, the use of medication and the presence of comorbid conditions, and emotional distress in ICD patients. These gaps should be bridged by future research in order to optimize the care and management of ICD patients in clinical practice.

Psychological functioning and clinical outcomes

The importance of psychological factors in heart disease has recently been endorsed in the European Guidelines on prevention of cardiovascular disease, with even stronger levels of evidence for psychological factors as risk factors for cardiovascular disease than for example the evidence for biomarkers or genetic factors.[58] Accumulating evidence suggests that psychological factors, such as depression, anxiety, mood disturbance, anger and personality, are associated with an increased risk of ventricular arrhythmias and mortality.[32,59,60] However, whether psychological factors increase the risk of worse clinical outcomes in their own right or whether they are risk markers of underlying mechanisms or disease severity is not yet known.

Explaining the link between emotional distress and clinical outcomes

Several bodily systems have been proposed as pathways that may explain the relationship between emotional distress and clinical outcomes (i.e. ventricular arrhythmias or mortality). Among these are the immune system, the hypothalamic-pituitary-adrenal (HPA) axis, and the autonomic nervous system. However, there is a knowledge gap in the arrhythmia literature regarding these potential explanatory pathways, with only a few studies investigating autonomic measures in relation to psychology and disease.

The role of the autonomic nervous system in the unhealthy heart

Being part of the peripheral nervous system, the ANS regulates a number of vital unconscious processes, including cardiac functioning. The ANS is connected with the heart via sympathetic and parasympathetic nerve branches. Activation of sympathetic neurons has a stimulating effect on the heart and circulatory system, resulting in increased heart rate, contractility and conduction speed, while activation of the parasympathetic neurons has an opposite, inhibiting effect on the heart.[61]

The autonomic nervous system has an important share in the generation and maintenance of ventricular arrhythmias, during which a shift from a sympatho-vagal balance to sympathetically dominated innervation is observed.[62] Several factors have been proposed as triggering or causal factors of ventricular arrhythmias, including a prolonged action potential, alterations in calcium homeostasis that account for abnormalities in excitation-contraction coupling, abnormal conduction of signals along the heart, the presence of coronary artery disease (CAD), altered neurohumoral signaling, including alterations in the adrenergic and renin-angiotensin-aldosterone system (RAAS), and genetic predisposition.[62,63]

Heart rate variability – a measure of autonomic control

Heart rate variability (HRV) is the oscillation in the time interval between consecutive heart beats and is a widely used measure of autonomic control.[64,65] HRV can be measured with Holter monitoring during which the electrical activity of the heart is monitored and registered. Variation in heart rate may be assessed by a number of methods.

First, time domain measures can be used. These measures are based on the normal-to-normal (NN) intervals, that is all intervals between adjacent QRS complexes resulting from sinus node depolarizations.[65] Time domain measures include the standard deviation of all normal-to-normal (NN) intervals (SDNN) and the HRV triangular index, both reflecting overall variability in heart rate (HR), the standard deviation of the average NN interval calculated over 5-minute periods (SDANN), as an estimate of long-term components of HRV, the proportion of NN intervals deviating >50 ms from the preceding interval (pNN50), and the root mean square of successive differences in NN intervals (RMSSD), both specifically reflecting parasympathetic efferent activity to the heart.[65,66] Second, power spectral analysis using Fast Fourier Transformation reveals frequency domain measures, including total spectral power, representing the total variance in HR pattern, high frequency (HF) HRV, describing parasympathetic modulation of heart rate, low frequency (LF), representing both sympathetic and parasympathetic modulation of the heart, very low frequency (VLF), displaying

long-term influences such as hormones, and ultra-low frequency (ULF), another long-term measure of HRV.[65] Next to these separate measures, the LF/HF ratio is used as an indicator of sympatho-vagal balance, although the evidence on the exact meaning of this measure is yet inconclusive.[67] Disturbed autonomic functioning, expressed by increased sympathetic and decreased parasympathetic innervation, is a strong predictor of cardiovascular events,[68-70] and in patients with an ICD, abnormal HRV patterns have been reported in the minutes before arrhythmia onset.[71]

Emotional distress, including symptoms or clinical syndromes of depression, anxiety, and posttraumatic stress disorder (PTSD), has been associated with disturbed heart rate variability in both people with and without cardiac disease. In the general population, reduced HRV has been found in patients with major depressive disorder (MDD) and/or anxiety disorders.[72-76] In the cardiac population, depression and anxiety are associated with reduced HRV in various subgroups of cardiac patients,[77-82] although there may be confounding mechanisms, such as use of antidepressants, physical activity and fitness, that warrant further examination.[74,75,83] Results with respect to PTSD are less clear, with some studies in the general population showing a reduced HRV,[84,85] while others have reported inconsistent results[86,87] or even no differences[88,89] in HRV between individuals with and without PTSD. The relationship between emotional distress and HRV in ICD patients remains understudied, with only one study reporting of a reduced parasympathetic modulation of the heart in patients with an ICD.[90]

The partner of the ICD patient – a neglected companion

In the field of cancer research, a lot of attention has been paid to the well-being of patients' partners, showing that emotional distress in patients and partners is related, and couples tend to react to the disease as an emotional system instead of reacting as an individual.[91,92] This means that partners have an important share in the disease- and recovery process of the patient. However, research on this topic in the field of cardiology in general and ICD patients in particular is scarce. Available research shows that levels of emotional distress in partners may be as high as in patients.[93] Anxiety plays an important role in partners, for similar reasons as in ICD patients,[93,94] and the type of distress (e.g. anxiety versus depression) experienced by patients and partners concurs within the dyad.[95] The role of the partner is not only important from a psychological point of view, but also from a clinical perspective. Emotional distress in partners[96] and reduced marital quality[97] have been associated with poorer prognosis in patients with CHD. Thus, although some evidence exists on the importance of partners in the psychological and physical recovery process of the patient, it remains unknown how emotional distress of ICD patients and their partners correlates over time, and whether partners' levels of emotional distress influence patients' health status. In addition, no research to date has been performed on the association between emotional distress in partners and prognosis of patients with an ICD.

Aims and outline of this dissertation

All studies described in this dissertation have been based on the 'Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter-Defibrillator: A prospective

Study' (MIDAS) cohort. A consecutive series of 448 patients implanted with a first-time ICD at the Erasmus Medical Center, Rotterdam, the Netherlands and their partners, were enrolled in the study between August 2003 and February 2010 and completed questionnaires pre implantation and at 10 days, 3, 6 and 12 months post implantation. A subset of 82 patients from the MIDAS cohort participated in the MIDAS-HRV sub study. This subset of patients was hooked up to a Holter monitor at 10 days, 6 and 12 months post to measure 24-hour HRV. In addition to the Holter recordings, patients were asked to complete an activity diary in order to register eating, sleeping and activity patterns.

The current dissertation is divided into four parts. Part one discusses the association between medical treatment and clinical patient characteristics on the one hand and emotional distress on the other hand. In Part two, the interrelationship between emotional distress, the autonomic nervous system and prognosis is examined. Part three extends the image of the patient as a single actor to a dyadic system of ICD patients and their partners, examining the influence of partner distress on patient well-being and prognosis. The aims of Part four were to map out the process of information provision around ICD implantation, to evaluate patients' satisfaction about the information provided and to investigate whether information provision and patient satisfaction are associated with emotional distress. Furthermore, Part four examines whether proposed psycho-educational and psychological care is actually implemented in clinical practice. A schematic representation of the studies in this dissertation is presented in **Figure 4**.

Part one: Medical treatment, clinical characteristics and their association with emotional distress

So far, little research has been performed on the association between medical treatment and clinical patient characteristics on the one hand and emotional distress on the other hand in ICD patients. This part of the dissertation aims to give an overview of the interrelationship between medical and emotional status. In **Chapter 2**, the association between procedure- and device-related complications around implantation and psychological morbidity during 12 months post implantation is investigated. Although the number of complications is decreasing due to improved techniques and changes in the programming of the ICD, the occurrence of infections, lead dysfunction and inappropriate shocks cannot be fully prevented.

The ICD population is very heterogeneous and chronic medical comorbidity is a rule rather than an exception. **Chapter 3** discusses the relationship between medical comorbidity and both emotional distress and health status. Furthermore, as a consequence of comorbidities, ICD patients often use multiple types of medication in order to control their heart disease and accompanying conditions. **Chapters 4** and **5** therefore examine the associations between beta-blocker therapy and statin therapy, and emotional distress.

Part two: In search of a psychophysiological link between emotional distress and clinical outcomes: Autonomic nervous system function as a candidate mechanism

It is known that there is a link between emotional distress and clinical outcomes in patients with an ICD. However, the pathways that may explain these links received little attention. As one possible mechanism, the autonomic nervous system, with HRV as a specific index of autonomic function, is highlighted in this part of the dissertation. **Chapter 6** reviews the relation between several indicators of emotional distress and HRV measures over 24 hours, and during resting activity and sleep. In **Chapter 7** subsequently, the association between heart rate and mortality in ICD patients is investigated.

Part three: Looking beyond the scope of the patient: The impact of partners of ICD patients

Instead of looking at the patient as a single actor solely responsible for his or her emotional status, partners should be incorporated in research on psychological functioning and treatment of ICD patients. Hence, in Part three, **Chapter 8** examines the interrelationship between emotional distress of patients and their partners and its influence on patients' health status. As little is known about the prognostic impact of partners' emotional distress on patients' survival, this will be examined in **Chapter 9**.

Part four: Inside the consulting room – helping the patient to get back on track

When it comes to medical psychology, scientific research and clinical practice should always be intertwined, indissoluble fields. With this fourth part, a further attempt is made to consolidate the bridge between research and practice. Since education about treatment with an ICD and what to expect, including potential psychological consequences, have been shown to influence patients' adaptation to living with an ICD,[98-100] the process of information provision around implantation and patients' satisfaction with this process is evaluated in **Chapter 10**. The relation between information provision, satisfaction and emotional distress in patients is also described in this chapter. Given that screening for emotional distress and periodic monitoring of distress in patients with an ICD is not yet part of standard clinical practice, there is a need for studies that elucidate whether patients receive adequate treatment for their distress and if not what the potential consequences might be. Hence, **Chapter 11** examines the frequency of psychological treatment in ICD patients and the influence of undertreatment of emotional distress on patients' health status.

The main findings of this dissertation will be discussed in **Chapter 12**. In this chapter, recommendations for future research and clinical practice will be outlined as well.

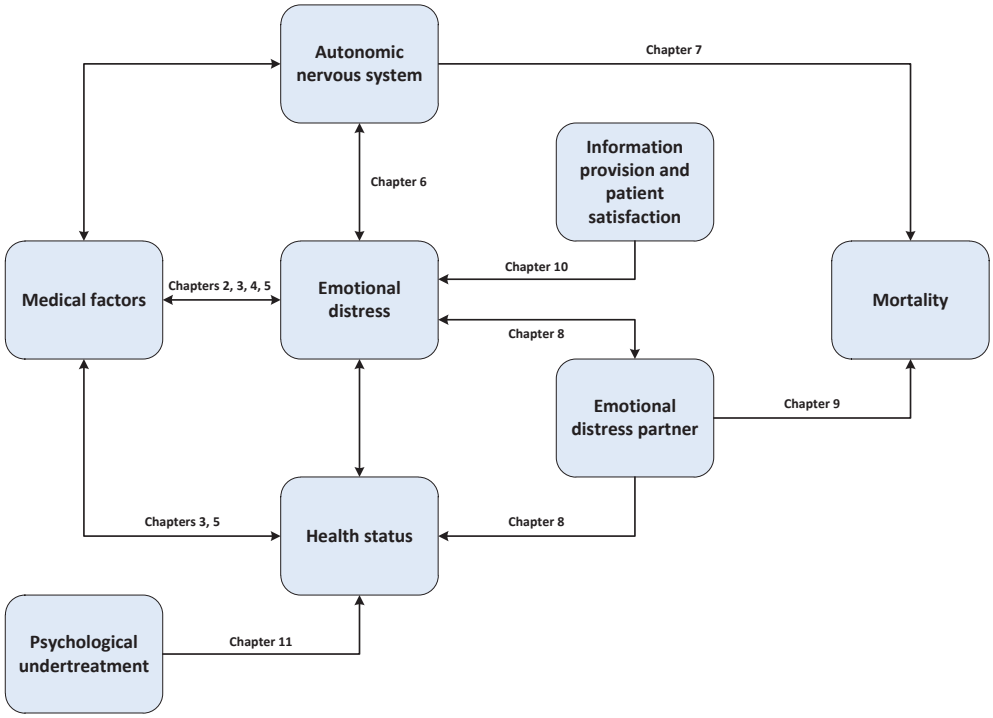

Figure 4. Schematic representation of studies in this dissertation.
Numbers indicate the relating chapters.

REFERENCES

1. Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. Circulation 2012; 125(4):620-637.
2. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death): Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006; 114(10):e385-e484.
3. Kong MH, Fonarow GC, Peterson ED, Curtis AB, Hernandez AF, Sanders GD, Thomas KL, Hayes DL, Al-Khatib SM. Systematic review of the incidence of sudden cardiac death in the United States. J Am Coll Cardiol 2011; 57(7):794-801.
4. De Vreede-Swagemakers JJM, Gorgels APM, Dubois-Arbouw WI, Van Ree JW, Daemen MJAP, Houben LGE, Wellens HJJ. Out-of-hospital cardiac arrest in the 1990s: A population-based study in the Maastricht area on incidence, characteristics and survival. J Am Coll Cardiol 1997; 30(6):1500-1505.
5. Hua W, Zhang L-F, Wu Y-F, Liu X-Q, Guo D-S, Zhou H-L, Gou Z-P, Zhao L-C, Niu H-X, Chen K-P, Mai J-Z, Chu L-N, Zhang S. Incidence of sudden cardiac death in China: Analysis of 4 regional populations. J Am Coll Cardiol 2009; 54(12):1110-1118.
6. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, Giles WH, Capewell S. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. N Engl J Med 2007; 356(23):2388-2398.
7. Finegold JA, Asaria P, Francis DP. Mortality from ischaemic heart disease by country, region, and age: Statistics from World Health Organisation and United Nations. Int J Cardiol 2013; 168(2):934-945.
8. Fox CS, Evans JC, Larson MG, Kannel WB, Levy D. Temporal trends in coronary heart disease mortality and sudden cardiac death from 1950 to 1999: The Framingham Heart Study. Circulation 2004; 110(5):522-527.
9. Dudas K, Lappas G, Stewart S, Rosengren A. Trends in out-of-hospital deaths due to coronary heart disease in Sweden (1991 to 2006). Circulation 2011; 123(1):46-52.
10. Glikson M, Friedman PA. The implantable cardioverter defibrillator. Lancet 2001; 357(9262):1107-1117.
11. Mirowski M, Reid PR, Mower MM, Watkins L, Gott VL, Schauble JF, Langer A, Heilman MS, Kolenik SA, Fischell RE, Weisfeldt ML. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. N Engl J Med 1980; 303(6):322-324.
12. http://mylifewithdilatedcardiomyopathy.blogspot.nl/2011/10/heart-failure-in-decline.html
13. Dewland TA, Pellegrini CN, Wang Y, Marcus GM, Keung E, Varosy PD. Dual-chamber implantable cardioverter-defibrillator selection is associated with increased complication rates and mortality among patients enrolled in the NCDR implantable cardioverter-defibrillator registry. J Am Coll Cardiol 2011; 58(10):1007-1013.
14. McMurray JJV, Pfeffer MA. Heart failure. Lancet 365(9474):1877-1889.
15. Farwell D, Patel NR, Hall A, Ralph S, Sulke AN. How many people with heart failure are appropriate for biventricular resynchronization? Eur Heart J 2000; 21(15):1246-1250.
16. Littmann L, Symanski JD. Hemodynamic implications of left bundle branch block. J Electrocardiol 2000; 33(Suppl):115-121.
17. Bardy GH, Smith WM, Hood MA, Crozier IG, Melton IC, Jordaens L, Theuns DAMJ, Park RE, Wright DJ, Connelly DT, Fynn SP, Murgatroyd FD, Sperzel J, Neuzner J, Spitzer SG, Ardashev AV, Oduro A, Boersma L, Maass AH, Van Gelder IC, Wilde AA, van Dessel PF, Knops RE, Barr CS, Lupo P, Cappato R, Grace AA. An entirely subcutaneous implantable cardioverter–defibrillator. N Engl J Med 2010; 363(1):36-44.
18. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, Greene HL, Boczor S, Domanski M, Follmann D, Gent M, Roberts RS. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics Vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg . Canadian Implantable Defibrillator Study. Eur Heart J 2000; 21(24):2071-2078.
19. Moss A, Hall W, Cannom D, Daubert J, Higgins S, Klein H, Levine J, Saksena S, Waldo A, Wilber D. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med 1996; 335(26):1933-1940.
20. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005; 352(3):225-237.

21. Nanthakumar K, Epstein AE, Kay GN, Plumb VJ, Lee DS. Prophylactic implantable cardioverter-defibrillator therapy in patients with left ventricular systolic dysfunction: A pooled analysis of 10 primary prevention trials. J Am Coll Cardiol 2004; 44(11):2166-2172.
22. Lee DS, Green LD, Liu PP, Dorian P, Newman DM, Grant FC, Tu JV, Alter DA. Effectiveness of implantable defibrillators for preventing arrhythmic events and death: A meta-analysis. J Am Coll Cardiol 2003; 41(9):1573-1582.
23. Ezekowitz JA, Rowe BH, Dryden DM, Hooton N, Vandermeer B, Spooner C, McAlister FA. Systematic review: Implantable cardioverter defibrillators for adults with left ventricular systolic dysfunction. Ann Intern Med 2007; 147(4):251-262.
24. Theuns DAMJ, Smith T, Hunink MGM, Bardy GH, Jordaens L. Effectiveness of prophylactic implantation of cardioverter-defibrillators without cardiac resynchronization therapy in patients with ischaemic or non-ischaemic heart disease: A systematic review and meta-analysis. Europace 2010; 12(11):1564-1570.
25. Tung R, Zimetbaum P, Josephson ME. A critical appraisal of implantable cardioverter-defibrillator therapy for the prevention of sudden cardiac death. J Am Coll Cardiol 2008; 52(14):1111-1121.
26. Hauser RG, Maisel WH, Friedman PA, Kallinen LM, Mugglin AS, Kumar K, Hodge DO, Morrison TB, Hayes DL. Longevity of Sprint Fidelis implantable cardioverter-defibrillator leads and risk factors for failure: Implications for patient management. Circulation 2011; 123(4):358-363.
27. Lee DS, Tu JV, Austin PC, Dorian P, Yee R, Chong A, Alter DA, Laupacis A. Effect of cardiac and noncardiac conditions on survival after defibrillator implantation. J Am Coll Cardiol 2007; 49(25):2408-2415.
28. Sohail MR, Henrikson CA, Braid-Forbes M, Forbes KF, Lerner DJ. Mortality and cost associated with cardiovascular implantable electronic device infections. Arch Intern Med 2011; 171(20):1821-1828.
29. Sears SF, Conti JB. Quality of life and psychological functioning of ICD patients. Heart 2002; 87(5):488-493.
30. Matchett M, Sears SF, Hazelton G, Kirian K, Wilson E, Nekkanti R. The implantable cardioverter defibrillator: Its history, current psychological impact and future. Expert Rev Med Devices 2009; 6(1):43-50.
31. Magyar-Russell G, Thombs BD, Cai JX, Baveja T, Kuhl EA, Singh PP, Montenegro Braga Barroso M, Arthurs E, Roseman M, Amin N, Marine JE, Ziegelstein RC. The prevalence of anxiety and depression in adults with implantable cardioverter defibrillators: A systematic review. J Psychosom Res 2011; 71(4):223-231.
32. Pedersen SS, Brouwers C, Versteeg H. Psychological vulnerability, ventricular tachyarrhythmias and mortality in implantable cardioverter defibrillator patients: Is there a link? Expert Rev Med Devices 2012; 9(4):377-388.
33. Kessler RC, Chiu W, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62(6):617-627.
34. Cho E-YN, von Känel R, Marten-Mittag B, Ronel J, Kolb C, Baumert J, Ladwig K-H. Determinants and trajectory of phobic anxiety in patients living with an implantable cardioverter defibrillator. Heart 2012; 98(10):806-812.
35. Pedersen SS, Theuns DAMJ, Jordaens L, Kupper N. Course of anxiety and device-related concerns in implantable cardioverter defibrillator patients the first year post implantation. Europace 2010; 12(8):1119-1126.
36. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the national comorbidity survey. Arch Gen Psychiatry 1995; 52(12):1048-1060.
37. Von Känel R, Baumert J, Kolb C, Cho E-YN, Ladwig K-H. Chronic posttraumatic stress and its predictors in patients living with an implantable cardioverter defibrillator. J Affect Disord 2011; 131(1-3):344-352.
38. Versteeg H, Theuns DAMJ, Erdman RAM, Jordaens L, Pedersen SS. Posttraumatic stress in implantable cardioverter defibrillator patients: The role of pre-implantation distress and shocks. Int J Cardiol 2011; 146(3):438-439.
39. Ladwig K-H, Baumert J, Marten-Mittag B, Kolb C, Zrenner B, Schmitt C. Posttraumatic stress symptoms and predicted mortality in patients with implantable cardioverter-defibrillators: Results from the prospective living with an implanted cardioverter-defibrillator study. Arch Gen Psychiatry 2008; 65(11):1324-1330.
40. Pedersen SS, Van Domburg RT, Theuns DAMJ, Jordaens L, Erdman RAM. Type D personality is associated with increased anxiety and depressive symptoms in patients with an implantable cardioverter defibrillator and their partners. Psychosom Med 2004; 66(5):714-719.
41. Graven LJ, Grant J. The impact of social support on depressive symptoms in individuals with heart failure: Update and review. J Cardiovasc Nurs 2012;
42. Trivedi RB, Blumenthal JA, O'Connor C, Adams K, Hinderliter A, Dupree C, Johnson K, Sherwood A. Coping styles in heart failure patients with depressive symptoms. J Psychosom Res 2009; 67(4):339-346.

43. Jacq F, Foulldrin G, Savouré A, Anselme F, Baguelin-Pinaud A, Cribier A, Thibaut F. A comparison of anxiety, depression and quality of life between device shock and nonshock groups in implantable cardioverter defibrillator recipients. Gen Hosp Psychiatry 2009; 31(3):266-273.
44. Denollet J, Tekle FB, Pedersen SS, Van der Voort PH, Alings M, Van den Broek KC. Prognostic importance of distressed (Type D) personality and shocks in patients with an implantable cardioverter defibrillator. Int J Cardiol 2013; 167(6):2705-2709.
45. Pedersen SS, Tekle FB, Hoogwegt MT, Jordaens L, Theuns DAMJ. Shock and patient preimplantation Type D personality are associated with poor health status in patients with implantable cardioverter-defibrillator. Circ Cardiovasc Qual Outcomes 2012; 5(3):373-380.
46. Pedersen SS, Van den Broek KC, Van den Berg M, Theuns DAMJ. Shock as a determinant of poor patient-centered outcomes in implantable cardioverter defibrillator patients: Is there more to it than meets the eye? Pacing Clin Electrophysiol 2010; 33(12):1430-1436.
47. Ahmad M, Bloomstein L, Roelke M, Bernstein AD, Parsonnet V. Patients' attitudes toward implanted defibrillator shocks. Pacing Clin Electrophysiol 2000; 23(6):934-938.
48. Habibović M, Versteeg H, Pelle AJM, Theuns DAMJ, Jordaens L, Pedersen SS. Poor health status and distress in cardiac patients: The role of device therapy vs. underlying heart disease. Europace 2013; 15(3):355-361.
49. Johansen JB, Pedersen SS, Spindler H, Andersen K, Nielsen JC, Mortensen PT. Symptomatic heart failure is the most important clinical correlate of impaired quality of life, anxiety, and depression in implantable cardioverter-defibrillator patients: A single-centre, cross-sectional study in 610 patients. Europace 2008; 10(5):545-551.
50. Luijendijk HJ, van den Berg JF, Hofman A, Tiemeier H, Stricker BH. Beta-blockers and the risk of incident depression in the elderly. J Clin Psychopharmacol 2011; 31(1):45-50.
51. Hyyppä MT, Kronholm E, Virtanen A, Leino A, Jula A. Does simvastatin affect mood and steroid hormone levels in hypercholesterolemic men? A randomized double-blind trial. Psychoneuroendocrinology 2003; 28(2):181-194.
52. Van Melle JP, Verbeek DEP, Van den Berg MP, Ormel J, Van der Linde MR, De Jonge P. Beta-blockers and depression after myocardial infarction: A multicenter prospective study. J Am Coll Cardiol 2006; 48(11):2209-2214.
53. Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. JAMA 2002; 288(3):351-357.
54. Stewart RA, Sharples KJ, North FM, Menkes DB, Baker J, Simes J. Long-term assessment of psychological well-being in a randomized placebo-controlled trial of cholesterol reduction with pravastatin. Arch Intern Med 2000; 160(20):3144-3152.
55. Baxter AJ, Spensley A, Hildreth A, Karimova G, O'Connell JE, Gray CS. Beta-blockers in older persons with heart failure: Tolerability and impact on quality of life. Heart 2002; 88(6):611-614.
56. Bulpitt CJ, Connor M, Schulte M, Fletcher AE. Bisoprolol and nifedipine retard in elderly hypertensive patients: Effect on quality of life. J Hum Hypertens 2000; 14(3):205-212.
57. Young-Xu Y, Chan KA, Liao JK, Ravid S, Blatt CM. Long-term statin use and psychological well-being. J Am Coll Cardiol 2003; 42(4):690-697.
58. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WMM, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvänne M, Scholte Op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F, guidelines Oewctpot, Cooney MT, Guidelines ECfP, Bax J, Baumgartner H, Ceconi C, Dean V, Fagard R, Funck-Brentano C, Hasdai D, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Ž, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Reviewers D, Aboyans V, Ezquerra EA, Baigent C, Brotons C, Burell G, Ceriello A, De Sutter J, Deckers J, Del Prato S, Diener HC, Fitzsimons D, Fras Z, Hambrecht R, Jankowski P, Keil U, Kirby M, Larsen ML, Mancia G, Manolis AJ, McMurray J, Pająk A, Parkhomenko A, Rallidis L, Rigo F, Rocha E, Ruilope LM, van der Velde E, Vanuzzo D, Viigimaa M, Volpe M, Wiklund O, Wolpert C. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). The fifth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2012; 33(17):2126.
59. Rumsfeld JS, Alexander KP, Goff DC, Graham MM, Ho PM, Masoudi FA, Moser DK, Roger VL, Slaughter MS, Smolderen KG, Spertus JA, Sullivan MD, Treat-Jacobson D, Zerwic JJ. Cardiovascular health: The importance of measuring patient-reported health status: A scientific statement from the American Heart Association. Circulation 2013; 127(22):2233-2249.

60. Van den Broek KC, Tekle FB, Habibović M, Alings M, Van der Voort PH, Denollet J. Emotional distress, positive affect, and mortality in patients with an implantable cardioverter defibrillator. Int J Cardiol 2013; 165(2):327-332.
61. Widmaier EP, Raff H, Strang KT, *Chapter 6: Neural signaling and the structure of the nervous system*, in *Vander's human physiology. The mechanisms of body function*. Widmaier EP, Raff H, Strang KT, Editors. 2008, McGraw-Hill: New York.
62. Tomaselli GF, Zipes DP. What causes sudden death in heart failure? Circ Res 2004; 95(8):754-763.
63. Elhendy A, Chapman S, Porter TR, Windle J. Association of myocardial ischemia with mortality and implantable cardioverter-defibrillator therapy in patients with coronary artery disease at risk of arrhythmic death. J Am Coll Cardiol 2005; 46(9):1721-1726.
64. Berntson GG, Thomas Bigger J, Eckberg DL, Grossman P, Kaufmann PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, Van Der Molen MW. Heart rate variability: Origins, methods, and interpretive caveats. Psychophysiology 1997; 34(6):623-648.
65. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. Circulation 1996; 93(5):1043-1065.
66. Ewing DJ, Neilson JM, Travis P. New method for assessing cardiac parasympathetic activity using 24 hour electrocardiograms. Br Heart J 1984; 52(4):396-402.
67. Goedhart AD, Willemsen G, Houtveen JH, Boomsma DI, De Geus EJC. Comparing low frequency heart rate variability and preejection period: Two sides of a different coin. Psychophysiology 2008; 45(6):1086-1090.
68. Chattipakorn N, Incharoen T, Kanlop N, Chattipakorn S. Heart rate variability in myocardial infarction and heart failure. Int J Cardiol 2007; 120(3):289-296.
69. Kotecha D, New G, Flather MD, Eccleston D, Pepper J, Krum H. Five-minute heart rate variability can predict obstructive angiographic coronary disease. Heart 2012; 98(5):395-401.
70. Kinoshita T, Asai T, Ishigaki T, Suzuki T, Kambara A, Matsubayashi K. Preoperative heart rate variability predicts atrial fibrillation after coronary bypass grafting. Ann Thorac Surg 2011; 91(4):1176-1181.
71. Lombardi F, Porta A, Marzegalli M, Favale S, Santini M, Vincenti A, De Rosa A. Heart rate variability patterns before ventricular tachycardia onset in patients with an implantable cardioverter defibrillator. Am J Cardiol 2000; 86(9):959-963.
72. Kemp AH, Quintana DS, Gray MA, Felmingham KL, Brown K, Gatt JM. Impact of depression and antidepressant treatment on heart rate variability: A review and meta-analysis. Biol Psychiatry 2010; 67(11):1067-1074.
73. Kemp AH, Quintana DS, Felmingham KL, Matthews S, Jelinek HF. Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: Implications for cardiovascular risk. PLoS One 2012; 7(2):e30777.
74. Licht CCM, De Geus EC, Zitman FG, Hoogendijk WG, Van Dyck R, Penninx BH. Association between major depressive disorder and heart rate variability in the Netherlands Study of Depression and Anxiety (NESDA). Arch Gen Psychiatry 2008; 65(12):1358-1367.
75. Licht CMM, de Geus EJC, van Dyck R, Penninx BWJH. Association between anxiety disorders and heart rate variability in the Netherlands Study of Depression and Anxiety (NESDA). Psychosom Med 2009; 71(5):508-518.
76. Pittig A, Arch JJ, Lam CWR, Craske MG. Heart rate and heart rate variability in panic, social anxiety, obsessive–compulsive, and generalized anxiety disorders at baseline and in response to relaxation and hyperventilation. Int J Psychophysiol 2013; 87(1):19-27.
77. Munk PS, Isaksen K, Brønnick K, Kurz MW, Butt N, Larsen AI. Symptoms of anxiety and depression after percutaneous coronary intervention are associated with decreased heart rate variability, impaired endothelial function and increased inflammation. Int J Cardiol 2012; 158(1):173-176.
78. Patron E, Messerotti Benvenuti S, Favretto G, Valfrè C, Bonfà C, Gasparotto R, Palomba D. Association between depression and heart rate variability in patients after cardiac surgery: A pilot study. J Psychosom Res 2012; 73(1):42-46.
79. Stapelberg NJ, Hamilton-Craig I, Neumann DL, Shum DH, McConnell H. Mind and heart: Heart rate variability in major depressive disorder and coronary heart disease - a review and recommendations. Aust N Z J Psychiatry 2012; 46(10):946-957.
80. Zimmermann-Viehoff F, Orth-Gomer K, Wang H-X, Deter H-C, Merswolken M, Ghadiyali Z, Weber CS. Depressive symptoms and heart rate variability in younger women after an acute coronary event. Eur J Cardiovasc Prev Rehabil 2010; 17(5):509-513.

81. Carney RM, Freedland KE. Depression and heart rate variability in patients with coronary heart disease. Cleve Clin J Med 2009; 76(Suppl 2):S13-S17.

82. Martens EJ, Nyklíček I, Szabó BM, Kupper N. Depression and anxiety as predictors of heart rate variability after myocardial infarction. Psychol Med 2008; 38(03):375-383.

83. Hughes JW, Casey E, Doe VH, Glickman EL, Stein PK, Waechter D, Josephson R, Rosneck J. Depression and heart rate variability in cardiac rehabilitation patients: Exploring the roles of physical activity and fitness. Percept Mot Skills 2010; 111(2):608-624.

84. Cohen H, Kotler M, Matar MA, Kaplan Z, Miodownik H, Cassuto Y. Power spectral analysis of heart rate variability in posttraumatic stress disorder patients. Biol Psychiatry 1997; 41(5):627-629.

85. Norte CE, Souza GGL, Vilete L, Marques-Portella C, Coutinho ESF, Figueira I, Volchan E. They know their trauma by heart: An assessment of psychophysiological failure to recover in PTSD. J Affect Disord 201; 150(1):136-141.

86. Hauschildt M, Peters MJV, Moritz S, Jelinek L. Heart rate variability in response to affective scenes in posttraumatic stress disorder. Biol Psychol 2011; 88(2–3):215-222.

87. Lee EAD, Theus SA. Lower heart rate variability associated with military sexual trauma rape and posttraumatic stress disorder. Biol Res Nurs 2012; 14(4):412-418.

88. Slewa-Younan S, Chippendale K, Heriseanu A, Lujic S, Atto J, Raphael B. Measures of psychophysiological arousal among resettled traumatized Iraqi refugees seeking psychological treatment. J Trauma Stress 2012; 25(3):348-352.

89. Tucker P, Pfefferbaum B, Jeon-Slaughter H, Khan Q, Garton T. Emotional stress and heart rate variability measures associated with cardiovascular risk in relocated Katrina survivors. Psychosom Med 2012; 74(2):160-168.

90. Francis JL, Weinstein AA, Krantz DS, Haigney MC, Stein PK, Stone PH, Gottdiener JS, Kop WJ. Association between symptoms of depression and anxiety with heart rate variability in patients with implantable cardioverter defibrillators. Psychosom Med 2009; 71(8):821-827.

91. Hagedoorn M, Sanderman R, Bolks HN, Tuinstra J, Coyne JC. Distress in couples coping with cancer: A meta-analysis and critical review of role and gender effects. Psychol Bull 2008; 134(1):1-30.

92. Moser MT, Künzler A, Nussbeck F, Bargetzi M, Znoj HJ. Higher emotional distress in female partners of cancer patients: Prevalence and patient–partner interdependencies in a 3-year cohort. Psychooncology 2013; 22(12):2693-2701.

93. Van den Broek KC, Habibović M, Pedersen SS. Emotional distress in partners of patients with an implantable cardioverter defibrillator: A systematic review and recommendations for future research. Pacing Clin Electrophysiol 2010; 33(12):1442-1450.

94. Sowell LV, Sears SFJ, Walker RL, Kuhl EA, Conti JB. Anxiety and marital adjustment in patients with implantable cardioverter defibrillator and their spouses. J Cardiopulm Rehabil Prev 2007; 27(1):46-49.

95. Van den Broek KC, Heijmans N, Van Assen MA. Anxiety and depression in patients with an implantable cardioverter defibrillator and their partners: A longitudinal study. Pacing Clin Electrophysiol 2013; 36(3):362-371.

96. Moser DK, Dracup K. Role of spousal anxiety and depression in patients' psychosocial recovery after a cardiac event. Psychosom Med 2004; 66(4):527-532.

97. Orth-Gomér K, Wamala SP, Horsten M, Schenck-Gustafsson K, Schneiderman N, Mittleman MA. Marital stress worsens prognosis in women with coronary heart disease: The Stockholm Female Coronary Risk Study. JAMA 2000; 284(23):3008-3014.

98. Vazquez LD, Conti JB, Sears SF. Female-specific education, management, and lifestyle enhancement for implantable cardioverter defibrillator patients: The FEMALE-ICD study. Pacing Clin Electrophysiol 2010; 33(9):1131-1140.

99. Dunbar SB, Langberg JJ, Reilly CM, Viswanathan B, McCarty F, Culler SD, O'Brien MC, Weintraub WS. Effect of a psychoeducational intervention on depression, anxiety, and health resource use in implantable cardioverter defibrillator patients. Pacing Clin Electrophysiol 2009; 32(10):1259-1271.

100. Eads AS, Sears SFJ, Sotile WM, Conti JB. Supportive communication with implantable cardioverter defibrillator patients: Seven principles to facilitate psychosocial adjustment. J Cardiopulm Rehabil Prev 2000; 20(2):109-114.

PART ONE

Medical treatment, clinical characteristics and their association with emotional distress

Procedure- and device-related complications and psychological morbidity in implantable cardioverter-defibrillator patients

2

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INTRODUCTION

Despite the unequivocal medical benefits of implantable cardioverter defibrillator (ICD) therapy for the prevention of sudden cardiac death,[1] there is a risk for procedure- (e.g. infection and bleeding) and device-related complications (e.g. inappropriate shocks and lead dysfunction).[2] Such complications may not only influence morbidity and mortality[3,4] but also patient well-being and quality of life.[2,5] To date, the majority of studies have focused on the separate impact of shocks and device advisories on patient well-being rather than procedure- and device-related complications, with results being mixed.[6,7]

METHODS

Patients and study design

We examined whether procedure- and device-related complications are associated with psychological morbidity in a consecutive cohort of ICD patients (N=443; *79% men; mean age*=58±12 *years) implanted between August 2003 and May 2010* at the Erasmus Medical Center, Rotterdam, the Netherlands, and *participating in the* Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter Defibrillator: A prospective Study (MIDAS).

Measures

Depression, anxiety and ICD concerns

Patients completed the 14-item Hospital Anxiety and Depression Scale (HADS)[8] and the 8-item ICD Patient Concerns questionnaire (ICDC)[9] at baseline, at 3, 6, and 12 months post implantation. Information on demographic and clinical characteristics was captured from the patients' medical records or purpose-designed questions. Information on ICD therapy during follow-up was obtained by means of device interrogation.

Statistical analyses

We used a composite of procedure- (i.e. any complication being directly or indirectly caused by the implantation procedure and occurring up to 30 days post implantation) and device-related complications (i.e. an event related to the implanted ICD system, including lead-related complications occurring also 30 days post implantation). Inappropriate and appropriate shocks were also considered as device-related complications; appropriate shocks were only included if the shock was given for a ventricular tachycardia (VT) with a cycle length >250 ms, as these rhythm disturbances essentially could have been terminated by antitachycardia pacing. Others have used a similar distinction between procedure- and device-related complications.[10,11] The association between procedure- and device-related complications and psychological morbidity was assessed with repeated measures univariable and multivariable analysis of variance using general linear mixed modeling analysis, with an unstructured covariance structure.

RESULTS

We found no systematic differences on baseline characteristics between patients with and without complications (all p>0.05). Of all patients, 70 (15.8%) experienced a complication, with 3 patients experiencing 2 complications during the 12 months follow-up, leading to a total complication rate of 73 (16.5%). Of these, 18 patients (4.1%) experienced a procedure-related complication, while 52 patients (11.7%) experienced a device-related complication (Table 1).

Table 1. Number and type of procedure- and device-related complications *

Complications	Type	N=73 (16.5%)
Procedure-related	Lead dislodgement (>30 days post implantation)	10 (2.2%)
	Hematoma	5 (1.1%)
	Infection	1 (0.2%)
	Pneumothorax	3 (0.7%)
Total		**18 (4.1%)**
Device-related	Lead dislodgement (>30 days post implantation)	7 (1.6%)
	Inadequate sensing	2 (0.4%)
	Non successful termination of VF	2 (0.4%)
	Inappropriate shock	19 (4.3%)
	Appropriate shock	22 (4.9%)
Total		**52 (11.7%)**
Non-device related	Pocket infection	2 (0.4%)
	Pericarditis	1 (0.2%)
Total		**3 (0.7%)**

* Results are presented as N (%); 3 patients had more than one event
Abbreviations: *N*, number; *VF*, ventricular fibrillation

The course of symptoms of anxiety and depression, and ICD concerns during the 12-month follow-up stratified by complications are displayed in Figure 1. In unadjusted analyses, there was a significant association between complications and anxiety (estimate (e)=1.15; p=.029) and ICD concerns (e=2.28; p=.019), but not with depression (e=0.99; p=.07). There was a significant time by complications interaction effect between baseline and 3 months follow-up for anxiety (e=1.41; p<.001), depression (e=0.51; p<.001), and ICD concerns (e=3.25; p<.001), indicating that patients with complications reported a slower decrease in psychological morbidity than patients without complications. In addition, a significant time by complications interaction effect was found between 3 and 6 months follow-up for ICD concerns (e=-0.93; p=.039), indicating that patients with complications reported a faster decrease in ICD concerns between 3 and 6 months post implantation than patients without complications. After adjusting for gender, type of implanted ICD, atrial fibrillation, symptomatic heart failure, coronary artery disease, appropriate shocks during follow-up with a cycle length <249 ms, and the use of beta-blockers, the associations between

complications and anxiety (e=1.15; p=.030) and between complications and ICD concerns (e=2.03; p=.038) remained significant. The relationship between complications and depression remained non significant (e=0.95; p=.08).

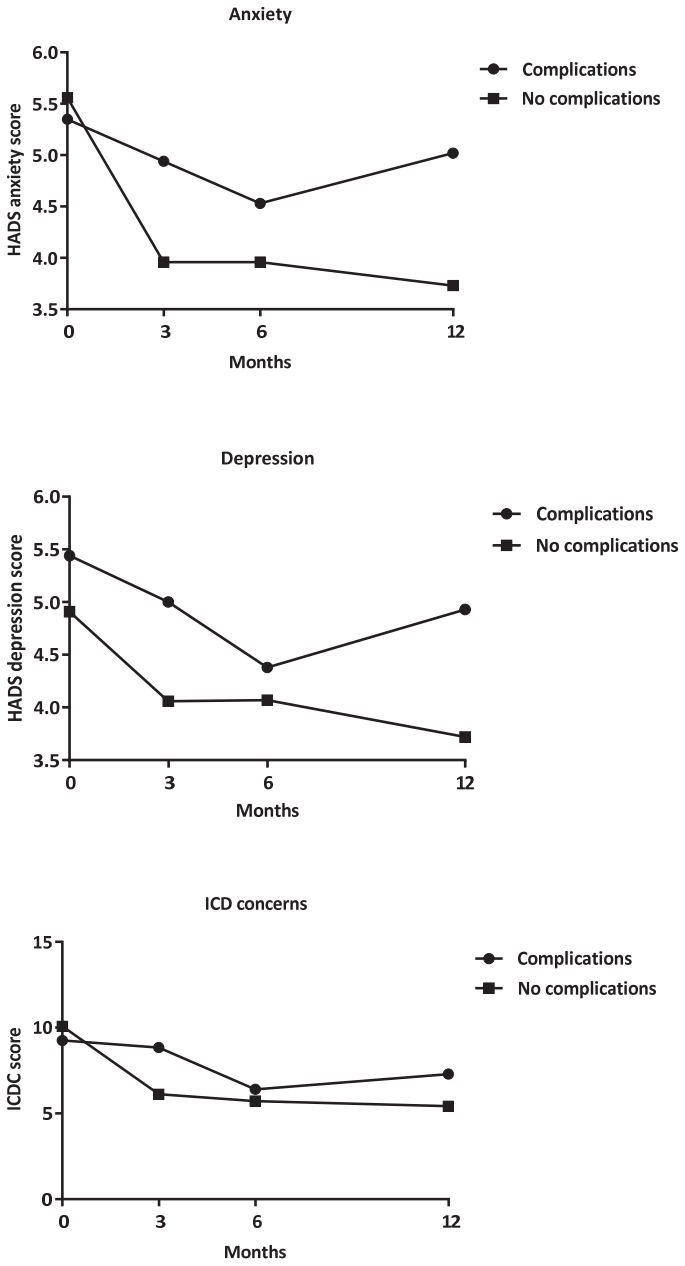

Figure 1. Association between a composite of procedure- and device-related complications and psychological morbidity at baseline, and at 3, 6 and 12 months post implantation*
* Presented as mean scores

DISCUSSION

To our knowledge, this is the first study to examine the impact of procedure- and device-related complications on psychological morbidity in ICD patients. Previous studies have examined the influence of complications on morbidity and mortality[3,4] and the separate impacts of shock and device advisories on patient well-being rather than procedure- and device-related complications, with results being mixed.[6,7] In the current study, patients experiencing a procedure- or device-related complication in the first 12 months post implant reported more anxiety and ICD concerns as compared to patients without complications, while no difference was found on depression. These analyses were adjusted statistically for a set of a priori determined potential demographic and clinical confounders, including appropriate shocks with a cycle length <249 ms. In clinical practice, ICD patients experiencing a complication should be monitored for symptoms of anxiety, as anxiety not only leads to impairments in quality of life but may also increase the risk of ventricular tachyarrhythmias and mortality independent of demographic and clinical risk factors.[12]

The limitations of this study should be acknowledged. Given the short-term follow-up, we do not know what the impact might be of complications on patient well-being long-term. Due to a complication rate of 15.8%, we were not able to examine whether different types of complications may exert a differential influence on outcome, as this would have required a larger sample size.

In conclusion, our findings show that ICD patients experiencing a procedure- or device-related complication in the first 12 months post implant may be at risk for anxiety and ICD concerns, while we found no impact on depression. Further studies are warranted that look at the impact of complications on patient well-being and psychological morbidity beyond 12 months, focusing on the impact of procedure- and device-related complications separately, as inappropriate shocks may have a larger influence than procedure-related complications. However, due to the application of new programming algorithms, the incidence of inappropriate shocks has decreased substantially, warranting large-scale studies to be able to elucidate this relationship, which might best be achieved by building in patient-reported assessments in current or new ICD registries.

REFERENCES

1. Ezekowitz JA, Armstrong PW, McAlister FA. Implantable cardioverter defibrillators in primary and secondary prevention: A systematic review of randomized, controlled trials. Ann Intern Med 2003;138(6):445-452.
2. Tung R, Zimetbaum P, Josephson ME. A critical appraisal of implantable cardioverter-defibrillator therapy for the prevention of sudden cardiac death. J Am Coll Cardiol 2008;52(14):1111-1121.
3. Sohail MR, Henrikson CA, Braid-Forbes M, Forbes KF, Lerner DJ. Mortality and cost associated with cardiovascular implantable electronic device infections. Arch Intern Med 2011;171(20):1821-1828.
4. Sweeney MO, Sherfesee L, DeGroot PJ, Wathen MS, Wilkoff BL. Differences in effects of electrical therapy type for ventricular arrhythmias on mortality in implantable cardioverter-defibrillator patients. Heart Rhythm 2010;7(3):353-360.
5. Pedersen SS, Tekle FB, Hoogwegt MT, Jordaens L, Theuns DAMJ. Shock and patient preimplantation Type D personality are associated with poor health status in patients with implantable cardioverter-defibrillator. Circ Cardiovasc Qual Outcomes 2012;5(3):373-380.
6. Pedersen SS, Van den Broek KC, Van den Berg M, Theuns DAMJ. Shock as a determinant of poor patient-centered outcomes in implantable cardioverter defibrillator patients: Is there more to it than meets the eye? Pacing Clin Electrophysiol 2010;33(12):1430-1436.
7. Pedersen SS, Versteeg H, Nielsen JC, Mortensen PT, Johansen JB. Patient-reported outcomes in Danish implantable cardioverter defibrillator patients with a Sprint Fidelis lead advisory notification. Europace 2011;13(9):1292-1298.
8. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67(6):361-370.
9. Pedersen SS, Van Domburg RT, Theuns DAMJ, Jordaens L, Erdman RAM. Concerns about the implantable cardioverter defibrillator: A determinant of anxiety and depressive symptoms independent of experienced shocks. Am Heart J 2005;149(4):664-669.
10. Lee DS, Krahn AD, Healey JS, Birnie D, Crystal E, Dorian P, Simpson CS, Khaykin Y, Carmeron D, Janmohamed A, Yee R, Austin PC, Chen Z, Hardy J, Tu JV. Investigators of the Ontario ICD database. Evaluation of early complications related to de novo cardioverter defibrillator implantation: Insights from the Ontario ICD database. J Am Coll Cardiol 2010;55(8):774-782.
11. Dewland TA, Pellegrini CN, Wang Y, Marcus GM, Keung E, Varosy PD. Dual-chamber implantable cardioverter-defibrillator selection is associated with increased complication rates and mortality among patients enrolled in the NCDR implantable cardioverter-defibrillator registry. J Am Coll Cardiol 2011;58(10):1007-1013.
12. Pedersen SS, Brouwers C, Versteeg H. Psychological vulnerability, ventricular tachyarrhythmias and mortality in implantable cardioverter defibrillator patients: Is there a link? Expert Rev Med Devices 2012;9(4):377-388.

Comorbidity burden is associated with poor psychological well-being and physical health status in patients with an implantable cardioverter-defibrillator

3

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ABSTRACT

Background: Comorbidity burden has been linked to survival in patients with an implantable cardioverter-defibrillator (ICD), but no study has examined the influence on psychological well-being and health status. We examined the relationship between comorbidity burden and anxiety, depression, and health status in patients with an ICD during the first 12 months post implantation using a prospective study design.

Methods: Consecutively implanted ICD patients (N=401; 78% men) completed the Hospital Anxiety and Depression Scale (HADS) and the Short Form Health Survey 36 (SF-36) at baseline, 3, 6, and 12 months post implantation. Data were analyzed using general linear mixed modeling repeated measures multivariable analysis of variance.

Results: The mean Charlson Comorbidity Index (CCI) score was 3.5 (±2.4). In adjusted analyses, comorbidity burden was significantly associated with depression (p=.003) and the physical health status domains of the SF-36 (physical functioning: p<.001; role limitations - physical: p=.023; bodily pain: p=.004; and general health: p=.025) but not with anxiety (p=.62) and the mental health status domains of the SF-36 (all p>.05). Chronic heart failure, chronic obstructive pulmonary disease (COPD), cerebrovascular disease and renal failure were the comorbidities with the most impact on depression and physical health status.

Conclusions: Comorbidity burden was a significant predictor of poorer psychological well-being and physical health status in ICD patients the first 12 months post implantation. In the care and management of ICD patients, it is important to recognize the impact of comorbidity burden on patients' mood and health status, and that adjunctive intervention may be warranted to enhance well-being.

INTRODUCTION

The implantable cardioverter-defibrillator (ICD) is the first-choice therapy for patients at risk for sudden cardiac death due to ventricular arrhythmias.[1,2] Despite the effectiveness of ICD therapy demonstrated in clinical trials, patients enrolled in clinical trials do not fully reflect ICD patients seen in the real-world clinical setting, due to the former being younger and having less comorbidities.[3] The presence of multiple comorbid conditions is associated with a poorer survival.[4-6] As a result of poorer physical functioning and increased problems in daily life, a higher number of comorbidities may also influence patients' psychological well-being, including symptoms of anxiety and depression, and health status.[6-8]

Monitoring psychological status of patients with multiple comorbidities is thus of utmost importance, in particular because the variability in clinical presentation and types of comorbidities present may hinder the detection of psychological distress.[9] To our knowledge, no previous study has examined the impact of comorbidities on the well-being and health status of ICD patients but rather tend to have focused on the impact of ICD therapy. In addition, as the population of ICD patients is very heterogeneous with patients receiving implantation for a wide range of indications, the risk of an increased comorbidity burden is high.

The purpose of the current study was to examine the association between patients' pre implantation Charlson Comorbidity Index (CCI) score, and anxiety, depression, and health status in patients with an ICD during the first 12 months post implantation using a prospective study design.

METHODS

Patients and study design

Between August 2003 and February 2010, 448 consecutive patients who were implanted with a first-time ICD in the Erasmus Medical Center, Rotterdam, the Netherlands, were enrolled in the Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter Defibrillator: A prospective Study (MIDAS). Patients with a life-expectancy of <1 year, being on the waiting list for heart transplantation, a history of psychiatric illness other than affective/anxiety disorders, or insufficient knowledge of the Dutch language were excluded. The study protocol was approved by the Medical Ethics Committee of the Erasmus Medical Center, and the study was conducted according to the Helsinki Declaration. An ICD nurse provided written and oral information on the study prior to ICD implantation. After obtaining written informed consent, patients were asked to complete a set of standardized and validated questionnaires at baseline (i.e. one day prior to implantation), and at 3, 6 and 12 months post implantation. Information on baseline demographic and clinical characteristics was extracted from patients' medical records and purpose-designed questions in the questionnaires.

Measures

Comorbidities and the Charlson Comorbidity Index

Information on comorbidities prior to ICD implantation was obtained via chart abstraction from the patients' medical records and laboratory values at baseline. Renal functioning was assessed by estimating the baseline glomerular filtration rate (eGFR), according to the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation.[10] In accordance with practice guidelines, an eGFR <60 mL/min/1.73 m^2 was considered as impaired renal functioning.[11] An abbreviated CCI score was composed with the following comorbid conditions: myocardial infarction (MI), congestive heart failure, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, peripheral vascular disease, renal failure, and any malignancy excluding metastatic tumors.[5] In order to obtain a comorbidity index that is in accordance with the original CCI, a weight of 2 was assigned to renal failure and any malignancy, and a weight of 1 to the other comorbid conditions.[12] By adding up the values assigned to each comorbid condition, a comorbidity score was calculated for each patient. Because age is a risk factor for mortality independent of the presence of comorbid conditions and the incidence of comorbidities increased with higher age in our sample, we adjusted the score by adding one point to the score for each decade of life over the age of 50 at time of study entry, according to the validated combined comorbidity index.[5,13] The advantage of this abbreviated index is that it reckons with the comorbid disorders most prevalent in and relevant to cardiac patients, and that age is included as an additional indicator of health.

Psychological well-being and health status

Symptoms of anxiety and depression were measured at baseline, and at 3, 6 and 12 months follow-up using the Hospital Anxiety and Depression Scale (HADS).[14] The HADS consists of 7 items measuring symptoms of anxiety (HADS-A) and 7 items measuring symptoms of depression (HADS-D), all scored on a 4-point Likert scale.[14] Scores range from 0 to 3 (total score range of 0-21), with higher scores reflecting more symptoms.[14] The HADS has good psychometric properties.[15]

The Short Form Health Survey 36 (SF-36) was used to assess patients' health status at baseline, and at 3, 6 and 12 months post implantation.[16] The items contribute to 8 subscales: physical functioning, role limitations - physical, bodily pain, social functioning, mental health, role limitations - emotional, vitality and general health. Scores on the individual subscales range from 0 to 100, with higher scores indicating better health status, and a higher score on the bodily pain subscale indicating the absence of pain.[17] Psychometric properties for the SF-36 are adequate.[16]

Type D personality is the combined tendency to experience increased negative affectivity and social inhibition. The 14-item Type D scale (DS14), consisting of 7 items measuring negative affectivity (i.e. *'I often feel unhappy'*) and 7 items measuring social inhibition (i.e. *'I am a closed kind of person'*) was used to assess Type D personality at baseline.[18] All items are scored on a 5-point Likert scale, ranging from 0 (false) to 4 (true), with a total score ranging from 0 to 28.[18] A cut-off score of ≥10 on both subscales defines individuals with a Type D personality.[19]

Statistical analyses

Repeated measures multivariable analysis of variance (RM-ANOVA) using general linear mixed modeling analysis was performed to test the longitudinal association between CCI and psychological well-being. This technique uses the data efficiently by also including incomplete cases in analyses. As a result of this, bias is limited and statistical power is preserved. Intra class correlations, a measure of score dependencies within patients, were computed for anxiety, depression and each of the SF-36 subscales. First, the CCI was tested as an associate of psychological well-being and health status over time; secondly, we assessed which individual comorbidities mainly accounted for the association between CCI and psychological well-being and health status.

A priori, we adjusted for gender, educational level, indication for ICD therapy, the presence of cardiac resynchronization therapy (CRT), ICD shocks, atrial fibrillation, smoking, the use of amiodarone, beta-blockers, and diuretics, the presence of psychological treatment, and Type D personality in multivariable analyses. All independent variables were defined as fixed variables (i.e. not varying over time). Analyses were performed using PASW Statistics 19 statistical software (PASW IBM Corp., Armonk, NY, USA). For all tests, a p-value of <.05 was considered statistically significant. The described effects in the results section are the relationship of CCI *at any time point* with the level of anxiety and depression symptoms, and health status over time, including all measurement occasions.

RESULTS

Baseline characteristics

Of the 448 patients, 18 had missing data on one or more psychological measures. Twenty-nine patients had additional missing data on one or more clinical baseline characteristics. No systematic differences were found between patients included (n=401) and patients excluded (n=47) from analyses (all p>.05). The population was predominantly male (78%), with a mean age of 58±12 years. Baseline characteristics of the study population are presented in Table 1. The prevalence of comorbid conditions included in the CCI is displayed in Figure 1.

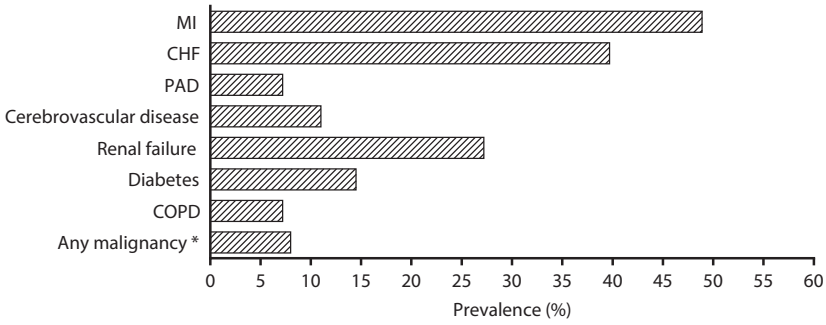

Figure 1. Prevalence (%) of the different comorbid conditions in the total study population
* Excluding metastatic tumors
Abbreviations: CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PAD, peripheral arterial disease

The most common non-cardiac comorbid conditions were renal failure, diabetes mellitus, and cerebrovascular disease. The number of comorbid conditions in patients varied from 0 to 6, with 25% of the patients having ≥3 comorbid conditions. Nineteen percent of the patients had ≥2 non-cardiac comorbidities. CCI scores ranged from 0 to 10, with the mean CCI score being 3.5±2.4. In the 12 months period post implantation, 15% of patients received a shock, of which 4% was inappropriate.

Table 1. Baseline characteristics of the study sample *

	Total study population (N=401)
Demographics	
Mean age (±SD)	58.4 (12.2)
Men	314 (78.3)
Single/no partner	26 (6.5)
Low education †	231 (57.6)
Clinical risk factors	
Primary prevention indication	265 (66.1)
CRT	112 (27.9)
Shocks during follow-up ‡	58 (14.5)
LVEF ≤35% §	300 (74.8)
Mean QRS (ms) (±SD)	130.3 (36.2)
CAD	231 (57.6)
Previous PCI	105 (26.2)
Previous CABG	83 (20.7)
Atrial fibrillation	91 (22.7)
Smoking	44 (11.0)
Medication use	
Amiodarone	74 (18.5)
Beta-blockers	320 (79.8)
Diuretics	229 (57.1)
ACE-inhibitors	288 (71.8)
Statins	237 (59.1)
Digoxin	63 (15.7)
Psychological treatment ‖	77 (19.2)

* Results are presented as N (%), unless otherwise indicated. † Education less than or equal to 13 years; ‡ both appropriate (N=44; 11.0%) and inappropriate (N=16; 4.0%) shocks; § 53/401 (13.2%) missing; ‖ both psychotropic medication and treatment by a psychologist

Abbreviations: *ACE*, angiotensin-converting enzyme; *CABG*, coronary artery bypass graft surgery; *CAD*, coronary artery disease; *CRT*, cardiac resynchronization therapy; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *N*, number; *PCI*, percutaneous coronary intervention; *QRS*, QRS duration; *SD*, standard deviation.

CCI as a determinant of psychological well-being and health status

Figure 2 depicts mean scores for anxiety, depression and health status during the 12-month follow-up period. First, intraclass correlations were computed as a measure of correlation between the different measurement occasions (i.e. baseline, 3, 6 and 12 months follow-up). The consecutive measurements of anxiety and depression both showed an intraclass correlation of 0.30. With regard to health status, intraclass correlations varied from 0.37 to 0.73 for role limitations - emotional and general health, respectively, indicating a moderate to high correlation between the measurement moments, supporting the use of this specific repeated measures technique.

In Table 2, the results of the mixed modeling analyses are expressed as estimates, 95% confidence intervals (CIs), t- and p-values. A higher CCI prior to implantation was associated with more symptoms of depression over the follow-up period (p=.003). No association was found between CCI and anxiety. In multivariable analyses, the CCI remained a significant predictor of depressive symptoms at any time point (p=.003) (Table 2).

Table 2. Charlson Comorbidity Index (CCI) as a determinant of anxiety, depression and health status (adjusted analysis)*

	Estimate	95% CI	t	p
Anxiety	-0.06	[-0.19 – 0.08]	-0.84	.40
Depression	0.21	[0.07 – 0.35]	2.95	**.003**
SF-36 subscales				
Physical functioning	-2.57	[-3.57 – -1.58]	-5.08	**<.001**
Role limitations - physical	-1.67	[-3.10 – -0.23]	-2.29	**.023**
Bodily pain	-1.31	[-2.19 – -0.43]	-2.92	**.004**
Social functioning	-0.36	[-1.20 – 0.49]	-0.83	.41
Mental health	-0.19	[-0.80 – 0.43]	-0.60	.55
Role limitations - emotional	-1.05	[-2.32 – 0.22]	-1.62	.11
Vitality	-0.64	[-1.41 – 0.13]	-1.64	.10
General health	-0.97	[-1.82 – -0.12]	-2.25	**0.025**

* Adjusted for gender, educational level, indication for ICD therapy, CRT, the occurrence of shocks (both appropriate and inappropriate) during 12 months post implantation, atrial fibrillation, smoking, the use of amiodarone, beta-blockers, and diuretics, the presence of psychological treatment, and Type D personality

With respect to the health status, in univariable analyses, a higher CCI prior to implantation was associated with poorer physical health status over the follow-up period, in terms of physical functioning (p<.001), role limitations - physical (p<.001), more bodily pain (p=.002), poorer role limitations - emotional (p=.026), vitality (p=.010) and general health (p<.001). In multivariable analyses, the association between CCI and health status remained significant for physical functioning (p<.001), role limitations - physical (p=.023), bodily pain (p=.004) and general health (p=.025) (Table 2).

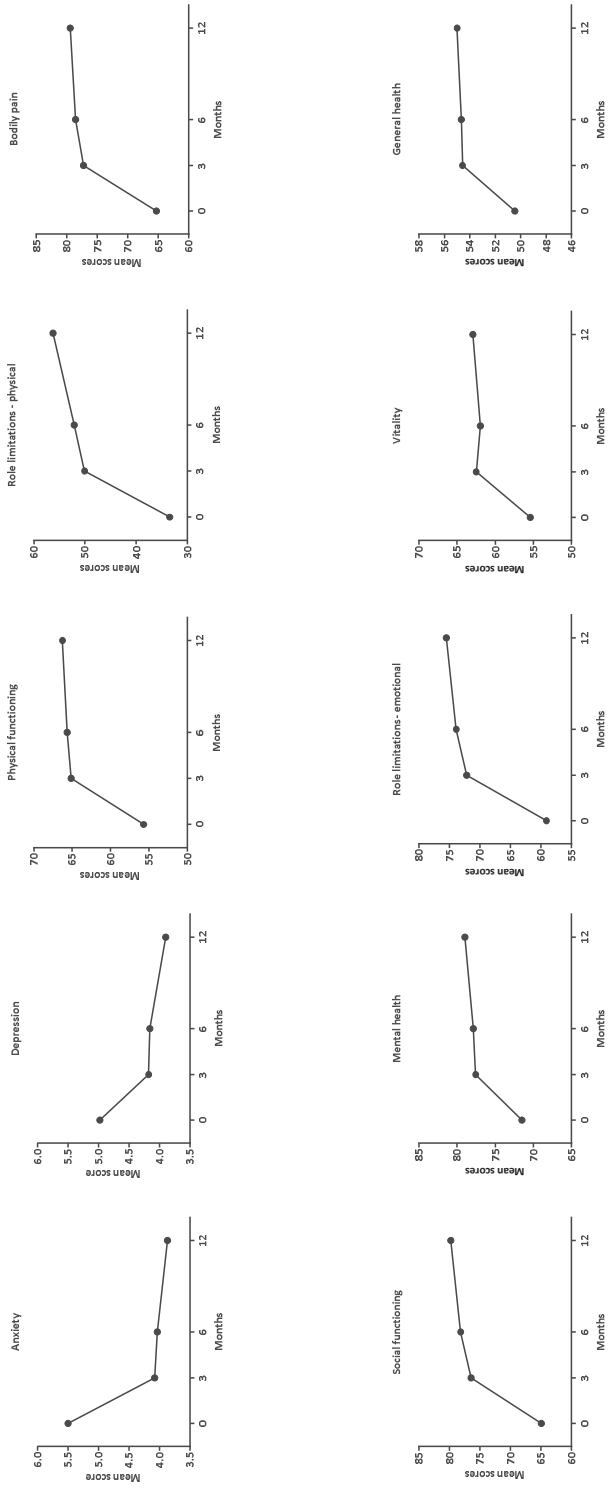

Figure 2. Mean scores of anxiety, depression and health status during 12 months post implantation

Table 3. Individual comorbidities from the CCI as predictors of psychological well-being and health status

Psychological measures	Age		Renal failure		MI		CHF		DM		PAD		CVA/TIA		COPD		Cancer	
HADS	**e**	**p**	**e**	**p**	**e**	**p**	**e**	**p**	**e**	**p**	**e**	**p**	**e**	**p**	**e**	**p**	**e**	**p**
Anxiety	-0.32	.06*	0.05	.89	0.14	.68	0.02	.95	0.49	.32	-0.40	.55	0.87	.12	1.18	.08	-0.62	.33
Depression	0.23	.20	1.09	**.006**	0.51	.15	0.79	**.030**	0.58	.25	1.10	.11	1.09	.06	1.52	**.026**	-.21	.75
SF-36																		
PF	-2.76	**.016**	-12.32	**<.001***	-2.69	.25	-14.03	**<.001‡**	-9.49	**.004**	-7.95	.08	-13.25	**<.001†**	-21.13	**<.001‡**	-5.38	.21
RL-P	-2.78	.08	-9.65	**.009**	-1.18	.72	-15.93	**<.001‡**	-9.40	**.044**	-4.52	.47	-10.19	.06	-20.93	**.001***	-4.28	.48
BP	-1.76	.07	-2.97	.19	-2.58	.20	-4.94	**.015**	-7.81	**.006***	-11.0	**.004***	-9.76	**.003***	-7.45	**.049**	-0.33	.93
SF	0.99	.32*	-3.89	.09	-1.62	.42	-7.44	**<.001‡**	-5.20	.07	-4.72	.22	-7.09	**.031**	-13.95	**<.001‡**	2.60	.48
MH	0.95	.22*	-2.20	.21	-1.30	.41	-1.70	.29	-1.98	.38	-3.19	.29	-3.95	.12	-6.40	**.033**	2.82	.33
RL-E	-1.71	.25	-6.31	.06	-7.84	**.008***	-3.67	.23	-7.27	.09	-0.71	.90	-6.39	.19	-5.60	.33	5.88	.28
VT	0.36	.69	-5.66	**.006**	1.20	.52	-8.51	**<.001†**	-2.22	.40	-4.74	.18	-7.50	**.012***	-9.81	**.005***	-0.49	.89
GH	0.15	.88*	-8.90	**<.001***	-2.15	.28	-12.59	**<.001‡**	-6.76	**.016**	-4.30	.26	-7.92	**.012**	-11.78	**.002***	-2.09	.57

Abbreviations: *BP*, bodily pain; *CHF*, chronic heart failure; *COPD*, chronic obstructive pulmonary disease; *CVA*, cerebrovascular accident; *DM*, diabetes mellitus; *e*, estimate; *GH*, general health; *MH*, mental health; *MI*, myocardial infarction; *PAD*, peripheral arterial disease; *PF*, physical functioning; *RL-E*, role limitations – emotional; *RL-P*, role limitations – physical; *SF*, social functioning; SF-*36*, Short Form health survey 36; *TIA*, transient ischemic attack; *VT*, vitality

* Significant on a p<.05 level in multivariable analyses (all comorbidities together in 1 model); † significant on a p<.01 level in multivariable analyses; ‡ significant on a p<.001 level in multivariable analyses

The individual components of the CCI as determinants of psychological well-being and health status

Subsequently, we investigated whether specific comorbidities included in the CCI accounted for the significant effects on psychological well-being and health status as displayed in Table 2. Chronic heart failure, COPD, cerebrovascular disease and renal failure were the most important predictors of depression and impaired health status (for all subscales, shown in Table 3). No individual effect of the different comorbidities was found on symptoms of anxiety. In multivariable analyses, when all comorbidities were entered in the model simultaneously, chronic heart failure, COPD, cerebrovascular disease and renal failure remained the most important predictors. Additionally, although age alone did not strongly predict psychological well-being and health status, it was an important determinant when all comorbidities were combined into one model.

DISCUSSION

To our knowledge, this is the first study in ICD patients to examine the influence of comorbidity burden on psychological well-being and health status. We found that patient's comorbidity burden was an important predictor of psychological well-being and health status over the 12 months post implantation. Having a higher comorbidity burden was associated with more symptoms of depression, but not anxiety, and with poorer physical functioning, more physical role limitations, more bodily pain and a poorer general health. Importantly, this association was present independent of the patient's pre implantation personality profile, which has also shown to be an important predictor of anxiety, depression and health status in patients with an ICD.[20] Our results correspond in part to findings of previous studies in the general older population[6,7] and in patients with acute MI,[8] where a higher comorbidity burden was found to be associated with more depressive symptoms and functional impairment. In patients with CRT, who also comprise an important group in our sample, the relationship between comorbidities and psychological well-being has not been investigated yet. However, as the course of health status in patients with CRT is comparable to the course of health status found in our study,[21,22] we expect that patients with CRT show a similar association between comorbidity burden and psychological well-being as patients with a defibrillator only.

We found no association between comorbidity score and anxiety. Around 25% of ICD patients report increased levels of anxiety.[20,23] However, the type of impairments in patients with multiple comorbidities might more easily induce symptoms of depression, by interfering with the patient's physical activity level, sleeping pattern, and social relationships, which in turn may lead to feelings of hopelessness and guilt.[6,8] This pattern corresponds more with depressive rather than anxious symptomatology.

No association was found between CCI score and mental health status. One would probably expect that in case of a positive association between CCI score and depressive symptoms, an association between CCI score and mental health status would also be present. However, the mental health status subscales of the SF-36, as used in the current study, may be too generally

formulated and do not measure specific psychological problems, including symptoms of anxiety and depression. In addition, the mental health subscale has shown to lack sensitivity to measure changes in mental health.[24]

Chronic heart failure, COPD, cerebrovascular disease, and renal failure were the most important associates of depressive symptoms and poorer health status. These comorbidities have both a worse short-term and long-term prognosis when compared to the other comorbidities. In addition, these patients may experience more restrictions both in physical and mental functioning. Their adverse impact on psychological well-being and health status is illustrated in our study. Cancer did not seem to have an influence on health status and symptoms of anxiety and depression in our patient group. However, as patients were asked to report on life time presence of cancer, a time span between the actual presence of cancer and the assessment of psychological problems could account for the absence of the relationship.

The finding that comorbid conditions are associated with poorer well-being and impaired health status is important for clinical practice. The variability in clinical presentation makes it difficult for physicians to detect psychological distress.[9] Physicians might attribute patients' psychological symptoms to their comorbidities rather than to psychological difficulties. However, it remains an important issue to focus on in daily practice, as both health status and depression have shown to be independent predictors of health care utilization in heart failure patients.[25,26] In addition, previous studies have shown that patients with comorbidities respond less well to psychological therapy than patients without such comorbidities.[27,28]

The limitations of this study should be acknowledged. First, it would have been interesting to investigate whether changes in CCI scores over time were predictive of psychological status during follow-up. However, information on comorbidities was only available at baseline. In addition, information on psychological well-being was based on self-report measures instead of clinical diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). However, minor depressive symptoms have also been associated with functional decline and mortality in cardiac patients.[29,30] Finally, the relatively short follow-up period does not allow drawing conclusions on the long-term relationship between CCI scores and psychological status.

This study also has important strengths. Research on the relationship between comorbid conditions and psychological functioning has mainly been focusing on symptoms of depression, while the influence on symptoms of anxiety and general daily functioning has been largely ignored. Furthermore, we used a powerful statistical technique to analyze the data, reducing non-response bias and increasing statistical power.

In conclusion, we found that patients with a higher comorbidity score reported more symptoms of depression and poorer health status on several domains. As the variability in clinical presentation of patients with comorbid conditions may hinder physicians from detecting psychological distress and referring the patient to adequate, tailor-made psychological care, in case of comorbidities, clinicians should be vigilant of the possibility that patients' psychological well-being and health status is at higher risk of being affected.

REFERENCES

1. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352(3):225-237.
2. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337(22):1576-1584.
3. Scott PA, Sterns LD, Tang AS. Do patients at high risk of nonsudden cardiac death benefit from prophylactic icd therapy? Curr Opin Cardiol 2012;27(1):1-7.
4. Lee DS, Tu JV, Austin PC, Dorian P, Yee R, Chong A, Alter DA, Laupacis A. Effect of cardiac and noncardiac conditions on survival after defibrillator implantation. J Am Coll Cardiol 2007;49(25):2408-2415.
5. Theuns DAMJ, Schaer BA, Soliman OII, Altmann D, Sticherling C, Geleijnse ML, Osswald S, Jordaens L. The prognosis of implantable defibrillator patients treated with cardiac resynchronization therapy: Comorbidity burden as predictor of mortality. Europace 2011;13(1):62-69.
6. Leong IY, Farrell MJ, Helme RD, Gibson SJ. The relationship between medical comorbidity and self-rated pain, mood disturbance, and function in older people with chronic pain. J Gerontol A Biol Sci Med Sci 2007;62(5):550-555.
7. Covinsky KE, Kahana E, Chin MH, Palmer RM, Fortinsky RH, Landefeld CS. Depressive symptoms and 3-year mortality in older hospitalized medical patients. Ann Intern Med 1999;130(7):563-569.
8. Watkins LL, Schneiderman N, Blumenthal JA, Sheps DS, Catellier D, Taylor CB, Freedland, KE; ENRICHD Investigators. Cognitive and somatic symptoms of depression are associated with medical comorbidity in patients after acute myocardial infarction. Am Heart J 2003;146(1):48-54.
9. Docherty JP. Barriers to the diagnosis of depression in primary care. J Clin Psychiatry 1997;58(Suppl 1):5-10.
10. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of diet in renal disease study group. Ann Intern Med 1999;130(6):461-470.
11. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 Suppl 1):S1-S266.
12. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40(5):373-383.
13. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47(11):1245-1251.
14. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67(6):361-370.
15. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997;27(2):363-370.
16. Aaronson NK, Muller M, Cohen PDA, Essink-Bot M-L, Fekkes M, Sanderman R, Sprangers MA, Te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51(11):1055-1068.
17. Ware J, Kosinski M. Interpreting SF-36 summary health measures: A response. Qual Life Res 2001;10(5):405-413.
18. Denollet J. DS14: Standard assessment of negative affectivity, social inhibition, and Type D personality. Psychosom Med 2005;67(1):89-97.
19. Emons WHM, Meijer RR, Denollet J. Negative affectivity and social inhibition in cardiovascular disease: Evaluating Type D personality and its assessment using item response theory. J Psychosom Res 2007;63(1):27-39.
20. Pedersen SS, Hoogwegt MT, Jordaens L, Theuns DAMJ. Pre implantation psychological functioning preserved in majority of implantable cardioverter-defibrillator patients. Int J Cardiol 2011;166(1):215-220.
21. Versteeg H, van den Broek KC, Theuns DAMJ, Mommersteeg PM, Alings M, Van der Voort PH, Jordaens L, Pedersen SS. Effect of cardiac resynchronization therapy-defibrillator implantation on health status in patients with mild versus moderate symptoms of heart failure. Am J Cardiol 2011;108(8):1155-1159.
22. Hoth KF, Nash J, Poppas A, Ellison KE, Paul RH, Cohen RA. Effects of cardiac resynchronization therapy on health-related quality of life in older adults with heart failure. Clin Interv Aging 2008;3(3):553-560.

23. Pedersen SS, Theuns DAMJ, Jordaens L, Kupper N. Course of anxiety and device-related concerns in implantable cardioverter defibrillator patients the first year post implantation. Europace 2010;12(8):1119-1126.
24. Bech P, Olsen LR, Kjoller M, Rasmussen NK. Measuring well-being rather than the absence of distress symptoms: A comparison of the SF-36 mental health subscale and the WHO-five Well-Being Scale. Int J Methods Psychiatr Res 2003;12(2):85-91.
25. Chan PS, Soto G, Jones PG, Nallamothu BK, Zhang Z, Weintraub WS, Spertus JA. Patient health status and costs in heart failure. Circulation 2009;119(3):398-407.
26. Sullivan M, Simon G, Spertus J, Russo J. Depression-related costs in heart failure care. Arch Intern Med 2002;162(16):1860-1866.
27. Schultz SK. Depression in the older adult: The challenge of medical comorbidity. Am J Psychiatry 2007;164(6):847-848.
28. Pohle K, Domschke K, Roehrs T, Arolt V, Baune BT. Medical comorbidity affects antidepressant treatment response in patients with melancholic depression. Psychother Psychosom 2009;78(6):359-363.
29. Penninx BWJH, Beekman ATF, Honig A, Deeg DJH, Schoevers RA, Van Eijk JTM, Van Tilburg W. Depression and cardiac mortality: Results from a community-based longitudinal study. Arch Gen Psychiatry 2001;58(3):221-227.
30. Vaccarino V, Kasl SV, Abramson J, Krumholz HM. Depressive symptoms and risk of functional decline and death in patients with heart failure. J Am Coll Cardiol 2001;38(1):199-205.

Beta-blocker therapy is not associated with symptoms of depression and anxiety in patients receiving an implantable cardioverter-defibrillator

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ABSTRACT

Background: Beta-blockers are frequently prescribed to implantable cardioverter-defibrillator (ICD) patients. Beta-blocker therapy has been proposed to induce emotional distress such as depression and anxiety, but a paucity of studies has examined the relationship between beta-blockers and distress. We investigated the association between beta-blocker therapy, including type and dosage, and symptoms of anxiety and depression in a consecutive cohort of patients receiving an ICD.

Methods: Between 2003 and 2010, 448 consecutively implanted ICD patients were enrolled in the prospective Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter Defibrillator: A prospective Study (MIDAS), of which 429 completed the Hospital Anxiety and Depression Scale (HADS) and the ICD Patient Concerns questionnaire (ICDC) at baseline.

Results: Eighty percent of all patients received beta-blocker therapy. In univariate analysis, beta-blocker therapy was not significantly associated with symptoms of anxiety, depression and ICD concerns (β=-0.030, β=0.007 and β=-0.045, respectively; all $p>0.36$). Type of beta-blocker showed a trend towards significance for mean levels of ICD concerns ($p=.09$). No association was found between dosage and emotional distress (all $p>.21$). After adjustment for relevant clinical and demographic variables, the association of beta-blocker therapy and symptoms of anxiety, depression and ICD concerns remained non-significant (β=0.009, β=0.037 and β=0.019, respectively; all $p>.47$).

Conclusions: In patients receiving an ICD, beta-blocker therapy is not associated with symptoms of anxiety, depression and ICD concerns. Further research is warranted that examines the link between beta-blocker therapy and emotional distress in this vulnerable patient group.

INTRODUCTION

The implantable cardioverter-defibrillator (ICD) has evolved to treatment of first choice in the prevention of arrhythmic death, both as primary and secondary prevention.[1,2] The majority of ICD patients report acceptable levels of quality of life (QoL),[3,4] with patients reporting increases in QoL some months after the implantation.[5] However, a subgroup of patients experiences adaptation problems, which include the manifestation of depression, anxiety, concerns about the ICD giving a shock, and posttraumatic stress.[3,6,7]

In addition to the ICD implant, ICD patients are often prescribed beta-blockers, lipid-lowering drugs, calcium antagonists and angiotensin-converting enzyme (ACE)-inhibitors to treat their underlying heart disease, with beta-blockers being among the most frequently prescribed drugs.[8] Beta-blockers are of major importance in the treatment post myocardial infarction (MI), reducing the odds of death after long-term use with up to 23%.[9] Beta-blockers also enhance survival in patients with chronic heart failure,[10,11] patients with idiopathic dilated cardiomyopathy[12] and patients with different types of arrhythmias.[13] Nevertheless, despite these well-established benefits, there is an ongoing debate concerning possible side-effects of beta-blocker therapy on the central nervous system,[14] which include the manifestation of depression.[15-18] However, many of these studies are dated, are based on small sample sizes or used prescribed antidepressants as a marker of depression rather than assessing depression.[15,17] In addition, the evidence is not consistent, with some studies finding no association between the use of beta-blockers and symptoms of depression,[14,19-22] mixed results depending on beta-blocker type[23] or even a reduction of depressive symptoms in beta-blocker users.[24,25] In contrast, less research has been conducted on the association between the use of beta-blockers and symptoms of anxiety, although there are some indications of beta-blockers having a protective effect in relation to symptoms of anxiety.[26-28] Moreover, most of these studies were conducted in patients with MI, heart failure or hypertension. Although a subset of patients with heart failure is treated with ICD therapy, none of these studies have focused specifically on patients with an ICD. Therefore, we investigated the association between beta-blocker therapy and symptoms of anxiety and depression, and examined whether beta-blocker type and dosage are correlated with psychological functioning in patients receiving an ICD.

METHODS

Patients and study design

Between August 2003 and February 2010, a consecutive series of 448 patients implanted with an ICD at the Erasmus Medical Center, Rotterdam, the Netherlands, were enrolled in the prospective Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter Defibrillator: A prospective Study (MIDAS). Exclusion criteria included a life-expectancy of <1 year, being on the waiting list for heart transplantation, having a history of psychiatric illness other than affective/anxiety disorders, or insufficient knowledge of the Dutch language. The Medical Ethics Committee of the Erasmus Medical Center approved the study. An ICD nurse approached patients

while being admitted to hospital, provided information regarding the study and asked them to complete a set of standardized and validated psychological questionnaires at baseline (i.e. 1 day prior ICD implantation). All patients provided written informed consent before enrollment in the study.

Measures

Demographic and clinical variables

All demographic and clinical variables were collected at baseline. Demographic variables included gender, age, marital status and education. Clinical variables were obtained from patients' medical records, and included indication for ICD therapy (primary or secondary prevention), treatment with cardiac resynchronization therapy (CRT), left ventricular ejection fraction (LVEF) ≤35%, QRS duration, the presence of coronary artery disease (CAD), previous MI, prior percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), symptomatic heart failure (defined as New York Heart Association (NYHA) class III+IV), atrial fibrillation, diabetes, smoking, and cardiac (i.e beta-blockers, amiodarone, diuretics, ACE-inhibitors, statins, and digoxin) and psychotropic medication. For patients on beta-blocker therapy, information on type and dosage was also obtained from patients' medical records. In order to be able to compare the dosages of different types of beta-blockers, we used the maximum recommended therapeutic dosages, as prescribed by the *Pharmacotherapeutic Reference Book*, a yearly published issue by the Dutch National College of Health Insurances.[29]

Anxiety and depression

Symptoms of anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS), a 14-item self-report questionnaire, which performs well in screening for separate symptoms of anxiety and depression in patients in non-psychiatric hospital settings.[30] The scale consists of 7 items measuring symptoms of anxiety (HADS-A) and 7 items assessing symptoms of depression (HADS-D), all scored on a 4-point Likert scale. Scores range from 0 to 3, with a score range of 0-21 for both subscales, with a high score indicating more symptoms.[31] A cut-off score of 8 or above, representing an optimal balance between sensitivity and specificity, is used to detect patients with clinically relevant levels of anxiety and depression.[30] The HADS is a valid and reliable scale, with mean Cronbach's alphas of 0.83 and 0.82 for the HADS-A and HADS-D, respectively, and a sensitivity score of 0.80 for both subscales.[30] Test-retest reliability over 3 weeks is high with a Pearson coefficient of 0.89 and 0.86 for the HADS-A and HADS-D respectively.[32]

ICD concerns

Patient concerns related to ICD treatment were assessed with the Dutch version of the 8-item Patient ICD Concerns questionnaire (e.g. *"I am worried about my ICD firing"* and *"I am worried about symptoms/ pain associated with my ICD firing*") (ICDC).[33] Items are rated on a 5-point Likert scale from 0 (not at all) to 4 (very much so), with a score range from 0 to 32, and with a higher score indicating more ICD related concerns. The ICDC is a disease-specific measure that assesses a different construct than general measures of anxiety and depression. The measure has also been shown to predict mortality

in ICD patients.[34] Both the original and the Dutch translation of the ICDC have good psychometric properties, with a Cronbach's alpha of 0.94 and 0.91, respectively.[33,35] For the current study, scores on the ICDC were divided into equal tertiles and dichotomized into a high score of ≥7 and a low score of ≤6.

Statistical analyses

Baseline demographic and clinical variables for patients on beta-blocker versus no beta-blocker therapy were compared with the χ^2 test (Fisher's Exact test when appropriate) for nominal variables and with Student's t-test for continuous variables, respectively. The association between beta-blocker therapy and symptoms of depression and anxiety and ICD concerns was assessed in main analysis using univariable and multivariable linear regression. In multivariable analyses using an enter approach, we adjusted for variables that have been associated with emotional distress in the arrhythmia literature, which include atrial fibrillation and symptomatic heart failure,[36,37] indication for ICD therapy,[38] diabetes mellitus,[39] and the use of amiodarone and psychotropic medication,[37] and variables that were expected to be related to emotional distress, including CAD and age. The rationale for a priori selection of variables is recommended by others.[40] We checked for multicollinearity between the independent variables using Spearman's ρ, with a threshold of >0.70 indicating multicollinearity. Results of the linear regression analyses are presented as β's with accompanying p-values. In a secondary analysis, the association between beta-blocker type and dosage and emotional distress, and possible interaction effects were examined with univariable analysis of variance (ANOVA), with a post hoc Bonferroni test when the ANOVA showed a significant main effect to investigate between group differences. For all tests, a p-value <.05 (two-sided) was considered significant. All statistical analyses were performed using SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

Participants versus non participants

A total of 448 patients were enrolled in the MIDAS study. Of these, 19 refused to participate. All remaining 429 patients (response rate = 96%) filled in sufficient items to obtain summary scores on the psychological measures and thus were eligible for analysis. Patients who refused to participate were more likely to have ischemic heart disease, atrial fibrillation and diabetes (all p<0.05). No systematic differences in medication use between responders and non responders were demonstrated (all p>.05).

Baseline characteristics

Baseline characteristics for the total patient sample and stratified by beta-blocker use are listed in Table 1. Of all patients, 342 (80%) were on beta-blocker therapy compared to 87 (20%) without beta-blocker therapy. The mean age was 58±12 years, 79% of the patients were male. Mean scores of anxiety, depression and ICD concerns were 5.53 (±4.00), 4.99 (±3.97) and 9.97 (±7.71) respectively.

Table 1. Baseline characteristics for the total study population and stratified by use of beta-blocking agents *

	Total	Beta-blocker users	Non beta-blocker users	p-value
N	429 (100)	342 (79.7)	87 (20.3)	
Demographics				
Mean age (±SD)	58.43 (12.1)	58.84 (11.5)	56.83 (14.5)	.17
Men	337 (78.6)	268 (78.4)	69 (79.3)	.85
Single/no partner †	28 (6.6)	20 (5.9)	8 (9.2)	.27
Lower education ‡	245 (58.2)	194 (57.7)	51 (60.0)	.71
Clinical risk factors				
Primary prevention indication	282 (65.7)	231 (67.5)	51 (58.6)	.12
CRT	122 (28.4)	103 (30.1)	19 (21.8)	.13
LVEF ≤35% §	318 (85.7)	263 (86.8)	55 (80.9)	.21
Mean QRS (±SD) ||	129.89 (36.4)	130.65 (36.2)	126.92 (37.1)	.39
CAD	247 (57.6)	204 (59.6)	43 (49.4)	.09
Previous MI	210 (49.0)	177 (51.8)	33 (37.9)	**.02**
Previous PCI	111 (25.9)	91 (26.6)	20 (23.0)	.49
Previous CABG	87 (20.3)	71 (20.8)	16 (18.4)	.62
Symptomatic heart failure ¶	137 (31.9)	113 (33.0)	24 (27.6)	.33
Atrial fibrillation	95 (22.1)	69 (20.2)	26 (29.9)	.05
Diabetes	62 (14.5)	54 (15.8)	8 (9.2)	.12
Smoking #	46 (10.8)	37 (10.9)	9 (10.3)	.89
Medication use				
Amiodarone	80 (18.6)	51 (14.9)	29 (33.3)	**<.001**
Diuretics	244 (56.9)	201 (58.8)	43 (49.4)	.12
ACE-inhibitors	307 (71.6)	264 (77.2)	43 (49.4)	**<.001**
Statins	253 (59.0)	225 (65.8)	28 (32.2)	**<.001**
Digoxin	65 (15.2)	52 (15.2)	13 (14.9)	.95
Psychotropic medication **	70 (16.5)	55 (16.2)	15 (17.4)	.79
Antidepressants ††	14 (3.3)	2 (2.3)	12 (3.5)	.57
Benzodiazepines	29 (6.8)	8 (9.2)	21 (6.1)	.31
Hypnotics	5 (1.2)	0 (0.0)	5 (1.5)	.26
>1 type	4 (0.9)	1 (1.1)	3 (0.9)	.81

* Results are presented as N (%), unless otherwise indicated. † 3/429 (0.7%) missing; ‡ Education less than or equal to 13 years, 8/429 (1.9%) missing; § 58/429 (13.5%) missing; || 1/429 (0.2%) missing; ¶ defined as NYHA class III and IV; # 2/429 missing (0.5%); ** 4/429 missing in general (0.9%), in 18/70 (25.7%) type of psychotropic medication was missing; †† SSRI (N=11), TCA (N=1), lithium (N=1), serotonergic/noradrenergic antidepressant (N=1). Abbreviations: *ACE*, angiotensin-converting enzyme; *CABG*, coronary artery bypass grafting; *CAD*, coronary artery disease; *CRT,* cardiac resynchronization therapy; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *N*, number; *PCI*, percutaneous coronary intervention; *QRS*, QRS duration; *SD*, standard deviation

Beta-blocker users were more likely to have had a previous MI (p=.02), and were more often treated with ACE-inhibitors (p<.001) and statins (p<.001). In contrast, beta-blocker users were less likely

to be treated with amiodarone compared with patients not on beta-blocker therapy (p<.001). No differences on symptoms of depression, anxiety and ICD concerns between beta-blocker users and non beta-blocker users were found (all p>.36).

Unadjusted analyses

Baseline scores on the HADS-A, HADS-D and ICDC of beta-blocker users were compared with those of non beta-blocker users. In univariable analysis, there was no significant association between beta-blocker therapy and symptoms of anxiety (β=-0.030, p=.54), depression (β=0.007, p=.89) and ICD concerns (β=-0.045, p=.36). In order to investigate the relationship between beta-blocker type and dosage and possible interaction effects with emotional distress, we performed univariable ANOVA analyses. The association between beta-blocker type and emotional distress is presented in Figure 1, whereas descriptive data on beta-blocker dosage stratified by type are displayed in Table 2.

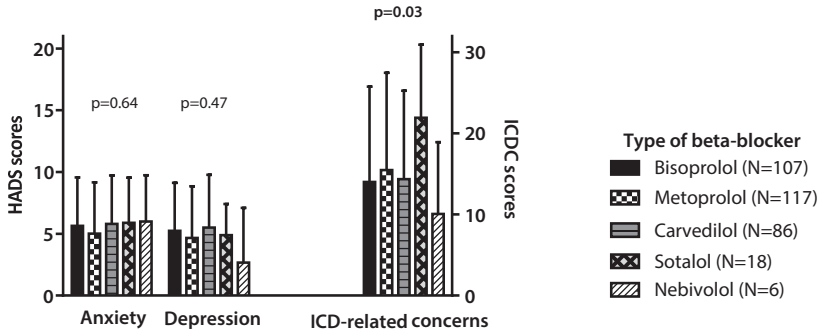

Figure 1. Association between beta-blocker type and emotional distress (unadjusted analysis)

Table 2. Descriptives beta-blockers *

Type †	Bisoprolol	Metoprolol	Carvedilol	Sotalol	Nebivolol	p-value
N	107	117	86	18	6	-
Daily dosage (mg)	3.89 (3.61)	86.44 (63.67)	27.99 (22.07)	144.44 (74.06)	4.79 (3.00)	-
% max. therapeutic dosage ‡	19.45 (18.06)	21.69 (15.96)	37.32 (29.43)	45.14 (23.14)	47.92 (30.02)	**<.001**

* Daily dosages and percentages of the maximum therapeutic dosages are presented as mean ± SD. † Atenolol, labetalol and pindolol omitted from analysis because N=1; in total, information on dosage missing in 8/342 patients (2.3%). ‡ maximum recommended therapeutic dosages as prescribed by the *Pharmacotherapeutic Reference Book*, a yearly published issue by the Dutch National College of Health Insurances [30]

Overall, type of beta-blocker was significantly associated with higher scores on the ICDC only (F=2.681, p=.03). After performing a post-hoc Bonferroni test, sotalol and bisoprolol were the only types of beta-blockers showing a trend towards significant differences in mean levels of ICD concerns. However, the difference fell short of significance (p=.09). No association between beta-blocker dosage and emotional distress was found (all p>.21), nor an interaction effect between type

of beta-blocker and percentage of the maximum recommended therapeutic dosage in relation to distress (all p>.06). As there was no association between beta-blocker type and dosage and emotional distress, respectively, these variables were not included in multivariable analysis.

Table 3. Multivariable associations between beta-blocker therapy and emotional distress *

	Anxiety		Depression		ICD concerns	
	β	**p**	**β**	**p**	**β**	**p**
Step 1						
+ CAD	-0.001	.98	0.028	.59	0.030	.57
+ Atrial fibrillation	-0.091	.09	0.069	.20	-0.064	.23
+ Amiodarone	0.043	.42	0.013	.82	0.056	.29
Step 2						
+ ICD indication	0.038	.49	0.056	.32	-0.018	.76
+ NYHA	0.023	.66	0.117	**.03**	-0.087	.11
+ DM	0.068	.18	0.022	.67	0.032	.54
+ Psychotropic medication	0.285	**<.001**	0.281	**<.001**	0.219	**<.001**
+ Age	-0.146	**.01**	-0.036	.53	-0.138	**.02**
Step 3						
+ LVEF≤35%	-0.108	**.047**	-0.059	.28	-0.021	.71
Step 4						
+ Beta-blocker	0.009	.86	0.037	.47	0.019	.72

* Abbreviations: *CAD*, coronary artery disease; *DM*, diabetes mellitus; *ICD*, implantable cardioverter defibrillator; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *NYHA*, New York Heart Association class

Adjusted analyses

Prior to adjusted analysis, we checked for multicollinearity between the independent variables using Spearman's ρ. There were no problems with multicollinearity as all Spearman's ρ's were <.36. Adjusting for the a priori selected covariates, we composed a four-step model. In step 1, variables significantly associated with beta-blocker therapy and variables showing a trend towards an association with beta-blocker therapy were included (CAD, atrial fibrillation and amiodarone). In step 2, ICD indication, NYHA functional class, diabetes mellitus, psychotropic medication and age were added. Because we had no information on LVEF for 13.5% of patients, LVEF was added in step 3. In order to assess the unique association between beta-blocker therapy and emotional distress, beta-blocker use was added in the final model (step 4, Table 3). The association between beta-blocker therapy and symptoms of anxiety, depression and ICD concerns remained non significant (β=0.009, β=0.037 and β=0.019, respectively; all p>.47) when controlling for the appropriate covariates.

DISCUSSION

In the present study, we examined the association between beta-blocker therapy and emotional distress in a consecutive cohort of patients receiving an ICD. Our results neither support a relationship between beta-blocker use and symptoms of anxiety, depression and ICD- concerns,

respectively, nor a type- or dose-dependent relationship. The relationship between beta-blocker use and symptoms of depression has been previously studied, specifically in post MI patients.[14,21,22] However, little is known about the relationship between beta-blocker therapy and anxiety in the general cardiovascular literature. In addition, to our knowledge this study is one of the first to investigate this relationship in patients implanted with an ICD.

In order to induce neuropsychological side-effects, beta-blockers have to be able to cross the blood-brain barrier and thus be lipophylic.[14] Therefore, hydrophilic beta-blockers cannot induce an anxiolytic effect due to their inability to bind on β-receptors in the brain, while lipophylic beta-blockers would. In our sample however, we found no significant differences between the various types of beta-blockers. Moreover, the question remains whether beta-blockers are able to cross the blood-brain barrier in the beginning, which also depends on the size of their molecules.

Overall, we found no indication that beta-blocking agents may be linked to anxiety, although this could be due to differences in pharmacokinetic characteristics of the various types of beta-blockers. Swartz (1998) found rapid improvements in levels of anxiety and obsessive-compulsive disorder symptoms after administration of the lipophylic beta-blocker betaxolol,[28] which is a long-acting beta-blocker. In general, beta-blockers prescribed to our patients are short-acting agents,[29] which could explain the absence of an anxiolytic effect. Although results from studies in both animals and humans indicate that the β_1-adrenoceptor in the basolateral amygdalae plays an important role in anxiety-like behavior,[27,41] suggesting that inhibition of this receptor by selective beta-blocking agents could produce anxiolytic effects, the relatively short half-life time of the beta-blockers prescribed to our patients might reduce this effect. In addition, beta-blocker dosages may also play a role. One might hypothesize that autonomic arousal involved in the somatic experience of anxiety is only suppressed by beta-blockers at higher dosages. As the subjective, cognitive/affective experience of anxiety always follows the somatic arousal in response to fear,[42] suppression of the subjective experience of anxiety - which patients report in the questionnaires - by beta-blockers may not occur at low dosages. In our sample, patients were prescribed relatively low percentages of the maximum therapeutic recommended dosage (ranging from 19-48% depending on beta-blocker type), which could explain the absence of an anxiolytic effect.

Twenty percent of the patients in the present study did not receive beta-blocker therapy. There were no indications that absence of beta-blocker therapy was due to problems with tolerating the beta-blockers. The prescription rates in the present patient cohort were comparable with those in other cohorts of ICD patients.[43,44]

The absence of an association between beta-blocker therapy and symptoms of depression is concurrent with the results of multiple recent studies.[14,19-22] In contrast to early findings in this field, when the hypothesis of the depression-inducing effect of beta-blockers was developed, more recent results find no support for this hypothesis. Rabiner et al. (2000) reported that there are certain beta-blockers, including pindolol and penbutolol, that bind to serotonin receptors in the brain, thereby increasing the amount of free serotonin, which could explain the absence of a negative effect of beta-blockers on mood.[45] In addition, arguments have been made that physical symptoms, including fatigue, are sometimes being misinterpreted as depression.[46] This could lead

to an overestimation of the prevalence of depressive symptoms. Besides, instead of examining the presence of depressive symptoms, a number of studies have investigated the relationship between beta-blocker therapy and the use of antidepressants, with antidepressant use serving as a proxy measure for depression.[15,17] Although symptoms of depression and the use of antidepressants are likely to be correlated, as was the case in our study, recent research suggests that ICD patients with clinical significant levels of depressive symptoms are undertreated.[47] It is unclear as to whether these studies[15,17] have used standardized and psychometrically sound instruments to measure depressive symptoms, or whether they did not assess these symptoms at all. In a recent comprehensive review on studies mainly investigating patients with hypertension, MI or heart failure, Verbeek et al. (2011) conclude that the risk of a beta-blocker induced depression is small and that only in vulnerable subpopulations, including patients with a positive personal or family history of depression, one should stay vigilant with prescribing certain types of beta-blockers, in particular propranolol.[48]

The results of this study should be interpreted with some caution. First, there was a relatively large difference between the number of patients who were prescribed beta-blocker therapy and the number of patients not using beta-blockers. However, this reflects clinical practice. Second, although a difficulty in most of these types of studies, we had no information on compliance rates, so that an underestimation of the real taken medication cannot be ruled out. Third, we used a cross-sectional study design given that we did not have information about changes in beta-blocker use - including type and dose - over time. Hence, we are not able to draw conclusions about cause and effect, and long-term effects of beta-blockers on emotional functioning remain unclear. Fourth, we relied on self-report measures to assess anxiety and depression rather than a clinical diagnostic interview. However, the instruments we used have good psychometric properties, enabling standardized, well-validated and reliable assessment, and have been frequently used in ICD patients.[30-33,35] Moreover, we used a disease-specific measure of anxiety, which is generally more sensitive to tap symptoms pertinent to patients.[49]

In conclusion, we found no association between beta-blocker use and symptoms of anxiety, depression and ICD concerns, and thus no evidence that beta-blockers might have an anxiolytic effect, nor induce depressive symptoms in ICD patients. Given the major reduction of morbidity and mortality associated with beta-blocker therapy, beta-blocker therapy should not be withheld from patients. Since anxiety and depression are common problems in ICD patients, which have been associated with decreased quality of life,[4] and risk of tachyarrhythmias and mortality,[34,50] we should strive for treatment of both the physical and psychological problems of these patients. Research is warranted that further elucidates the link between anxiety and depression and beta-blocker therapy in this specific patient group.

REFERENCES

1. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter defibrillator for congestive heart failure. N Engl J Med 2005;352(3):225-237.
2. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337(22):1576 - 1584.
3. Pedersen SS, Theuns DAMJ, Muskens-Heemskerk A, Erdman RAM, Jordaens L. Type D personality but not implantable cardioverter defibrillator indication is associated with impaired health-related quality of life 3 months post-implantation. Europace 2007;9(8):675-680.
4. Sears SF, Conti JB. Quality of life and psychological functioning of ICD patients. Heart 2002;87(5):488-493.
5. Godemann F, Butter C, Lampe F, Linden M, Werner S, Behrens S. Determinants of the quality of life (QOL) in patients with an implantable cardioverter defibrillator (ICD). Qual Life Res 2004;13(2):411-416.
6. Ladwig K-H, Baumert J, Marten-Mittag B, Kolb C, Zrenner B, Schmitt C. Posttraumatic stress symptoms and predicted mortality in patients with implantable cardioverter-defibrillators: Results from the prospective living with an implanted cardioverter-defibrillator study. Arch Gen Psychiatry 2008;65(11):1324-1330.
7. Versteeg H, Theuns DAMJ, Erdman RAM, Jordaens L, Pedersen SS. Posttraumatic stress in implantable cardioverter defibrillator patients: The role of pre-implantation distress and shocks. Int J Cardiol 2011;146(3):438-439.
8. Ermis C, Zadeii G, Zhu AX, Fabian W, Collins J, Lurie KG, Sakaguchi S, Benditt DG. Improved survival of cardiac transplantation candidates with implantable cardioverter defibrillator therapy. J Cardiovasc Electrophysiol 2003;14(6):578-583.
9. Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta-blockade after myocardial infarction: Systematic review and meta regression analysis. BMJ 1999;26(318):1730-1737.
10. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL randomised intervention trial in-congestive heart failure (MERIT-HF). Lancet 1999;353(9169):2001-2007.
11. Packer M, Coats AJS, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, Holcslaw TL, Amann-Zalan I, DeMets DL; Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344(22):1651-1658.
12. Di Lenarda A, Sabbadini G, Salvatore L, Sinagra G, Mestroni L, Pinamonti B, Gregori D, Ciani F, Muzzi A, Klugmann S, Carmerini F. Long-term effects of carvedilol in idiopathic dilated cardiomyopathy with persistent left ventricular dysfunction despite chronic metoprolol. J Am Coll Cardiol 1999;33(7):1926-1934.
13. Bangalore S, Messerli FH, Kostis JB, Pepine CJ. Cardiovascular protection using beta-blockers: A critical review of the evidence. J Am Coll Cardiol 2007;50(7):563-572.
14. Van Melle JP, Verbeek DEP, Van den Berg MP, Ormel J, Van der Linde MR, De Jonge P. Beta-blockers and depression after myocardial infarction: A multicenter prospective study. J Am Coll Cardiol 2006;48(11):2209-2214.
15. Avorn J, Everitt DE, Weiss S. Increased antidepressant use in patients prescribed beta-blockers. JAMA 1986;255(3):357-360.
16. Cremona-Barbaro A. Propranolol and depression. Lancet 1983;321(8317):185.
17. Thiessen BQ, Wallace SM, Blackburn JL, Wilson TQ, Bergman U. Increased prescribing of antidepressants subsequent to beta-blocker therapy. Arch Intern Med 1990;150(11):2286-2290.
18. Waal HJ. Propranolol-induced depression. Br Med J 1967;250.
19. Bright RA, Everitt DE. Beta-blockers and depression. Evidence against an association. JAMA 1992;267(13):1783-1787.
20. Carney RM, Rich MW, tevelde A, Saini J, Clark K, Freedland KE. Prevalence of major depressive disorder in patients receiving beta-blocker therapy versus other medications. Am J Med 1987;83(2):223-226.
21. Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. JAMA 2002;288(3):351-357.
22. Schleifer SJ, Slater WR, Macari-Hinson MM, Coyle DA, Kahn M, Zucker HD, Gorlin R. Digitalis and beta-blocking agents: Effects on depression following myocardial infarction. Am Heart J 1991;121(5):1397-1402.
23. Luijendijk HJ, van den Berg JF, Hofman A, Tiemeier H, Stricker BH. Beta-blockers and the risk of incident depression in the elderly. J Clin Psychopharmacol 2011;31(1):45-50.

24. Beta-blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001;344(22):1659-1667.
25. Baxter AJ, Spensley A, Hildreth A, Karimova G, O'Connell JE, Gray CS. Beta-blockers in older persons with heart failure: Tolerability and impact on quality of life. Heart 2002;88(6):611-614.
26. Bulpitt CJ, Connor M, Schulte M, Fletcher AE. Bisoprolol and nifedipine retard in elderly hypertensive patients: Effect on quality of life. J Hum Hypertens 2000;14(3):205-212.
27. Fu A, Li X, Zhao B. Role of beta1-adrenoceptor in the basolateral amygdala of rats with anxiety-like behavior. Brain Res 2008;121185-92.
28. Schwartz P, De Ferrari G. Sympathetic-parasympathetic interaction in health and disease: Abnormalities and relevance in heart failure. Heart Fail Rev 2011;16(2):101-107.
29. College voor zorgverzekeringen (CVZ). College of health care insurances. Farmacotherapeutisch kompas 2010. Pharmacotherapeutic reference book. Utrecht: Roto Smeets Utrecht, 2010.
30. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: An updated literature review. J Psychosom Res 2002;52(2):69-77.
31. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67(6):361-370.
32. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997;27(2):363-370.
33. Pedersen SS, Van Domburg RT, Theuns DAMJ, Jordaens L, Erdman RAM. Concerns about the implantable cardioverter defibrillator: A determinant of anxiety and depressive symptoms independent of experienced shocks. Am Heart J 2005;149(4):664-669.
34. Pedersen SS, Van den Broek KC, Erdman RAM, Jordaens L, Theuns DAMJ. Pre-implantation implantable cardioverter defibrillator concerns and Type D personality increase the risk of mortality in patients with an implantable cardioverter defibrillator. Europace 2010;12(10):1446-1452.
35. Frizelle DJ, Lewin B, Kaye G, Moniz-Cook ED. Development of a measure of the concerns held by people with implanted cardioverter defibrillators: The ICDC. Br J Health Psychol 2006;11(Pt 2):293-301.
36. Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers GM, Camm J, Akhtar m, Luderitz B. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: Implications for the assessment of investigational therapy. J Am Coll Cardiol 2000;36(4):1303-1309.
37. Johansen JB, Pedersen SS, Spindler H, Andersen K, Nielsen JC, Mortensen PT. Symptomatic heart failure is the most important clinical correlate of impaired quality of life, anxiety, and depression in implantable cardioverter-defibrillator patients: A single-centre, cross-sectional study in 610 patients. Europace 2008;10(5):545-551.
38. Pedersen SS, Van den Berg M, Erdman RAM, Van Son J, Jordaens L, Theuns DAMJ. Increased anxiety in partners of patients with a cardioverter-defibrillator: The role of indication for ICD therapy, shocks, and personality. Pacing Clin Electrophysiol 2009;32(2):184-192.
39. Nouwen A, Winkley K, Twisk J, Lloyd C, Peyrot M, Ismail K, Pouwer F; European Depression in Diabetes (EDID) Research Consortium. Type 2 diabetes mellitus as a risk factor for the onset of depression: A systematic review and meta-analysis. Diabetologia 2010;53(12):2480-2486.
40. Babyak MA. What you see may not be what you get: A brief, nontechnical introduction to overfitting in regression-type models. Psychosom Med 2004;66(3):411-421.
41. Bremner JD, Krystal JH, Southwick SM, Charney DS. Noradrenergic mechanisms in stress and anxiety: II. Clinical studies. Synapse 1996;23(1):39-51.
42. LeDoux JE. *The emotional brain*. Malden Massachusetts USA: Blackwell Publishers, 1998.
43. Lampert R, Joska T, Burg MM, Batsford WP, McPherson CA, Jain D. Emotional and physical precipitants of ventricular arrhythmia. Circulation 2002;106(14):1800-1805.
44. Verma A, Wulffhart Z, Lakkireddy D, Khaykin Y, Kaplan A, Sarak B, Biria M, Pillarisetti J, Bhat P, Di Biase L, Constantini O, Quan K, Natale A. Incidence of left ventricular function improvement after primary prevention ICD implantation for non-ischaemic dilated cardiomyopathy: A multicentre experience. Heart 2010;96(7):510-515.
45. Rabiner EA, Gunn RN, Castro ME, Sargent PA, Cowen PJ, Koepp MJ, Meyer JH, Bench CJ, Harrison PJ, Pazos A, Sharp T, Grasby PM. Beta-blocker binding to human 5-HT(1a) receptors in vivo and in vitro: Implications for antidepressant therapy. Neuropsychopharmacology 2000;23(3):285-293.

46. Patten SB, Barbui C. Drug-induced depression: A systematic review to inform clinical practice. Psychother Psychosom 2004;73(4):207-215.

47. Suzuki T, Shiga T, Kuwahara K, Kobayashi S, Suzuki S, Nishimura K, Suzuki A, Ejima K, Manaka T, Shoda M, Ishigooka J, Kasanuki H, Hagiwara N. Prevalence and persistence of depression in patients with implantable cardioverter defibrillator: A 2-year longitudinal study. Pacing Clin Electrophysiol 2010;33(12):1455-1461.

48. Verbeek DEP, Van Riezen J, De Boer RA, Van Melle JP, De Jonge P. A review on the putative association between beta-blockers and depression. Heart Fail Clin 2011;7(1):89-99.

49. Hevey D, McGee HM, Horgan J. Responsiveness of health-related quality of life outcome measures in cardiac rehabilitation: Comparison of cardiac rehabilitation outcome measures. J Consult Clin Psychol 2004;72(6):1175-1180.

50. Van den Broek KC, Nyklícek I, van der Voort PH, Alings M, Meijer A, Denollet J. Risk of ventricular arrhythmia after implantable defibrillator treatment in anxious Type D patients. J Am Coll Cardiol 2009;54(6):531-537.

Relation of statin therapy to psychological functioning in patients with an implantable cardioverter-defibrillator

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ABSTRACT

Background: Statin therapy is an important secondary prevention measure in cardiovascular disease. However, side effects associated with statin use may potentially affect patients' quality of life. Little is known about the influence of statin therapy on the well-being and health status of cardiac patients in general, and patients with an implantable cardioverter-defibrillator (ICD) in particular. We investigated the association between statin therapy and symptoms of anxiety and depression, and patients' health status during the 12 months after implantation, reckoning with statin type and dosage.

Methods: Consecutively implanted ICD patients (N=409; 78% men) completed the Hospital Anxiety and Depression Scale (HADS) and the Short Form Health Survey 36 (SF-36) at baseline, 3, 6, and 12 months after implantation. Data were analyzed using general linear mixed modeling repeated measures multivariable analysis of variance.

Results: Of the 409 patients, 60% were prescribed statins. Statin use was independently associated with poorer role limitations - physical (p=.001), social functioning (p=.007) and role limitations - emotional (p=.007) during the 12 months after implantation, independent of statin type, dosage and other potential confounders. The associations between statin therapy and depression (p=.06) and statin therapy and physical functioning (p=.05) were borderline significant, and no association was found with anxiety (p>.05).

Conclusions: In conclusion, statin therapy was associated with impaired health status on 3 of the 8 SF-36 health status subdomains. This is the first study in ICD patients to examine the association between statin therapy and patient well-being. Future research is warranted to replicate these findings.

INTRODUCTION

The effect of statin therapy on psychological functioning in patients with cardiovascular disease is inconclusive. Some studies have found a link between statin therapy and increased depressive symptoms[1] and impaired psychomotor and attentional functioning.[2] However, statins have also been linked to improved psychological functioning, with a decrease in depressive symptoms,[3-6] major depressive disorder (MDD),[7] and symptoms of anxiety and hostility.[3] Other studies have found no association between statin therapy and psychological functioning.[8,9] No studies to date have examined the association between statin therapy and psychological functioning in ICD patients, nor the potential influence of statin type on these outcomes. Lipophilic and hydrophilic statins might exert differential effects on psychological functioning, because lipophilic statins are capable of crossing the blood-brain barrier, while hydrophilic statins are not.[10] Therefore, the aims of this study were to investigate (1) the association between statin use and psychological functioning, defined as symptoms of anxiety and depression, and patients' health status, and (2) the impact of specific types and dosages of statins on psychological functioning.

METHODS

Patients and study design

Consecutive patients (N=448) implanted with a first-time ICD in the Erasmus Medical Center, Rotterdam, the Netherlands, between August 2003 and February 2010, were enrolled in the Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter Defibrillator: A prospective Study (MIDAS). Exclusion criteria were a life-expectancy of <1 year, being on the waiting list for heart transplantation, a history of psychiatric illness other than affective/anxiety disorders, or insufficient knowledge of the Dutch language. The Medical Ethics Committee of the Erasmus Medical Center approved the study protocol, and the study was conducted according to the Helsinki Declaration. An ICD nurse provided written and oral information on the study before ICD implantation to all patients, and all patients provided written informed consent. The aim of the present study was part of the broader objective to create a more complete picture of the interrelation between ICD patients' psychological functioning and clinical risk profile.

Measures

Demographic and clinical variables

Patients' medical records and purpose-designed questions in the questionnaires were used to obtain baseline demographic and clinical information. The demographic variables included age, gender, marital status and educational level. The clinical variables included indication for ICD therapy (primary versus secondary), treatment with cardiac resynchronization therapy (CRT), left ventricular ejection fraction (LVEF) ≤35%, QRS duration, mean heart rate, the presence of coronary artery disease (CAD), symptomatic heart failure (defined as New York Heart Association (NYHA) functional class III+IV), atrial fibrillation, peripheral artery disease (PAD), prior percutaneous

coronary intervention (PCI) or coronary artery bypass grafting (CABG), smoking, and use of cardiac (i.e. beta-blockers, amiodarone, diuretics, ACE-inhibitors, and digoxin) and psychotropic medication. Information with respect to statin use, including the type and dosage, was also collected at baseline. Because statin use was stable during the 12 months of follow-up in almost all patients, we used the baseline information on statin use for analyses during all follow-up occasions.

Type and dosage of statins

In our cohort, 5 types of statins were prescribed: rosuvastatin, atorvastatin, simvastatin, pravastatin and fluvastatin. Because of differences in pharmacological efficacy and potency, we assigned relative weights to the different types and calculated a relative dose for each patient. According to the literature, the following relative potencies were allocated: fluvastatin, 1; pravastatin, 2; simvastatin, 4; atorvastatin, 8; and rosuvastatin, 16.[11,12] Thus, rosuvastatin is 16 times more potent than fluvastatin in the same dosage. Subsequently, the original statin dosage was multiplied by the relative potency to obtain a relative dosage for each patient, enabling comparisons among the different statin types. Furthermore, a distinction was made between lipophilic (atorvastatin, simvastatin and fluvastatin) and hydrophilic (rosuvastatin and pravastatin) statins according to their capacity to penetrate the blood-brain barrier to compare the effects of the statin types on patients' psychological functioning.

Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS), a 14-item self-report questionnaire with 7 items measuring anxiety (HADS-A) and 7 items measuring depression (HADS-D),[13] was administered at baseline, and at 3, 6 and 12 months after implantation. All items are rated on a 4-point Likert scale, with scores ranging from 0 to 3 (total score range of 0-21), and higher scores reflecting more symptoms.[13] The psychometric properties of the HADS are good.[14]

Health status

Patients' health status at baseline, and at 3, 6 and 12 months after implantation was assessed with the validated Dutch language version of the Short Form Health Survey 36 (SF-36).[15] The questionnaire consists of 36 items that contribute to 8 subscales: physical functioning, role limitations - physical, bodily pain, social functioning, mental health, role limitations - emotional, vitality and general health. Each subscale has a score range from 0 to 100, with higher scores indicating better health status.[16] The psychometric characteristics of the SF-36 are adequate.[15]

Statistical analyses

The baseline demographic and clinical variables for patients with versus without statin therapy were compared with the χ^2 test for nominal variables and the Student's t-test for continuous variables, respectively. To assess the longitudinal association between statin therapy and psychological functioning, generalized linear mixed modeling was used. The major advantage of this technique is that missing data on 1 measurement occasion do not lead to exclusion of that patient from the analyses. Thus, the available data were used optimally. The described effects in the Results section

are the relation of statin use *at any measurement point* with the level of psychological functioning over time, including all measurement occasions. We adjusted for variables that have been associated with impaired psychological functioning in the published arrhythmia literature, including atrial fibrillation,[17] symptomatic heart failure,[18] CAD,[19] diabetes mellitus,[20] appropriate and inappropriate shocks during follow-up,[21] the use of amiodarone[18,22] and psychotropic medication,[23] and smoking.[24] In addition, we adjusted for variables that were expected to be related to psychological functioning or functioning of the cardiovascular system, including age, sex, educational level, PAD, and the use of beta-blockers. Statin use, including type and dosage, was set as a fixed variable (i.e. not varying over time) after ascertaining the stability of statin use in our data set during the 12-month follow-up period. All covariates were also set as fixed variables. The results of the generalized linear mixed modeling analyses are presented as estimates with accompanying t- and p-values, and 95% confidence intervals (CI). In a secondary analysis, the association between statin type (lipophilic versus hydrophilic statins) and psychological functioning was longitudinally assessed with generalized linear mixed modeling, adjusting for the same covariates. For all tests, a p-value <.05 (two sided) was considered significant. Analyses were performed using PASW Statistics 19 statistical software (PASW IBM Corp., Armonk, NY, USA).

RESULTS

Patient baseline characteristics

The original patient sample consisted of 448 patients, of whom 39 had missing information on ≥1 covariates and were therefore automatically excluded from the analyses. Also, 14 patients died during the follow-up period. However, owing to the use of this specific statistical technique, all obtained measurement occasions until moment of death could be included, leaving 409 patients for analyses. We compared the baseline characteristics of the patients included in and excluded from the analyses. No significant differences in the demographic and clinical baseline characteristics were found between the 2 groups (all p>.05). The general response rate was 96% at baseline and 81% at 12 months after implantation.

The baseline demographic and clinical characteristics of the total patient sample and stratified by statin therapy are listed in Table 1. Of all patients, 246 (60%) were using statins. The mean age of the total study sample was 59±12 years and 78% of the patients were men. The median equivalent dosage was 160 mg/day (interquartile range 80-320). During the follow-up period, 59 (14%) patients experienced a shock (both appropriate and inappropriate). No difference in the prevalence of shocks was found between statin users and non statin users (p=.06). In Figure 1, mean scores of anxiety, depression and the 8 health status domains, stratified by statin use, are shown.

Table 1. Baseline characteristics for the total study population and stratified by statin use

	Statin therapy			
	Total (N = 409)	**Yes (N = 246)**	**No (N = 163)**	**p**
Variable				
Mean age (±SD) (years)	58.5 (12.2)	61.6 (9.0)	53.8 (14.6)	**<.001**
Men	320 (78%)	213 (87%)	107 (66%)	**<.001**
Single/no partner	26 (6%)	13 (5%)	13 (8%)	.28
Lower education *	234 (58%)	143 (59%)	91 (57%)	.68
Primary prevention indication	141 (35%)	86 (35%)	55 (34%)	.80
CRT	113 (28%)	80 (33%)	33 (20%)	**.007**
LVEF ≤35% †	305 (86%)	197 (88%)	108 (84%)	.32
Mean QRS (±SD)	130.2 (36.4)	132.9 (34.7)	126.0 (38.6)	.06
CAD	236 (58%)	205 (83%)	31 (19%)	**<.001**
PAD	29 (7%)	25 (10%)	4 (3%)	**.003**
Previous PCI	107 (26%)	95 (39%)	12 (7%)	**<.001**
Previous CABG	85 (21%)	77 (31%)	8 (5%)	**<.001**
Symptomatic heart failure †	133 (33%)	81 (33%)	52 (32%)	.83
Atrial fibrillation	91 (22%)	50 (20%)	41 (25%)	.25
Diabetes	59 (14%)	48 (20%)	11 (7%)	**<.001**
Smoking †	44 (11%)	23 (9%)	21 (13%)	.26
Mean heart rate	68.2 (13.4)	68.7 (14.1)	67.5 (12.2)	.40
Amiodarone use	76 (19%)	43 (18%)	33 (20%)	.48
Beta-blocker use	325 (80%)	219 (89%)	106 (65%)	**<.001**
Diuretics use	232 (57%)	151 (61%)	81 (50%)	**.019**
ACE-inhibitors use	293 (72%)	195 (79%)	98 (60%)	**<.001**
Digoxin use	63 (15%)	34 (14%)	29 (18%)	.28
Psychotropic medication use	67 (16%)	38 (15%)	29 (18%)	.53

* Education ≤13 years; † defined as NYHA functional class III+IV. Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention

The association between statin use and emotional distress

We separately assessed the relation between statin use and the individual psychological measures. Overall, anxiety, depression and health status significantly improved between baseline and 3 months after implantation (all p<.001) and remained stable between 3 and 12 months after implantation. In the unadjusted analyses, statin use was significantly associated with increased depressive symptoms (p=.024), and with impaired health status on the domains physical functioning (p=.001), role limitations - physical (p<.001), social functioning (p=.005), role limitations - emotional (p=.001) and general health (p=.039). No association was found between statin use and symptoms of anxiety, and the health status domains bodily pain, mental health, and vitality.

Table 2. Longitudinal association between statin therapy and anxiety, depression and health status (adjusted analysis)*

	Estimate	t	p	95% CI
Psychological distress				
Anxiety	-0.81	-1.60	.11	-1.80 – 0.18
Depression	-0.97	-1.87	.06	-1.99 – 0.05
SF-36 subdomains				
Physical functioning	6.42	1.93	.05	-0.11 – 12.94
Role limitations – physical	18.02	3.33	**.001**	7.40 – 28.64
Bodily pain	4.31	1.34	.18	-2.03 – 10.65
Social functioning	8.11	2.68	**.008**	2.16 – 14.07
Mental health	2.36	0.96	.34	-2.46 – 7.19
Role limitations – emotional	14.26	2.87	**.004**	4.49 – 24.03
Vitality	4.81	1.74	.08	-0.64 – 10.25
General health	4.06	1.34	.18	-1.89 – 10.01

Abbreviations: *CI*, confidence interval; *SF-36*, Short Form Health Survey 36. * Statin users were the reference group. Adjusted for gender, age, educational level, indication for ICD therapy, occurrence of shocks (both appropriate and inappropriate) during 12 months after implantation, coronary artery disease, symptomatic heart failure, atrial fibrillation, diabetes mellitus, peripheral arterial disease, smoking, the use of amiodarone, beta-blockers, and psychotropic medication

Results of the adjusted analyses are listed in Table 2. After adjusting for demographic and clinical covariates, the association between statin use and depressive symptoms (p=.06) and between statin use and impaired physical functioning (p=.05) was reduced to borderline significance, and the association between statin use and general health was no longer statistically significant. Statin use remained significantly related to role limitations - physical (p=.001), impaired social functioning (p=.007) and role limitations - emotional (p=.006). Just as in the unadjusted analyses, statin use was still not related to anxiety, bodily pain, mental health, or vitality.

A significant time by group interaction effect was seen between the measurements at baseline and 3 months after implantation, with non statin users experiencing a greater reduction in depressive symptoms (from baseline to 3 months follow-up, an extra improvement on the scale of 0.86 points reflected by the estimate (e)=0.86; p=.009), and a larger improvement in physical functioning (e=6.34; p=.019), role limitations - physical (e=16.54; p=.001), social functioning (e=10.82; p=.001), mental health, (e=3.98; p=.039), role limitations - emotional (e=16.28; p.002), and vitality (e=4.75; p=.030) than statin users during this 3-month period. In addition, non statin users improved significantly more on role limitations - physical from 3 to 6 months after implantation (e=11.55; p=.007), and in physical functioning (e=4.72; p=.010) and general health (e=3.18; p=.048) from 6 to 12 months after implantation. The most important other associates of poor psychological functioning were the use of psychotropic medication, symptomatic heart failure, the occurrence of shocks during follow-up, and lower education (results not shown).

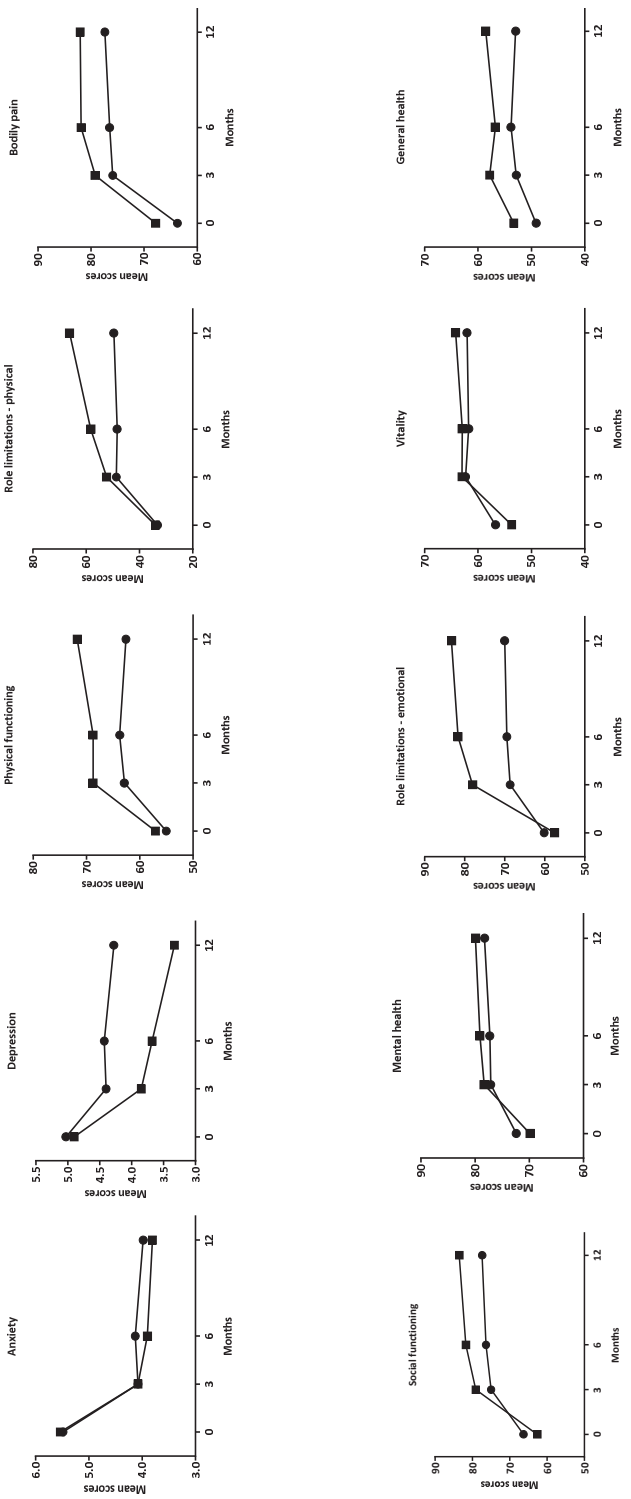

Figure 1. Mean scores on anxiety, depression and the 8 SF-36 health status sub domains stratified by statin use

With respect to the second aim of our study, we compared psychological functioning of patients using different types of statins, reckoning with the relative dosage of each statin type. The number of patients using the different statin types is displayed in Figure 2. We found no significant relation between statin type and psychological functioning after adjusting for the relative statin dosage. Dichotomizing statin type into lipophilic versus hydrophilic also did not result in significant differences in psychological functioning.

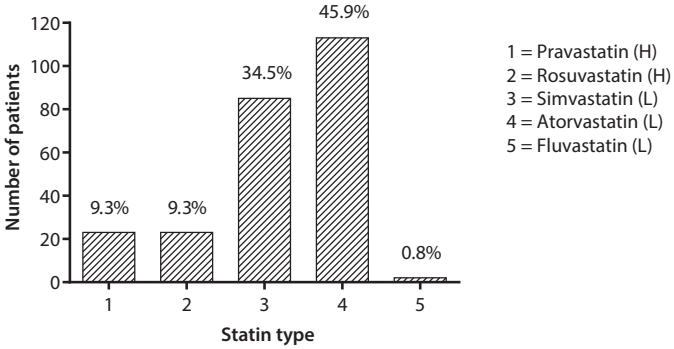

Figure 2. Statin prescription pattern stratified by type *
* H = Hydrophilic; L = Lipophilic

DISCUSSION

This is the first study to investigate the association between statin use and symptoms of anxiety and depression, and health status in patients with an ICD. We found that patients using statins had an impaired health status with respect to the role limitations - physical, social functioning, and role limitations - emotional domains of the SF-36, independent of the type and dosage of statin and other potential demographic and clinical confounders. Patients receiving statin therapy differed systematically on some baseline characteristics from non statin users and had more advanced disease. Thus, this subset of patients constitutes a group that warrants particular attention, given their increased risk of poor health status.

Attention to the impact of drug therapy on psychological functioning is important, because patients' functioning and quality of life can be impaired due to side effects. In ICD patients, this is particularly important, because these patients often use anti-arrhythmic agents, such as amiodarone, together with statin therapy. These drugs can interact with each other, increasing the risk of severe or hampering side effects,[22,25] Examination of the patient's tolerance for specific types and dosages and closer monitoring during follow-up might reduce the possible burden that patients experience. Several studies have investigated the relation between statin use and psychological functioning, with mixed results. Depression in particular has been the target of investigation, with a number of studies reporting improved depressive mood in patients using statins,[3-5,7] other studies reporting worse psychological functioning,[1,2] and still other studies not finding any significant associations.[8,9] Comparing these studies is difficult owing to differences in methodological design, study samples (i.e.

general population versus patients with established heart disease), statin types, and psychological measures. In addition, several studies included a relatively low number of patients using statins[6] or reported a low prevalence of depression.[4,7] Future research should include larger sample sizes, and compare the influence of types matched by means of a daily equivalent dosage, as we were not able to demonstrate a significant relationship between statin type and psychological functioning, probably due to the small number of patients using pravastatin, rosuvastatin and fluvastatin. In addition, future research should focus on a broader spectrum of psychological measures, because depression has been the main focus of investigation so far.

We found no association between statin use and anxiety. However, the type of impairments in patients with side effects might more easily induce depressive rather than anxious symptoms, by interfering with the patient's physical activity level and social relations, possibly inducing feelings of hopelessness and guilt. This pattern corresponds more with depressive rather than anxious symptomatology, and is also reflected by the trend that we found for the relation between statin use and depressive symptoms.

The results of this study should be interpreted in the light of the following limitations. First, we had no information on compliance with prescribed statin therapy, although compliance with statins has proven to be better than compliance with other cardiac medications.[26] Second, because information on serum cholesterol levels was lacking in a considerable number of patients, we did not include serum cholesterol as a covariate in adjusted analyses. However, previous results have shown that baseline cholesterol levels had no influence on the relation between statin use and psychological functioning.[3] Third, we did not have a clear picture of the differences in psychological functioning between statin users and non statin users before to ICD implantation. However, we have presumed a relatively stable difference in psychological functioning between statin and non statin users both before and after implantation, with a short-term decrease in psychological functioning around implantation for both statin and non statin users.

Strengths of the present study included the prospective, repeated measures design, the high response rate, and the use of generalized linear mixed modeling which is the latest statistical approach for analyzing prospective data with repeated measures. In addition, we had detailed information on the patients' baseline demographic and clinical characteristics.

Additional research is warranted to replicate these findings, because, to our knowledge, this is the first study in ICD patients to examine the association between statin therapy and psychological functioning. In the clinical management and care of ICD patients, it is important to be aware of the potential influence of statin therapy on health status, and to discuss this with patients, because decreased psychological functioning is negatively associated with medication adherence.

REFERENCES

1. Hyyppä MT, Kronholm E, Virtanen A, Leino A, Jula A. Does simvastatin affect mood and steroid hormone levels in hypercholesterolemic men? A randomized double-blind trial. Psychoneuroendocrinology 2003;28(2):181-194.
2. Muldoon MF, Barger SD, Ryan CM, Flory JD, Lehoczky JP, Matthews KA, Manuck SB. Effects of lovastatin on cognitive function and psychological well-being. Am J Med 2000;108(7):538-546.
3. Young-Xu Y, Chan KA, Liao JK, Ravid S, Blatt CM. Long-term statin use and psychological well-being. J Am Coll Cardiol 2003;42(4):690-697.
4. Yang CC, Jick SS, Jick H. Lipid-lowering drugs and the risk of depression and suicidal behavior. Arch Intern Med 2003;163(16):1926-1932.
5. Stafford L, Berk M. The use of statins after a cardiac intervention is associated with reduced risk of subsequent depression: Proof of concept for the inflammatory and oxidative hypotheses of depression? J Clin Psychiatry 2011;72(9):1229-1235.
6. Ormiston T, Wolkowitz OM, Reus VI, Manfredi F. Behavioral implications of lowering cholesterol levels: A double-blind pilot study. Psychosomatics 2003;44(5):412-414.
7. Pasco JA, Jacka FN, Williams LJ, Henry MJ, Nicholson GC, Kotowicz MA, Berk M. Clinical implications of the cytokine hypothesis of depression: The association between use of statins and aspirin and the risk of major depression. Psychother Psychosom 2010;79(5):325-325.
8. Wardle J, Armitage J, Collins R, Wallendszus K, Keech A, Lawson A. Randomised placebo controlled trial of effect on mood of lowering cholesterol concentration. BMJ 1996;313(7049):75-78.
9. Stewart RA, Sharples KJ, North FM, Menkes DB, Baker J, Simes J. Long-term assessment of psychological well-being in a randomized placebo-controlled trial of cholesterol reduction with pravastatin. Arch Intern Med 2000;160(20):3144-3152.
10. Sierra S, Ramos MC, Molina P, Esteo C, Vázquez JA, Burgos JS. Statins as neuroprotectants: A comparative in vitro study of lipophilicity, blood-brain-barrier penetration, lowering of brain cholesterol, and decrease of neuron cell death. J Alzheimers Dis 2011;23(2):307-318.
11. Weng TC, Yang YHK, Lin SJ, Tai SH. A systematic review and meta-analysis on the therapeutic equivalence of statins. J Clin Pharm Ther 2010;35(2):139-151.
12. Kostis WJ, Cheng JQ, Dobrzynski JM, Cabrera J, Kostis JB. Meta-analysis of statin effects in women versus men. J Am Coll Cardiol 2012;59(6):572-582.
13. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67(6):361-370.
14. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997;27(2):363-370.
15. Aaronson NK, Muller M, Cohen PDA, Essink-Bot M-L, Fekkes M, Sanderman R, Sprangers MA, Te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51(11):1055-1068.
16. Ware J, Kosinski M. Interpreting SF-36 summary health measures: A response. Qual Life Res 2001;10(5):405-413.
17. Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers GM, Camm J, Akhtar M, Luderitz B. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: Implications for the assessment of investigational therapy. J Am Coll Cardiol 2000;36(4):1303-1309.
18. Johansen JB, Pedersen SS, Spindler H, Andersen K, Nielsen JC, Mortensen PT. Symptomatic heart failure is the most important clinical correlate of impaired quality of life, anxiety, and depression in implantable cardioverter-defibrillator patients: A single-centre, cross-sectional study in 610 patients. Europace 2008;10(5):545-551.
19. Kendler KS, Gardner CO, Fiske A, Gatz M. Major depression and coronary artery disease in the Swedish twin registry: Phenotypic, genetic, and environmental sources of comorbidity. Arch Gen Psychiatry 2009;66(8):857-863.
20. Nouwen A, Winkley K, Twisk J, Lloyd C, Peyrot M, Ismail K, Pouwer F; European Depression in Diabetes (EDID) Research Consortium. Type 2 diabetes mellitus as a risk factor for the onset of depression: A systematic review and meta-analysis. Diabetologia 2010;53(12):2480-2486.

21. Pedersen SS, Tekle FB, Hoogwegt MT, Jordaens L, Theuns DAMJ. Shock and patient preimplantation Type D personality are associated with poor health status in patients with implantable cardioverter-defibrillator. Circ Cardiovasc Qual Outcomes 2012;5(3):373-380.
22. Armitage J. The safety of statins in clinical practice. Lancet 2007;370(9601):1781-1790.
23. Hoogwegt MT, Kupper N, Theuns DAMJ, Zijlstra WP, Jordaens L, Pedersen SS. Undertreatment of anxiety and depression in patients with an implantable cardioverter-defibrillator: Impact on health status. Health Psychol 2012;31(6):745-753.
24. Taira DA, Seto TB, Ho KKL, Krumholz HM, Cutlip DE, Berezin R, Kuntz RE, Cohen DJ. Impact of smoking on health-related quality of life after percutaneous coronary revascularization. Circulation 2000;102(12):1369-1374.
25. Bowman L, Armitage J, Bulbulia R, Parish S, Collins R. Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH): Characteristics of a randomized trial among 12064 myocardial infarction survivors. Am Heart J 2007;154(5):815-823.e816.
26. Bedell SE, Jabbour S, Goldberg R, Glaser H, Gobble S, Young-Xu Y, Graboys TB, Ravid S. Discrepancies in the use of medications: Their extent and predictors in an outpatient practice. Arch Intern Med 2000;160(14):2129-2134.

PART TWO

In search of a psychophysiological link between emotional distress and clinical outcomes: Autonomic nervous system function as a candidate mechanism

Relation between emotional distress and heart rate variability in patients with an implantable cardioverter-defibrillator

6

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ABSTRACT

Background: We investigated the relationship between Type D personality, depression and anxiety, and heart rate variability (HRV) in 64 patients with an implantable cardioverter-defibrillator (ICD).

Methods: HRV was obtained via 24-hour Holter monitoring, and 24-hour, 30 minutes daytime rest and 30 minutes nighttime sleep HRV were analyzed.

Results: In adjusted analyses, significant associations (standard deviation of normal-to-normal (NN) intervals (SDNN): p=.043 and standard deviation of NN intervals over 5-minute periods (SDANN): p=.010) and a trend (HRV triangular index: p=.09) were found for Type D personality, and trends were found for depression (lower root mean square of successive differences in NN intervals (RMSSD): p=.10 and lower proportion of NN intervals deviating >50 ms from the preceding interval (pNN50): p=.09). During daytime rest, similar results were found for anxiety and depression. During nighttime sleep, only noteworthy adjusted associations were found for depression (lower RMSSD: p=.06; lower pNN50=.043). A Benjamini-Hochberg correction for multiple testing lead to reduction of the number of significant relationships, but there was still support for lower autonomic control patients with Type D personality and depression.

Conclusions: A shift towards sympathetic dominance and reduced vagal activity was observed in ICD patients with emotional distress. This may trigger the development of ventricular tachycardia, resulting in a poorer prognosis. Future research with larger sample sizes is warranted.

INTRODUCTION

Patients with an implantable cardioverter-defibrillator (ICD) constitute a high-risk group in terms of emotional distress, with prevalence rates of 20-35% for symptoms of anxiety and depression[1,2] and 20-30% for the distressed personality type (Type D),[3] reflecting the combined tendency to experience a wide range of negative emotions, while inhibiting the expression of these emotions in social contexts.[4] Anxiety appears to be particularly important in ICD patients, due to the potential of the device to provide uncontrollable and often unpredictable shocks.[1]

Emotional distress including depression and anxiety, as well as more stable personality traits such as Type D, have been associated with cardiac events and poor prognosis in both persons without[7] and patients with cardiac diseases.[3,5,6] In both patients with coronary artery disease (CAD) and patients with an ICD, emotional distress is known to increase the risk of ventricular arrhythmias[8,9] and mortality,[10,11] independent of traditional biomedical risk factors. In heart failure patients and patients who were treated with percutaneous coronary intervention (PCI) though, null findings have been reported for the association of Type D personality and depression with mortality as well.[12-14]

We know little about the mechanisms that may explain the association between emotional distress and worse prognosis in ICD patients. One potential mechanism involves the autonomic nervous system, which may be deregulated in patients with an ICD.[15] Heart rate variability (HRV) is a widely used noninvasive measure reflecting the autonomic regulation of the heart,[16] and is measured by beat-to-beat changes in heart rate.[17] Reduced HRV (i.e. increased sympathetic and/or decreased parasympathetic activity) is a well-known predictor of cardiac mortality, including sudden cardiac death due to ventricular fibrillation, in post myocardial infarction patients.[18,19] Hence, HRV might be an important explaining mechanism of the relationship between emotional distress and prognosis. In the general cardiac population, there is evidence to suggest that HRV is decreased in patients with clinical levels of depression[20] and anxiety[21] as compared to patients without emotional distress. However, to date, only one study has investigated the relationship between emotional distress and HRV in ICD patients,[22] and evidence on the association between Type D personality and HRV is only present in non-medical samples, reporting absence of a relationship[23] and, in contrast, a reduced HRV in European-Americans with Type D personality.[24]

As this merits further examination, the purpose of our study was to investigate the relationship between psychological risk factors that have been demonstrated to be associated with increased risk of ventricular tachyarrhythmias and mortality[25] and HRV, with a specific focus on Type D personality, depression and ICD related anxiety.

METHODS

Patients and study design

A subset of 79 patients from the prospective Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter Defibrillator: A prospective Study (MIDAS) comprised the current sample. Information on the MIDAS study, its design and patient inclusion has been described previously.[26] This subset of patients received a Holter monitor 10 days after implantation during a

scheduled wound healing control visit to measure 24-hour HRV. HRV measurement was planned 10 days post implantation so that patients would not be burdened directly after implantation. After excluding incomplete cases with respect to information on HRV and psychological risk factors, 64 patients were available for statistical analyses when examining the relationship between Type D personality and HRV, and 63 patients when examining the association between depression and HRV, and ICD concerns and HRV. A flow chart of the patient selection is displayed in Figure 1. The Medical Ethics Committee of the Erasmus Medical Center, the Netherlands approved the study protocol and the study was conducted according to the Helsinki Declaration. An ICD nurse provided oral and written information regarding the study while patients were admitted to the hospital. At 10 days post implantation, instructions about the Holter monitor (i.e. that being hooked up to the Holter monitor would not interfere with the therapy given by the ICD and vice versa) were provided. Patients were asked to complete a set of standardized and validated questionnaires at 10 days post implantation. Before participation in the study, all patients provided written informed consent.

Measures

Demographic and clinical variables

Information on demographic and clinical characteristics was obtained from patients' medical records at baseline (i.e. the time of implantation) and purpose-designed questions in the questionnaires at 10 days post implantation. Demographic variables included age, gender, marital status and educational level. Clinical variables included indication for ICD therapy (primary versus secondary prevention), treatment with cardiac resynchronization therapy (CRT), left ventricular ejection fraction (LVEF) ≤35%, QRS duration, the presence of CAD, symptomatic heart failure (defined as New York Heart Association (NYHA) functional class III+IV), atrial fibrillation, prior PCI or coronary artery bypass grafting (CABG), smoking, and use of cardiac (i.e. beta-blockers, statins, amiodarone, diuretics, angiotensin-converting enzyme (ACE)-inhibitors, and digoxin) and psychotropic medication.

Heart rate variability

Heart rate variability (HRV) was measured via 24-hour Holter monitoring from a 7-lead configuration. A sampling rate of 1440 Hz was used to digitize electrocardiogram (ECG) data. Computer software (Holter LX® Analysis Pro Software, NorthEast Monitoring, Maynard, MA, USA) was used to scan for rhythm disturbances (of both ventricular and atrial origin) and to detect and label each QRS complex. All ECG recordings were processed by a qualified Holter analyst, who was not otherwise involved in the study. Holter recordings with >100/h premature ventricular contractions (PVCs) were excluded from analyses (N=12). Rhythm disturbances were discarded automatically by the computer program. On average, 75 of the 82 recordings (91%) contained normal sinus rhythm, which was then used to calculate the HRV measures. Only non-paced means of HRV measures were used in order to create a clear picture of pure autonomic functioning independent of pacemaker action.

The following time domain measures were used as a measure of HRV: the standard deviation of all normal-to-normal (NN) intervals (SDNN) and the HRV triangular index, both reflecting overall variability in heart rate (HR), the standard deviation of the average NN interval calculated over

5-minute periods (SDANN), as an estimate of long-term components of HRV, and the proportion of NN intervals deviating >50 ms from the preceding interval (pNN50), a measure of parasympathetic activity of the heart. Finally, the root mean square of successive differences in NN intervals (RMSSD) was calculated, which reflects parasympathetic efferent activity to the heart.[27]

Information on activity levels during the monitoring period

In order to capture HRV during resting activity and sleep, patients completed an activity diary. In this diary, patients registered two 30-minute periods of resting activity, such as reading or watching television. In addition, the time of going to bed and waking up were recorded. The diary enabled comparison between HRV of the overall 24-hour period and HRV during resting and night-time sleep. Potential noise, including noise from physical activity, was minimized during the resting and nighttime sleep HRV measurement occasions. During nighttime sleep, a 30-minute period was selected between 2.00 am and 3.00 am to calculate HRV variables. On average, this period was 3 hours after going to bed, hereby avoiding interfering mechanisms associated with falling asleep and waking up. Data consisted of 6 5-minute intervals for each separate resting activity and 6 5-minute intervals during sleep that were combined into one mean value for SDNN, RMSSD and pNN50, both for resting activity and nighttime sleep.

Type D personality

Type D was measured at baseline with the 14 item Type D Scale (DS14), with items rated on a 5-point Likert scale from 0 to 4. The DS14 is composed of a 7-item negative affectivity (NA) and a 7-item social inhibition (SI) subscale, both with a total score range from 0 to 28. Patients with a score of ^{3}10 on both subscales were defined as having a Type D personality, which has been defined as the best cut-off using item response therapy.[4,28] With Cronbach's alphas of 0.88 and 0.86 for NA and SI, respectively, the DS14 has shown to be a valid and internally consistent measure which is stable over time.[4] Type D is not confounded by indicators of disease severity, such as left ventricular ejection fraction.[29]

Depression

The Hospital Anxiety and Depression Scale (HADS) was used to measure depressive symptoms.[30] The HADS is a 14-item self-report questionnaire consisting of 7 items measuring symptoms of anxiety (HADS-A) (not used in the current study) and 7 items measuring symptoms of depression (HADS-D). A 4-point Likert scale is used to rate the items, with scores ranging from 0 to 3 (total score range of 0-21) and higher scores reflecting more symptoms. The psychometric properties of the HADS are good, with mean Cronbach's alphas of 0.83 and 0.82 for the HADS-A and HADS-D subscales, respectively.[31,32] The HADS is a valid instrument for measuring separate symptoms of anxiety and depression in a non psychiatric hospital setting.[31,32]

ICD concerns

Patients' concerns related to their ICD were measured with the 8-item ICD Patient Concerns questionnaire (ICDC),[33] a disease-specific anxiety questionnaire originally developed in the United Kingdom,[34] abbreviated and validated for the Dutch setting.[33] Items are rated on a 5-point Likert scale from 0 *(not at all)* to 4 *(very much so)*. All items are summed to a total score with a maximum of 32, with a higher score reflecting more ICD concerns.[33] The internal consistency of the ICDC is good, with a Cronbach's alpha of 0.91.[33]

Statistical analyses

HRV distributions were examined for outliers. Values >3 standard deviations (SD) from the mean and exceeding the plausible range proposed by the HRV Task Force,[17] were not included in analyses. With respect to the 10 24-hour HRV measures, 4 patients had one or more outlying values (N_{values}=9). Regarding the HRV measures during resting activity, 7 patients had one or more outlying values (N_{values}=25) and for the HRV measures during sleep, 4 patients had one or more outlying values (N_{values}=22). HRV distributions were examined for normality via skewness and Shapiro-Wilk tests. As none of the HRV variables were normally distributed, natural log (ln) transformation was performed.

Baseline demographic and clinical variables for patients with complete versus incomplete data were compared with the χ^2 test (Fisher's Exact test when appropriate) for nominal variables and Student's t-test for continuous variables, respectively. Baseline demographic and clinical variables for patients with emotional distress (i.e. Type D personality and the presence of clinically significant levels of depression and ICD concerns as determined by frequently used cut-off scores of ≥8 for depression[32] and ≥13 for ICD concerns[3] were also compared with the χ^2 test (Fisher's Exact test when appropriate) for nominal variables and Student's t-test for continuous variables, respectively. The relationship between the psychological measures and HRV was assessed with linear regression analyses using the natural log transformed HRV measures. Results of these analyses are presented as standardized β-coefficients with accompanying p-values, and effect sizes (f^2) as indicators of the strength of the associations. Analyses for Type D personality were repeated using the continuous subscales NA and SI and their interaction, and results were compared with the dichotomous measure of Type D personality.

In multivariable analyses, we adjusted for age, rhythm control by CRT-D, the use of beta-blockers, and the use of psychotropic medication, as these covariates are known to influence HRV.[35-38] As beta-blockers mainly act on ventricular receptors controlled by the sympathetic nervous system, beta-blocker use was omitted as a covariate in the analyses of the parasympathetic and non-autonomic nervous system HRV measures, to preserve statistical power. For all tests, a p-value of <.05 (two-sided) was considered significant.

We decided to report a correction for multiple testing in addition to the regular results. It is important to acknowledge that we are dealing with multiple, *dependent* comparisons in the current study, as the outcome variables are all part of the same biological regulatory system. A simple Bonferroni correction would therefore not suffice and would lead to an increase of false negatives. Instead, we followed the Benjamini-Hochberg procedure, which controls for the false discovery

rate.[39] Following this procedure, the individual p-values were put in order from smallest to largest. The smallest p-value was ranked as i=1, the next p-value as i=2, etc. Each individual p-value was then compared to (i/m)*Q, with m=the total number of tests and Q=the chosen false discovery rate, which was set at Q=.05 according to common guidelines. If p<(i/m)*Q, the result is regarded significant, controlled for the false discovery rate.[39] All statistical analyses were performed using PASW Statistics 19 statistical software (PASW IBM Corp., Armonk, NY, USA).

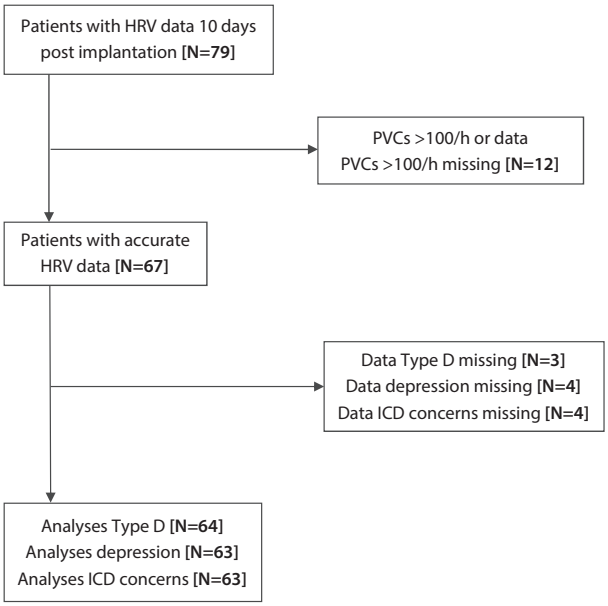

Figure 1. Flow chart of patient inclusion in the analyses
Abbreviations: *h*, hour; *HR*, heart rate; *HRV*, heart rate variability; *ICD*, implantable cardioverter-defibrillator; *N*, number; *PVCs*, premature ventricular contractions

RESULTS

Patient baseline characteristics

Patients included in and patients excluded from analyses were compared on baseline characteristics. Excluded patients were less likely to have a LVEF ≤35% (p=.048) and use psychotropic medication (p=.035). No other systematic differences were found between these 2 groups.

Baseline demographic and clinical characteristics of the total patient sample are displayed in Table 1. The mean age was 58±13 years, and 83% of the patients (N=53) were male. In total, 23% (N=15) were classified as having a Type D personality. Mean depression score was 3.3±3.2, mean ICD concerns score was 8.0±7.4. Mean values for the original, non-transformed HRV measures are displayed in Table 2.

Table 1. Baseline characteristics for the total study population *

	Total (N = 64)
Demographics	
Mean age (±SD) (years)	52.78 (13.4)
Men	53 (82.8%)
Single/no partner †	4 (6.3%)
Lower education †‡	35 (55.6%)
Clinical factors	
Primary prevention indication	13 (81.2%)
CRT	113 (20.3%)
LVEF ≤35% §	54 (91.5%)
Mean QRS (±SD)	130.39 (35.3)
CAD	35 (54.7%)
Previous PCI	17 (26.6%)
Previous CABG	8 (12.5%)
Symptomatic heart failure #	17 (26.6%)
Atrial fibrillation	7 (10.9%)
Diabetes	9 (14.1%)
Smoking †	6 (9.5%)
Mean heart rate	71.5 (9.0)
Medication use	
Amiodarone	2 (3.1%)
Beta-blocker	52 (81.2%)
Diuretics	27 (42.2%)
ACE-inhibitors	33 (51.6%)
Digoxin	6 (9.4%)
Psychotropic medication †	15 (23.8%)

* Data are presented as N (%), unless otherwise indicated. Abbreviations: *ACE*, angiotensin-converting enzyme; *CABG*, coronary artery bypass grafting; *CAD*, coronary artery disease; *CRT,* cardiac resynchronization therapy; *LVEF*, left ventricular ejection fraction; *N*, number; *PCI*, percutaneous coronary intervention; *QRS*, QRS duration; *SD*, standard deviation. † 1 (1.6%) missing; ‡ education less than or equal to 13 years; § 5 (7.8%) missing; # defined as NYHA functional class III+IV.

When comparing demographic and clinical baseline characteristics of patients with versus without emotional distress (i.e. Type D personality, and clinically significant symptoms of depression and ICD concerns), we found that patients with emotional distress significantly more often used psychotropic medication (Type D personality: p=.017; depression: p=.002; ICD concerns: p=.037). In addition, we found that patients with depression more often suffered from symptomatic heart failure (p=.048) and had a higher heart rate (p=.030). No other systematic differences were found between patients with versus without emotional distress.

Table 2. Mean values (SD) of heart rate variability components over 24 hours, resting activity and sleep (N=64) *

Time domain measures		**Frequency domain measures**	
24 hours			
SDNN (ms)	103.86 (35.73)	Total power (ms^2) †‡	0.13 (0.12)
SDANN (ms)	82.44 (30.59)	VLF (ms^2) ‡	0.09 (0.09)
pNN50 (%)†	6.65 (7.66)	LF(ms^2) ‡§	0.04 (0.03)
RMSSD †	29.78 (14.48)	Hf (ms^2) ‡	0.02 (0.03)
HRV triangular index	26.35 (9.77)	LF/HF ratio #	4.31 (3.12)
Resting activity			
SDNN (ms) ‖	40.72 (19.21)		
pNN50 (%)	25.79 (14.19)		
RMSSD ‖	5.67 (7.74)		
Sleep			
SDNN (ms) ‡	45.00 (23.90)		
pNN50 (%) **	25.69 (13.29)		
RMSSD ‡	6.33 (8.04)		

* For descriptive purposes, the original, non transformed values for each HRV measure are mentioned.
† 2 outliers (3.1%); ‡ 7 missing (10.9%); § 3 outliers (4.7%); # 6 missing (9.4%); || 14 missing (21.9%); ** 15 missing (23.4%). Abbreviations: *HF*, high frequency; *HRV*, heart rate variability; *LF*, low frequency; *N*, number; *NN*; normal-to-normal intervals; *pNN50*, proportion of the total number of successive NN intervals greater than 50 ms; *RMSDD*, square root of the mean squared difference of successive NN intervals; *SDANN*, standard deviation of the average NN interval; *SDNN*, standard deviation of the NN interval; *VLF*, very low frequency

Association between emotional distress and HRV over 24 hours

Type D personality - In unadjusted analyses, Type D personality was associated with lower overall autonomic control, as reflected by lower levels of SDNN (p=.014), SDANN (p=.004) and HRV triangular index (p=.016) (Table 3). When adjusting for the selected covariates, the association between Type D personality and SDNN (p=.043) and SDANN (p=.010) remained significant, and the relation with HRV triangular index (p=.09) was reduced to trend level. No significant relationships were found between Type D personality and the other HRV measures, although a trend was observed for patients with a Type D personality to show a reduced parasympathetic control as measured by a lower pNN50 (p=.08).

Results from the analyses including the continuous subscales were comparable to those using the dichotomous Type D classification for the NA x SI interaction term (unadjusted analyses: SDNN: β=0.63, p=.10; SDANN: β=0.61, p=.11; HRV triangular index: β=0.66; p=.08, all other HRV measures: p>.15). No significant associations were found between the individual subscales of the DS14 and HRV. Effect sizes regarding the association between Type D personality and HRV measures were small to medium, range f^2 [0.01-0.13] in adjusted analyses.

Depression - In unadjusted analyses, depression was only associated with lower pNN50 (p=.050), that is, decreased parasympathetic cardiac control. This association was reduced to trend level in adjusted analyses (p=.09). Depression was also related to lower RMSSD values on a trend level in

both unadjusted (p=.09) and adjusted (p=.10) analyses. Effect sizes with respect to these associations were small, range f^2 [0.00-0.06] in adjusted analyses.

ICD concerns - Analogous to Type D personality, a higher level of ICD concerns was related to lower overall autonomic cardiac control, reflected by a lower SDNN (p=.033), SDANN (p=.030) and HRV triangular index (p=.027). However, these associations became borderline (SDANN: p=.10) or non-significant in adjusted analyses. ICD concerns were not associated with other HRV measures in this sample. Small effect sizes, range f^2 [0.00-0.05] in adjusted analyses, were found for the relationship between ICD concerns and HRV.

Association between emotional distress and HRV during resting activity and sleep

In Table 4, results of the unadjusted and adjusted analyses on the relationship between emotional distress and HRV during resting activity and sleep are displayed.

Type D personality - Type D personality was associated with a lower overall autonomic control during the 30-minute resting activity as reflected by significant lower SDNN in unadjusted (p=.026) analysis. In addition, parasympathetic cardiac control was decreased, reflected by a lower pNN50 (p=.023). When adjusting for relevant covariates, we found a trend for the relationship between Type D personality and overall autonomic control (p=.08) with a small to medium effect size, while the association between Type D personality and lower parasympathetic control remained significant (p=.028), again with a small to medium effect size, range f^2 [0.01-0.12] in adjusted analyses. No significant relationships were found between Type D personality and HRV during sleep.

Depression - In unadjusted analysis of the resting activity data, a significant association was found between depressive symptoms and lower parasympathetic control (pNN50: p=.033). This relationship remained significant in adjusted analysis (p=.006) with a medium to large effect size (f^2=0.22 in adjusted analyses). The relationship between depression and lower RMSSD (p=.08) became borderline significant in adjusted analysis. The use of psychotropic medication largely accounted for this effect. During sleep, pNN50 was significantly decreased in patients with more depressive symptoms (p=.043), which was supported by a small to medium effect size. Furthermore, we found a trend for a lower RMSSD in patients with depressive symptoms (p=.06) in adjusted analysis, both indicative of decreased parasympathetic control. Again, the use of psychotropic medication largely accounted for this effect.

ICD-concerns - No significant associations were found between ICD concerns and HRV, neither in unadjusted or adjusted analyses, nor during resting activity nor during sleep. Effect sizes regarding these associations were rather small, range f^2 [0.00-0.04] in adjusted analyses.

The Benjamini-Hochberg correction

After applying the Benjamini Hochberg correction (see the formula in Tables 3 and 4), the association between Type D personality and SDNN remained significant regarding 24-hour HRV in unadjusted analysis. In addition, trends were found for the relation between Type D personality and 24-hour SDNN and HRV triangular index, also in unadjusted analysis.

Table 3. Unadjusted and adjusted association between Type D personality, depression and ICD concerns, and HRV over 24 hours

	Type D								Depression								ICD concerns							
	Unadjusted				Adjusted				Unadjusted				Adjusted				Unadjusted				Adjusted			
HRV measures	β	p	(i/M) *Q	f^2	β	p	(i/M) *Q	f^2	β	p	(i/M) *Q	f^2	β	p	(i/M) *Q	f^2	β	p	(i/M) *Q	f^2	β	p	(i/M) *Q	f^2
Overall*																								
Total power	-0.18	.20	0.03	0.03	-0.18	.24	0.025	0.03	-0.17	.23	0.02	0.03	-0.21	.18	0.02	0.04	-0.19	.18	0.025	0.04	-0.15	.33	0.025	0.02
SDNN	-0.31	**.014**	0.01	0.10	-0.25	**.043**	0.01	0.08	-0.13	.32	0.025	0.02	-0.13	.34	0.035	0.02	-0.27	**.033**	0.015	0.08	-0.20	.14	0.01	0.04
SDANN	-0.36	**.004**	0.005	0.15	-0.33	**.010**	0.005	0.13	-0.12	.37	0.035	0.01	-0.13	.37	0.04	0.02	-0.27	**.030**	0.01	0.08	-0.23	***.10***	0.005	0.05
HRV triangular index	-0.30	**.016**	0.015	0.10	-0.21	***.09***	0.015	0.05	-0.12	.35	0.03	0.01	-0.08	.55	0.045	0.01	-0.28	**.027**	0.005	0.08	-0.13	.32	0.02	0.02
Sympathovagal*																								
LF	-0.18	.19	0.025	0.03	-0.17	.25	0.03	0.03	-0.14	.32	0.025	0.02	-0.17	.28	0.025	0.03	-0.12	.41	0.035	0.01	-0.04	.79	0.05	0.00
LF/HF ratio	-0.12	.37	0.045	0.03	-0.07	.61	0.05	0.01	-0.02	.88	0.04	0.00	0.04	.79	0.05	0.00	-0.03	.85	0.045	0.00	0.07	.62	0.04	0.01
Parasympathetic †																								
HF	-0.13	.35	0.04	0.02	-0.12	.41	0.04	0.01	-0.19	.16	0.015	0.04	-0.22	.12	0.015	0.05	-0.16	.24	0.03	0.03	-0.13	.40	0.03	0.01
RMSSD	-0.12	.38	0.05	0.01	-0.08	.56	0.045	0.01	-0.22	***.09***	0.01	0.05	-0.24	***.10***	0.01	0.05	-0.11	.42	0.04	0.01	-0.07	.63	0.045	0.01
pNN50	-0.12	***.08***	0.02	0.05	-0.20	.15	0.02	0.04	-0.25	**.050**	0.005	0.07	-0.25	***.09***	0.005	0.06	-0.20	.12	0.02	0.04	-0.17	.25	0.015	0.03
Non ANS †																								
VLF	-0.17	.22	0.035	0.03	-0.12	.39	0.035	0.02	-0.16	.23	0.02	0.03	-0.15	.30	0.03	0.02	-0.18	.18	0.025	0.03	-0.11	.47	0.035	0.01

* Adjusted for age, CRT, the use of beta-blockers and the use of psychotropic medication. † Adjusted for age, CRT, and the use of psychotropic medication. (i/m)Q reflects the Benjamini-Hochberg test which controls for the false discovery rate, with i=rank of the p-value for each test, m=total number of hypotheses tested and Q=the chosen false discovery rate which is set at .05 in this study. If p<(i/m)Q then the result is significant, controlled for the false discovery chance. f^2 refers to effect size. Bold p-values and (i/m)Q values are significant, and bold and italic p-values are on a trend level. Abbreviations: *ANS*, autonomic nervous system; *CAD*, coronary artery disease; *CRT*, cardiac resynchronization therapy; *HF*, high frequency; *HRV*, heart rate variability; *LF*, low frequency; *NN*, normal-to-normal intervals; *pNN50*, proportion of the total number of successive NN intervals greater than 50 ms; *PTSD*, posttraumatic stress disorder; *RMSDD*, square root of the mean squared difference of successive NN intervals; *SDANN*, standard deviation of the average NN interval; *SDNN*, standard deviation of the NN interval; *VLF*, very low frequency

Table 4. Unadjusted and adjusted association between Type D personality, depression and ICD concerns, and HRV during resting activity and sleep

	Type D								Depression								ICD concerns							
	Unadjusted				Adjusted				Unadjusted				Adjusted				Unadjusted				Adjusted			
HRV measures	β	p	(i/M) *Q	f^2	β	p	(i/M) *Q	f^2	β	p	(i/M) *Q	f^2	β	p	(i/M) *Q	f^2	β	p	(i/M) *Q	f^2	β	p	(i/M) *Q	f^2
Resting activity																								
Overall*																								
SDNN	-0.31	**.026**	**0.03**	0.11	-0.27	***.08***	0.03	0.08	-0.13	.39	0.05	0.02	-0.27	.11	0.05	0.07	-0.05	.74	0.03	0.00	0.00	.98	0.03	0.00
Parasympathetic †																								
RMSSD	-0.16	.27	0.05	0.03	-0.15	.36	0.05	0.02	-0.16	.29	0.03	0.03	-0.31	***.08***	0.03	0.09	0.03	.85	0.05	0.00	0.01	.98	0.03	0.00
pNN50	-0.32	**.023**	***0.02***	0.11	-0.35	**.028**	***0.02***	0.12	-0.31	**.033**	0.02	0.11	-0.48	**.006**	**0.02**	0.22	-0.18	.24	0.02	0.03	-0.20	.24	0.02	0.04
Sleep																								
Overall*																								
SDNN	-0.13	.33	0.05	0.02	-0.11	.42	0.03	0.01	-0.10	.44	0.05	0.01	-0.19	.22	0.05	0.03	-0.08	.54	0.02	0.00	-0.04	.80	0.05	0.00
Parasympathetic †																								
RMSSD	-0.15	.25	0.02	0.03	-0.20	.17	0.02	0.04	-0.15	.26	0.03	0.02	-0.29	**.06**	0.03	0.08	-0.06	.67	0.03	0.00	-0.09	.58	0.03	0.01
pNN50	-0.16	.26	0.03	0.03	-0.20	.17	0.02	0.04	-0.21	.13	0.02	0.05	-0.32	**.043**	0.02	0.09	-0.09	.54	0.02	0.00	-0.12	.44	0.02	0.01

* Adjusted for age, CRT, the use of beta-blockers and the use of psychotropic medication. † Adjusted for age, CRT, and the use of psychotropic medication. f^2 refers to effect size. Bold and italic p-values are on a trend level. Abbreviations: *ANS*, autonomic nervous system; *CAD*, coronary artery disease; *CRT*, cardiac resynchronization therapy; *HF*, high frequency; *HRV*, heart rate variability; *LF*, low frequency; *NN*, normal-to-normal intervals; *pNN50*, proportion of the total number of successive NN intervals greater than 50 ms; *PTSD*, posttraumatic stress disorder; *RMSDD*, square root of the mean squared difference of successive NN intervals; *SDANN*, standard deviation of the average NN interval; *SDNN*, standard deviation of the NN interval; *VLF*, very low frequency

With respect to HRV measured during resting activity, the relation between Type D personality and SDNN remained significant after correction for the false positive rate in unadjusted analysis, as well as the association between depression and pNN50 in adjusted analysis. During sleep, the only significant association and association on a trend level between depression and RMSSD and pNN50 respectively, became non-significant after the Benjamini-Hochberg correction (see Table 4).

DISCUSSION

The current study examined the association between emotional distress (i.e. Type D personality, depression and patient ICD concerns) and time and frequency measures of HRV in a subsample of a consecutive cohort of patients with an ICD. Results demonstrated that Type D personality was independently associated with lower overall autonomic control over the 24-hour period and lower parasympathetic cardiac control during rest. We found trends for depression being associated with decreased parasympathetic functioning during rest and over the 24-hour period, and a trend for ICD related concerns to be associated with decreased overall autonomic control over 24 hours. After applying the Benjamini-Hochberg correction, adjusting for the false discovery rate, we only found a strong indication for Type D personality being related to a lower 24-hour SDANN in unadjusted analysis, to lower SDNN during resting activity in unadjusted analysis and for depression to be associated with lower pNN50 in adjusted analysis.

When comparing the results of the 24-hour measurement and the measurements during resting activity and sleep, largely similar findings were revealed with respect to Type D personality. An even more pronounced decline of parasympathetic control in Type D patients was detected when patients performed a resting activity when compared to the 24-hour measurement. The relationship between depression and decreased parasympathetic control was also more clearly manifested during the resting activity and sleep measurements, indicating an inability of the parasympathetic nervous system to recover during rest in patients with a Type D personality and/or depressive symptomatology. In contrast, the relationship between ICD concerns and HRV was only visible during the 24-hour measurement, and only with respect to overall HRV measures.

When comparing the different types of distress, ICD concerns may be identified as a specific type of anxiety, while Type D personality and depression are mood related types of distress. In more detail, several items of the ICD Patient Concerns questionnaire specifically examine ICD patients' anxiety related to engaging in active behavior. Anxiety is associated with symptoms of arousal and therefore with sympathetic control, explaining why we only found significant decreases in HRV for the 24-hour, sympathetic driven HRV-measures. Although we do not have data of pure sympathetic HRV measures to support this hypothesis, this may imply that the arousal response in patients with increased levels of ICD concerns may be stronger than in patients with lower levels of ICD concerns. The mental association between becoming active and fear for the ICD firing may result in physiological arousal and sympathetic activation in patients with increased levels of ICD concerns which is only visible during 24-hour measurement with periods of active behavior.

Overall autonomic and parasympathetic control were the HRV indices most likely to be associated with emotional distress in our patients. This corresponds to results of Francis et al. (2009),

who found a reduced parasympathetic control as measured by a lower RMSSD and pNN50 in ICD patients with elevated depressive symptoms,[22] and to findings in patients who were treated with PCI, also pointing towards lower parasympathetic control in patients with depressive and anxious symptomatology.[40] Only a few studies have examined the relation between HRV and Type D personality, looking at healthy adults and only taking frequency measures of HRV into account. These studies demonstrated that during rest there were no differences in HF and LF HRV, which was confirmed in the current study.[7,24]

The question remains how the relationship between emotional distress and disturbed autonomic functioning may be facilitated. According to the psychophysiological reactivity model of Lovallo and Gerin (2003), responses to psychological stress that contribute to cardiovascular reactivity take place on three levels. The cortical and limbic systems facilitate cognitive-emotional responses (level I), the hypothalamus and brainstem support autonomic and endocrine outputs in response to stress (level II), and on the peripheral level altered tissue function may influence stress reactivity (level III).[41] Level I reactivity has also been described as temperament, with personal habitual response style being linked to physiological response disposition.[41] People with higher levels of negative affectivity for example have shown to de-activate their limbic system, including the amygdala and hippocampus, while facing threatening stimuli, whereas people with high levels of social inhibition tend to over-activate brain areas related to decision making and action goals.[42] These higher level cognitive-emotional processes control autonomic response patterns (level II), including activity of the hypothalamus-pituitary-adrenocortical axis and the secretion of neurotransmitters such as serotonin. Recent studies have shown an improvement in HRV in cardiac patients using selective serotonin reuptake inhibitors (SSRIs).[43] With serotonin acting as an inhibitor of the sympathetic branch of the autonomic nervous system, autonomic dysregulation may be centrally modulated by serotonergic pathways in the brain, which are affected in patients with emotional distress. The role of psychotropic medication in relation to HRV should be investigated further, as available results are inconclusive.[43,44] Level II reactions are interrelated with peripheral tissue reactions (level III) that could impact on the development of cardiovascular disease. An example of this is oxidative stress, which is increased in chronic heart failure patients with a Type D personality.[45]

Moreover, behavioral mechanisms could also play a role. In a broader context, patients with emotional distress are known to be at higher risk for unhealthy lifestyle patterns, including reduced physical activity and smoking. Reduced levels of physical activity are related to impaired autonomic balance in terms of increased sympathetic and decreased parasympathetic tone.[46] Smoking results in similarly disturbed autonomic functioning.[47] Further studies on these explanatory behavioral pathways are warranted.

Associations between Type D personality and HRV measures tended to be stronger than associations of respectively depression and ICD concerns with HRV, as we found only significant adjusted results for Type D personality. This may be due to the fact that Type D personality is a more stable patient characteristic than symptoms of depression and anxiety and thus shows a more consequent and long term association with the autonomic nervous system. Additionally, previous research has shown that negative affectivity, one of the components of Type D personality, may be a combining element, linking individual negative emotions such as depression and anxiety,

to impaired autonomic control.[48,49] Our findings correspond to those of Rottenberg (2007), who finds small to medium effect sizes with respect to the relationship between depression and cardiac vagal control in a meta-analysis.[50] Future research should focus on specific subtypes of emotional distress, for example depression, in relation to autonomic functioning. In addition, other biomarkers of emotional distress could be included in future research, as the picture of the complex interrelationship between emotional distress and autonomic functioning will be more complete when mapping HRV to other central and autonomic nervous system dysfunctions.[50,51]

The results of this study should be interpreted with appropriate caution. First, the sample size was relatively small. With a larger sample size, we would have had more statistical power and might have been able to demonstrate more associations. Regarding the interpretation of our results, it is important to acknowledge that one should both pay attention to the initial results, and to the results corrected according to the Benjamini-Hochberg procedure. Because of the multiple testing, adequate application of a correction is desirable. However, as a result of the correction, the least significant results automatically turn non-significant, while these are not necessarily the false positive findings. Thus, careful interpretation of both results and replication of our findings with larger sample sizes are warranted. Second, the cross-sectional study design does not allow for drawing conclusions on causality. Third, we did not have information on emotional distress based on a structured clinical interview and were, in case of depression and anxiety, not able to differentiate between subclinical symptoms and clinical disorders. The relationship between emotional distress and HRV is expected to be stronger in patients with clinical diagnoses of emotional distress.[21] Finally, there are a number of other variables that could be influential in the relationship between emotional distress and HRV. Exerting a vagal effect on the heart, digoxin is one of these variables. However, due to the fact that only a small percentage of the patients were using digoxin (9.4% of the patients with Type D personality and 9.5% of the patients with depression and anxiety), we did not include the use of digoxin as a covariate in adjusted analyses. The potential influence of digoxin should nevertheless be examined in future studies.

The strengths of this study include the use of ambulatory 24-hour measurement in a real-life setting for evaluating HRV, taking into account activity levels, as data was available for patients during resting activity and sleep. Furthermore, both time and frequency domain measures were included, as there is as yet no consensus about the best available index of HRV for clinical use.[52] Third, although depression and anxiety have been investigated in relation to HRV in cardiac patients, Type D personality has not.

In conclusion, we found that patients with a Type D personality suffered from a lower overall autonomic control over 24 hours and lower parasympathetic control during rest. There was also an indication for a disturbed parasympathetic nervous system in patients with depression, especially during rest. The shift towards sympathetic dominance and reduced vagal activity, observed in ICD patients with emotional distress, may trigger the development ventricular tachycardia.[53] Reduced autonomic nervous control may thus increase the risk of ventricular arrhythmias in ICD patients, resulting in a poorer prognosis.[54] Future research with larger sample sizes, including fMRI studies investigating the role of specific brain areas in autonomic regulation, are warranted to replicate and expand on these findings.

REFERENCES

1. Pedersen SS, Theuns DAMJ, Jordaens L, Kupper N. Course of anxiety and device-related concerns in implantable cardioverter defibrillator patients the first year post implantation. Europace 2010;12(8):1119-1126.
2. Sears SF, Conti JB. Quality of life and psychological functioning of ICD patients. Heart 2002;87(5):488-493.
3. Pedersen SS, Van den Broek KC, Erdman RAM, Jordaens L, Theuns DAMJ. Pre-implantation implantable cardioverter defibrillator concerns and Type D personality increase the risk of mortality in patients with an implantable cardioverter defibrillator. Europace 2010;12(10):1446-1452.
4. Denollet J. DS14: Standard assessment of negative affectivity, social inhibition, and Type D personality. Psychosom Med 2005;67(1):89-97.
5. Leung YW, Flora DB, Gravely S, Irvine J, Carney RM, Grace SL. The impact of premorbid and postmorbid depression onset on mortality and cardiac morbidity among patients with coronary heart disease: Meta-analysis. Psychosom Med 2012;74(8):786-801.
6. Watkins LL, Blumenthal JA, Babyak MA, Davidson JRT, McCants CB, O'Connor C, Sketch MH Jr. Phobic anxiety and increased risk of mortality in coronary heart disease. Psychosom Med 2010;72(7):664-671.
7. Einvik G, Dammen T, Namtvedt SK, Hrubos-Strøm H, Randby A, Kristiansen HA, Nordhus IH, Somers VK, Omland T. Type D personality is associated with increased prevalence of ventricular arrhythmias in community-residing persons without coronary heart disease. Eur J Prev Cardiol 2012. Epub ahead of print. doi:10.1177/2047487312462800
8. Van den Broek KC, Nyklícek I, Van der Voort PH, Alings M, Meijer A, Denollet J. Risk of ventricular arrhythmia after implantable defibrillator treatment in anxious Type D patients. J Am Coll Cardiol 2009;54(6):531-537.
9. Watkins LL, Blumenthal JA, Davidson JRT, Babyak MA, McCants CB, Sketch MH. Phobic anxiety, depression, and risk of ventricular arrhythmias in patients with coronary heart disease. Psychosom Med 2006;68(5):651-656.
10. Friedmann E, Thomas SA, Liu F, Morton PG, Chapa D, Gottlieb SS. Relationship of depression, anxiety, and social isolation to chronic heart failure outpatient mortality. Am Heart J 2006;152(5):940.e1-e8.
11. Denollet J, Tekle FB, Pedersen SS, Van der Voort PH, Alings M, Van den Broek KC. Prognostic importance of distressed (Type D) personality and shocks in patients with an implantable cardioverter defibrillator. Int J Cardiol 2013;167(6):2705-2709.
12. Grande G, Romppel M, Barth J. Association between Type D personality and prognosis in patients with cardiovascular diseases: A systematic review and meta-analysis. Ann Behav Med 2012;43(3):299-310.
13. Coyne JC, Jaarsma T, Luttik M-L, Van Sonderen E, Van Veldhuisen DJ, Sanderman R. Lack of prognostic value of Type D personality for mortality in a large sample of heart failure patients. Psychosom Med 2011;73(7):557-562.
14. Damen NL, Versteeg H, Boersma E, Serruys PW, Van Geuns R-JM, Denollet J, Van Domburg RT, Pedersen SS. Depression is independently associated with 7-year mortality in patients treated with percutaneous coronary intervention: Results from the RESEARCH registry. Int J Cardiol 2013;167(6):2496-2501.
15. Jankowska EA, Ponikowski P, Piepoli MF, Banasiak W, Anker SD, Poole-Wilson PA. Autonomic imbalance and immune activation in chronic heart failure - pathophysiological links. Cardiovasc Res 2006;70(3):434-445.
16. Berntson GG, Thomas Bigger J, Eckberg DL, Grossman P, Kaufmann PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, Van der Molen MW. Heart rate variability: Origins, methods, and interpretive caveats. Psychophysiology 1997;34(6):623-648.
17. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology**.** Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. Circulation 1996;93(5):1043-1065.
18. Carpeggiani C, Emdin M, Bonaguidi F, Landi P, Michelassi C, Trivella MG, Macerata A, L'Abbate A. Personality traits and heart rate variability predict long-term cardiac mortality after myocardial infarction. Eur Heart J 2005;26(16):1612-1617.
19. Carney RM, Blumenthal JA, Freedland KE, Stein PK, Howells WB, Berkman LF, Watkins LL, Czajkowski SM, Hayano L, Domitrovich PP, Jaffe AS. Low heart rate variability and the effect of depression on post-myocardial infarction mortality. Arch Intern Med 2005;165(13):1486-1491.
20. Krittayaphong R, Cascio WE, Light KC, Sheffield D, Golden RN, Finkel JB, Glekas G, Kocht GG, Sheps DS. Heart rate variability in patients with coronary artery disease: Differences in patients with higher and lower depression scores. Psychosom Med 1997;59(3):231-235.

21. Martens EJ, Nyklíček I, Szabó BM, Kupper N. Depression and anxiety as predictors of heart rate variability after myocardial infarction. Psychol Med 2008;38(03):375-383.
22. Francis JL, Weinstein AA, Krantz DS, Haigney MC, Stein PK, Stone PH, Gottdiener JS, Kop WJ. Association between symptoms of depression and anxiety with heart rate variability in patients with implantable cardioverter defibrillators. Psychosom Med 2009;71(8):821-827.
23. Nyklíček I, Vorselaars A, Denollet J. Type D personality and cardiovascular function in daily life of people without documented cardiovascular disease. Int J Psychophysiol 2011;80(2):139-142.
24. Martin LA, Doster JA, Critelli JW, Lambert PL, Purdum M, Powers C, Prazak M. Ethnicity and Type D personality as predictors of heart rate variability. Int J Psychophysiol 2010;76(2):118-121.
25. Pedersen SS, Brouwers C, Versteeg H. Psychological vulnerability, ventricular tachyarrhythmias and mortality in implantable cardioverter defibrillator patients: Is there a link? Expert Rev Med Devices 2012;9(4):377-388.
26. Pedersen SS, Theuns DAMJ, Muskens-Heemskerk A, Erdman RAM, Jordaens L. Type D personality but not implantable cardioverter-defibrillator indication is associated with impaired health-related quality of life 3 months post-implantation. Europace 2007;9(8):675-680.
27. Ewing DJ, Neilson JM, Travis P. New method for assessing cardiac parasympathetic activity using 24 hour electrocardiograms. Br Heart J 1984;52(4):396-402.
28. Emons WHM, Meijer RR, Denollet J. Negative affectivity and social inhibition in cardiovascular disease: Evaluating Type D personality and its assessment using item response theory. J Psychosom Res 2007;63(1):27-39.
29. Martens EJ, Kupper N, Pedersen SS, Aquarius AE, Denollet J. Type D personality is a stable taxonomy in post-MI patients over an 18-month period. J Psychosom Res 2007;63(5):545-550.
30. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67(6):361-370.
31. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale - a review of validation data and clinical results. J Psychosom Res 1997;42(1):17-41.
32. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: An updated literature review. J Psychosom Res 2002;52(2):69-77.
33. Pedersen SS, Van Domburg RT, Theuns DAMJ, Jordaens L, Erdman RAM. Concerns about the implantable cardioverter defibrillator: A determinant of anxiety and depressive symptoms independent of experienced shocks. Am Heart J 2005;149(4):664-669.
34. Frizelle DJ, Lewin B, Kaye G, Moniz-Cook ED. Development of a measure of the concerns held by people with implanted cardioverter defibrillators: The ICDC. Br J Health Psychol 2006;11(Pt 2):293-301.
35. Antelmi I, De Paula RS, Shinzato AR, Peres CA, Mansur AJ, Grupi CJ. Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. Am J Cardiol 2004;93(3):381-385.
36. Fantoni C, Raffa S, Regoli F, Giraldi F, La Rovere MT, Prentice J, Pastori F, Fratini S, Salerno-Uriarte JA, Klein HU, Auricchio A. Cardiac resynchronization therapy improves heart rate profile and heart rate variability of patients with moderate to severe heart failure. J Am Coll Cardiol 2005;46(10):1875-1882.
37. Tuininga YS, Crijns HJGM, Brouwer J, Van den Berg MP, Man in 't Veld AJ, Mulder G, Lie KI Evaluation of importance of central effects of atenolol and metoprolol measured by heart rate variability during mental performance tasks, physical exercise, and daily life in stable post-infarct patients. Circulation 1995;92(12):3415-3423.
38. Yeragani VK, Pesce V, Jayaraman A, Roose S. Major depression with ischemic heart disease: Effects of paroxetine and nortriptyline on long-term heart rate variability measures. Biol Psychiatry 2002;52(5):418-429.
39. Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. J Royal Stat Soc: Series B (Statistical Methodology) 1995;57(1):289-300.
40. Munk PS, Isaksen K, Brønnick K, Kurz MW, Butt N, Larsen AI. Symptoms of anxiety and depression after percutaneous coronary intervention are associated with decreased heart rate variability, impaired endothelial function and increased inflammation. Int J Cardiol 2012;158(1):173-176.
41. Lovallo WR, Gerin W. Psychophysiological reactivity: Mechanisms and pathways to cardiovascular disease. Psychosom Med 2003;65(1):36-45.
42. Kret ME, Denollet J, Grèzes J, De Gelder B. The role of negative affectivity and social inhibition in perceiving social threat: An fMRI study. Neuropsychologia 2011;49(5):1187-1193.

43. McFarlane A, Kamath MV, Fallen EL, Malcolm V, Cherian F, Norman G. Effect of sertraline on the recovery rate of cardiac autonomic function in depressed patients after acute myocardial infarction. Am Heart J 2001;142(4):617-623.
44. Kemp AH, Quintana DS, Gray MA, Felmingham KL, Brown K, Gatt JM. Impact of depression and antidepressant treatment on heart rate variability: A review and meta-analysis. Biol Psychiatry 2010;67(11):1067-1074.
45. Kupper N, Gidron Y, Winter J, Denollet J. Association between Type D personality, depression, and oxidative stress in patients with chronic heart failure. Psychosom Med 2009;71(9):973-980.
46. Rennie KL, Hemingway H, Kumari M, Brunner E, Malik M, Marmot M. Effects of moderate and vigorous physical activity on heart rate variability in a British study of civil servants. Am J Epidemiol 2003;158(2):135-143.
47. Dinas PC, Koutedakis Y, Flouris AD. Effects of active and passive tobacco cigarette smoking on heart rate variability. Int J Cardiol 2013;163(2):109-115.
48. Bleil ME, Gianaros PJ, Jennings JR, Flory JD, Manuck SB. Trait negative affect: Toward an integrated model of understanding psychological risk for impairment in cardiac autonomic function. Psychosom Med 2008;70(3):328-337.
49. Chen H-C, Yang CC, Kuo TB, Su T-P, Chou P. Cardiac vagal control and theoretical models of co-occurring depression and anxiety: A cross-sectional psychophysiological study of community elderly. BMC Psychiatry 2012;12(1):93.
50. Rottenberg J. Cardiac vagal control in depression: A critical analysis. Biol Psychol 2007;74(2):200-211.
51. Duivis HE, Kupper N, Penninx BW, Na B, De Jonge P, Whooley MA. Depressive symptoms and white blood cell count in coronary heart disease patients: Prospective findings from the heart and soul study. Psychoneuroendocrinology 2013;38(4):479-487.
52. Lombardi F, Mäkikallio TH, Myerburg RJ, Huikuri HV. Sudden cardiac death: Role of heart rate variability to identify patients at risk. Cardiovasc Res 2001;50(2):210-217.
53. Lombardi F, Porta A, Marzegalli M, Favale S, Santini M, Vincenti A, De Rosa A; Implantable Cardioverter-Defibrillator-Heart Rate Variability Italian Study Group. Heart rate variability patterns before ventricular tachycardia onset in patients with an implantable cardioverter defibrillator. Am J Cardiol 2000;86(9):959-963.
54. Moss A, Greenberg H, Case R, Zareba W, Hall W, Brown M, Daubert JP, McNitt S, Andrews ML, Elkin AD; Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II) Research Group. Long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator. Circulation 2004;110(25):3760 - 3765.

Long-term mortality risk in patients with an implantable cardioverter-defibrillator: Influence of heart rate and QRS duration

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ABSTRACT

Background: A paucity of studies has investigated the role of autonomic cardiac regulation as well as cardiac conduction in relation to prognosis in implantable cardioverter-defibrillator (ICD) patients. Therefore, we examined the association of heart rate and QRS duration with long-term mortality risk in first-time ICD patients, adjusting also for measures of emotional distress.

Methods: Resting heart rate and QRS duration were assessed prior to ICD implantation in 448 patients. Primary study endpoint was all-cause mortality (up to 6.0 years follow-up, median follow-up 5.6 years (IQR: 1.9). The impact of heart rate and QRS duration on time to all-cause mortality was separately assessed with Cox proportional hazard regression analysis, adjusting for clinical factors and symptoms of depression and anxiety.

Results: Mean (SD) heart rate was 68.0±13.3 bpm and mean QRS duration 130.9±36.9 ms. Heart rate of ≥80 bpm was associated with increased risk of mortality (HR=1.86; 95% CI=1.15-3.00; p=.011) in unadjusted analysis. In adjusted analyses, this relationship remained significant both with depression (HR=1.86, 95% CI=1.12-3.09; p=.017) and anxiety (HR=1.82, 95% CI=1.10-3.03; p=.021) and clinical measures as covariates. QRS duration of ≥120 ms was associated with impaired prognosis in unadjusted analysis (HR=2.00, 95% CI=1.27-3.14; p=.003), but was reduced to non-significance in adjusted analysis when medical comorbidities were included (HR=1.15, 95% CI=0.70-1.89; p=.60).

Conclusions: This study shows that increased heart rate is associated with impaired prognosis. Since heart rate is a relatively easy measurable parameter of autonomic functioning, heart rate should be included as a measure for risk stratification in daily clinical practice.

INTRODUCTION

In patients at high risk for sudden cardiac death due to ventricular arrhythmias, the implantable cardioverter-defibrillator (ICD) is treatment of first choice, with mortality risk reductions of 37% for all-cause mortality to 57% compared to antiarrhythmic drug treatment.[1-3] Despite the unequivocal benefits of ICD therapy, risk stratification in these patients still remains a major challenge in clinical cardiology practice.[4]

In order to optimize care for ICD patients and reduce health care costs, it is crucial to identify factors associated with risk for morbidity and mortality. Deregulation of the autonomic nervous system, evident in the presence of an increased heart rate, has been shown to impact survival in the general population[5,6] as well as in cardiac patients.[7,8] Autonomic deregulation is particularly relevant in ICD patients, since the autonomic nervous system plays an important role in the generation of ventricular arrhythmias by impacting on the electrical and contractile functions of the heart.[9] Only one study has examined the role of heart rate as prognostic factor in ICD patients. This study showed a strong association of heart rate with survival and hospitalization for decompensated heart failure.[10] However, this study did not adjust for the patient's mood status, which has shown to be an independent predictor of ventricular tachyarrhythmias and mortality.[4]

Few studies examined the relation between QRS duration and mortality risk in ICD patients, with longer QRS duration - indicating a conduction delay in the heart's ventricles - being associated with mortality risk.[11-13] However, relatively small samples[12,13] and different definitions of prolonged QRS duration have been used.[11,12] Given the relative paucity of studies examining the association between cardiovascular physiological functioning and prognosis in ICD patients, we investigated the association between heart rate and QRS duration and long-term mortality risk in patients with an ICD, while also adjusting for patients' mood state (i.e. symptoms of anxiety and depression) in addition to traditional clinical risk factors.

METHODS

Patients and study design

Between August 2003 and February 2010, consecutive patients (N=448) were enrolled in the *M*ood and personality as precipitants of arrhythmia in patients with an *I*mplantable cardioverter *D*efibrillator: *A* prospective *S*tudy (MIDAS) in the Erasmus Medical Center, Rotterdam, in collaboration with Tilburg University, the Netherlands. Exclusion criteria were a life-expectancy <1 year, being on the waiting list for heart transplantation, a history of psychiatric illness other than affective/anxiety disorders, and insufficient knowledge of the Dutch language.

The Medical Ethics Committee of the Erasmus Medical Center approved the study protocol. Prior to ICD implantation, written and oral information on the study was given to patients by an ICD nurse, after which written informed consent was obtained.

Measures

Demographic and clinical variables

Purpose-designed questions were used to collect data on demographic characteristics (i.e. age, gender, marital status and education), while the Central Bureau of Statistics Netherlands provided information on patients' socio-economic status (SES). Baseline clinical characteristics were captured from patients' medical records, including indication for ICD therapy (primary versus secondary prevention), treatment with cardiac resynchronization therapy (CRT), left ventricular ejection fraction (LVEF) ≤35%, QRS duration, the presence of coronary artery disease (CAD), symptomatic heart failure (defined as New York Heart Association (NYHA) functional class III+IV), atrial fibrillation, prior percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), smoking, use of cardiac (i.e. beta-blockers, statins, amiodarone, diuretics, ACE-inhibitors, and digoxin) and psychotropic medication, and systolic (SBP) and diastolic blood pressure (DBP). Hypertension was defined as a SBP of ≥140 mmHg, and a DBP of ≥90 mmHg. Furthermore, the abbreviated Charlson Comorbidity Index (CCI) was constructed using information on the presence of renal failure, previous myocardial infarction (MI), chronic heart failure, diabetes mellitus, peripheral arterial disease, cerebrovascular disease, chronic obstructive pulmonary disease and cancer.[14] The sum score of this index was subsequently adjusted for age, with addition of 1 extra point for each decade >50 years of age.

Electrocardiographic measures

Information on heart rate and QRS duration was collected several days before ICD implantation via an electrocardiogram (ECG) in a standardized, clinical setting and as part of the regular medical check-up prior to ICD implantation. Registration of the ECG took place while patients were lying down on a bed and information was collected for 10 consecutive seconds. The ECG was interpreted using auto-interpretation, which was always checked and confirmed by an experienced cardiologist. A cut-off heart rate of ≥80 bpm, based on two large studies on heart rate as prognostic factor in CAD,[15,16] was used to compare patients with increased versus normal heart rate. For QRS duration, a cut-off of QRS ≥120 ms, based on a risk stratification model for first-time ICD implantation,[17] was used to compare patients with prolonged versus normal QRS duration.

Depression and anxiety

Symptoms of depression and anxiety were measured at baseline (1 day prior to implantation) using the Hospital Anxiety and Depression Scale (HADS), a 14-item self-report questionnaire consisting of 7 items measuring anxiety (HADS-A) and 7 items measuring depression (HADS-D).[18] All items are rated on a 4-point Likert scale, with scores ranging from 0 to 3 and higher scores reflecting more symptoms.[18] Psychometric qualities of the HADS are good.[19] In the current study, a cut-off score of ≥8 was used to detect patients with clinically significant levels of anxiety and depression.[20]

Endpoint

All-cause mortality was used as endpoint in this study. The Dutch municipal register was consulted for information on survival status up to 6 years post implantation.

Statistical analyses

Baseline demographic and clinical variables for patients with complete versus incomplete data were compared with the Chi-square test (Fisher's Exact test when appropriate) for nominal variables, and Student's t-test for continuous variables.

Assumptions of the proportional hazards were checked by using log-minus-log plots for nominal variables and partial residual plots for continuous variables. The association between heart rate and time to all-cause mortality, and QRS duration and time to all-cause mortality was separately assessed. Covariates - indication for ICD implantation,[21] age-adjusted CCI,[22] hypertension,[23] appropriate and inappropriate shocks during follow-up,[24,25] and use of beta-blockers[26] and amiodarone[27] - were a priori selected based on the literature and included using the Enter method. Patient anxiety and depression were included in a final step, as these psychological factors have been associated with poor prognosis[28,29] and previous research has demonstrated a relation between depression and heart rate variability.[30] In order to avoid multicollinearity, separate analyses were performed with patient anxiety and depression as covariates and mortality as endpoint, resulting in four Cox proportional hazard regression models: (1) heart rate and depression; (2) heart rate and anxiety; (3) QRS duration and depression; and (4) QRS duration and anxiety. Results of the Cox regression analyses were reported using hazard ratios (HR) with corresponding 95% confidence intervals (CI). A p-value of <.05 (two-sided) was used to indicate statistical significance. Cumulative survival curves for mortality risk predicted by heart rate ≥80 bpm and QRS duration ≥120 ms with accompanying log-rank tests were constructed using the Kaplan-Meier method. Results were repeated with continuous values for heart rate and QRS duration. Patients who underwent heart transplantation were excluded from analyses, while patients who were transferred to another hospital or lost to follow-up were censored alive at time of file closure. Data were analyzed with PASW Statistics 19 (PASW IBM Corp., Armonk, NY, USA).

RESULTS

Patient baseline characteristics

In total, 448 patients were included in the study. Twenty-six patients had missing values on the hypertension (N=2), age-adjusted CCI (N=6) and emotional distress measures (N=18). Patients with incomplete data were more likely to have a secondary prevention indication (p<.001), to suffer from CAD (p=.012), atrial fibrillation (p=.028), to have a shorter QRS duration (p=.002) and to have a low SES (p=.019). In addition, 23 patients underwent heart transplantation at some point during follow-up. These patients were excluded from the analyses, since their prognosis was expected to be significantly worse than for patients not undergoing heart transplantation, which was confirmed by higher rates of symptomatic heart failure (p<.001) and atrial fibrillation (p=.001), and more frequent use of digoxin (p<.001), diuretics (p=.002) and psychotropic medication (p=.014). Patients with missing data on covariates were also excluded from the analyses, leaving 399 patients. Table 1 displays baseline demographic and clinical characteristics of the complete sample. The mean age was 59±12 years, and 317 (79%) of the patients were male.

Table 1. Baseline characteristics for the total study sample *

	Patients (N=399)
Demographics	
Mean age (±SD)	58.8 (12.2)
Men	317 (79.4)
Lower SES †	185 (46.6) ‡
Clinical factors	
Primary prevention indication	258 (64.7)
CRT	117 (29.3)
LVEF ≤35% ‡	292 (85.1)
CAD	234 (58.6)
Previous PCI	103 (25.8)
Previous CABG	84 (21.1)
Symptomatic heart failure †§	118 (29.7) ‡
Atrial fibrillation	82 (20.6)
Diabetes	56 (14.0)
Smoking †	45 (11.3) ||
Cardiovascular physiological measures	
Mean heart rate (bpm, ±SD)	68.0 (13.3)
Mean systolic blood pressure (mmHg, ±SD)	121.4 (18.2)
Mean diastolic blood pressure (mmHg, ±SD)	73.6 (11.6)
Mean QRS (ms, ±SD)	130.9 (36.9)
Medication	
Amiodarone	74 (18.5)
Beta-blockers	318 (79.7)
Diuretics	220 (55.1)
ACE-inhibitors	286 (71.7)
Statins	242 (60.7)
Digoxin	54 (13.5)
Psychotropic medication #	61 (15.4) ††
Psychological measures	
Mean score depression (±SD)	5.0 (4.0)
Mean score anxiety (±SD)	5.6 (4.1)

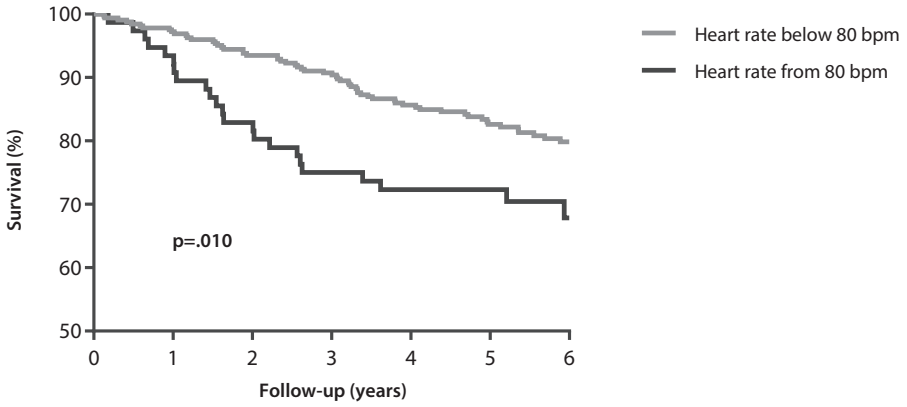
* Data presented as N (%), unless otherwise indicated. † N=2 (0.5%) missing; ‡ N=56 (14.0%) missing; § defined as New York Heart Association (NYHA) functional class III+IV, # N=4 (1.0%) missing. Abbreviations: *ACE*, angiotensin-converting enzyme; *bpm*, beats per minute; *CABG*, coronary artery bypass grafting; *CAD*, coronary artery disease; *CRT*, cardiac resynchronization therapy; *LVEF*, left ventricular ejection fraction; *N*, number; *PCI*, percutaneous coronary intervention; *QRS*, QRS duration; *SD*, standard deviation; SES, socio-economic status

All-cause mortality

During a mean follow-up period of 4.8±1.5 years (range 0.1-6.0 years, inter quartile range 1.9), 83 patients (20.8%) died. In adjusted analyses, 25 patients (6.3%) were censored as alive due to hospital transfer (and absence of clinical follow-up), just as 22 (5.5%) patients who were lost to follow-up for other reasons.

Heart rate and QRS duration as predictors of mortality

All variables, except the use of beta-blockers and the occurrence of shocks during follow-up met the proportional hazards assumptions. In order to enable their inclusion in the analyses, these two variables were transformed into time-dependent variables.



Number of patients at risk

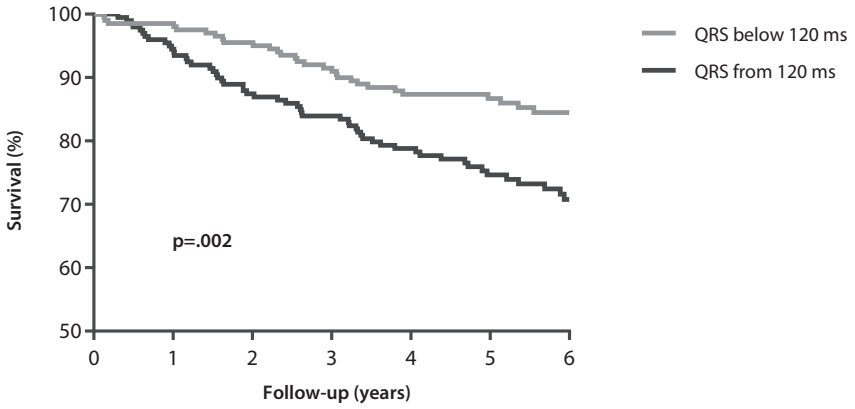
	Baseline	1 year	2 years	3 years	4 years	5 years	6 years
Heart rate <80 bpm	323	314	302	293	277	269	263
Heart rate ≥80 bpm	76	71	63	57	55	55	53
Total # of patients	399	385	365	350	332	324	316

Figure 1. Cumulative survival curve stratified by heart rate ≥ 80 bpm

Heart rate – Cumulative hazard functions were significantly different for patients with a heart rate of ≥80 bpm versus <80 bpm (log-rank χ^2=6.60; p=.010) (Figure 1). A heart rate of ≥80 bpm was associated with a cumulative increased risk for all-cause mortality (HR=1.86; 95% CI=1.15-3.00; p=.011) in unadjusted Cox regression analysis. After adjusting for the a priori selected clinical covariates (indication for ICD implantation, the age-adjusted CCI, hypertension, occurrence of appropriate and inappropriate shocks during follow-up, and use of beta-blockers and amiodarone), the relationship between heart rate of ≥80 bpm and risk for all-cause mortality remained significant (HR=1.85, 95% CI=1.11-3.06, p=.017), also when additionally adjusting for depressive symptoms (HR=1.86; 95% CI=1.12-3.09; p=.017), and when adjusting for symptoms of anxiety instead of

depression (HR=1.82; 95% CI=1.10-3.03; p=.021) (Table 2). Repeating the results with continuous values for heart rate yielded similar findings in both unadjusted (HR=1.02; 95% CI=1.01-1.03; p=.025) and adjusted analyses (depression as covariate: HR=1.02; 95% CI=1.01-1.04; p=.027; anxiety as covariate: HR=1.02; 95% CI=1.01-1.04; p=.025).

QRS duration – Cumulative hazard functions were significantly different for patients with a QRS duration of ≥120 ms versus <120 ms (log-rank χ^2=9.44; p=.002) (Figure 2). In unadjusted Cox regression analysis, a QRS duration ≥120 ms was associated with a cumulative increased risk for all-cause mortality (HR=2.00; 95% CI=1.27-3.14; p=.003) (Figure 2). However, when adjusting for the a priori selected clinical covariates, the relation between QRS duration ≥120 ms and risk for all-cause mortality was non-significant and remained so after additional adjustment for depressive symptoms (HR=1.15; 85% CI=0.70-1.89; p=.60) and symptoms of anxiety (HR=1.14; 95% CI=0.70-1.88, p=.60) (Table 3). Inclusion of the CCI in adjusted analysis accounted for the non-significant effect of QRS duration ≥120 ms on mortality. Again, repeating the results with continuous values of QRS duration led to comparable results, with a significant association between QRS duration and risk for all-cause mortality in unadjusted analysis (HR=1.01; 95% CI=1.01-1.02; p=.003), and a non-significant relationship in adjusted analysis (depression as covariate: HR=1.00; 95% CI=1.00-1.01; p=.70; anxiety as covariate: HR=1.00; 95% CI=1.00-1.01; p=.79).



Number of patients at risk

	Baseline	1 year	2 years	3 years	4 years	5 years	6 years
QRS duration <120 ms	200	197	191	183	175	174	171
QRS duration ≥120 ms	199	188	174	167	157	150	145
Total # of patients	399	385	365	350	332	324	316

Figure 2. Cumulative survival curve stratified by QRS duration ≥ 120 ms

Table 2. Heart rate and mortality (Cox proportionate hazard regression analysis) *

		Heart Rate	
Block 1	**HR**	**95% CI**	**p**
Heart rate	1.86	1.15-3.00	**.011**
Block 2	**HR**	**95% CI**	**p**
Heart rate	1.85	1.11-3.06	**.017**
Secondary prevention indication	1.18	0.74-1.90	.48
CCI	1.32	1.20-1.44	**<.001**
Hypertension	0.76	0.24-2.43	.65
Shocks during follow-up †	1.25	1.08-1.44	**.004**
Use of beta-blocker	1.21	0.96-1.52	.10
Use of amiodarone	2.04	1.23-3.36	**.005**
Block 3 – with depressive symptoms	**HR**	**95% CI**	**p**
Heart rate	1.86	1.12-3.09	**.017**
Secondary prevention indication	1.23	0.77-1.98	.39
CCI	1.30	1.19-1.43	**<.001**
Hypertension	0.83	0.26-2.66	.75
Shocks during follow-up †	1.24	1.07-1.43	**.005**
Use of beta-blocker	1.23	0.98-1.54	.08
Use of amiodarone	1.86	1.11-3.11	**.018**
Depression	1.95	1.25-3.04	**.003**
Block 3 – with anxiety symptoms	**HR**	**95% CI**	**p**
Heart rate	1.82	1.10-3.03	**.021**
Secondary prevention indication	1.21	0.76-1.94	.43
CCI	1.32	1.21-1.45	**<.001**
Hypertension	0.77	0.24-2.47	.66
Shocks during follow-up †	1.24	1.07-1.44	**.004**
Use of beta-blocker	1.21	0.96-1.51	.11
Use of amiodarone	2.02	1.22-3.34	**.006**
Anxiety	1.32	0.83-2.11	.24

* Analyses were separately performed with patient depression and anxiety as covariates, respectively. † Appropriate and inappropriate shocks. Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; ICD, implantable cardioverter-defibrillator

Table 3. QRS duration and mortality (Cox proportionate hazard regression analysis) *

		QRS Duration	
Block 1	**HR**	**95% CI**	**p**
QRS duration	2.00	1.27-3.14	**.003**
Block 2	**HR**	**95% CI**	**p**
QRS duration	1.09	0.67-1.79	.72
Secondary prevention indication	1.15	0.72-1.84	.56
CCI	1.33	1.21-1.47	**<.001**
Hypertension	0.73	0.23-2.33	.59
Shocks during follow-up †	1.23	1.06-1.43	**.007**
Use of beta-blocker	1.17	0.94-1.46	.17
Use of amiodarone	1.84	1.13-3.00	**.014**
Block 3 – with depressive symptoms	**HR**	**95% CI**	**p**
QRS duration	1.15	0.70-1.89	.60
Secondary prevention indication	1.21	0.75-1.95	.43
CCI	1.31	1.19-1.45	**<.001**
Hypertension	0.79	0.25-2.54	.69
Shocks during follow-up †	1.22	1.05-1.41	**.011**
Use of beta-blocker	1.18	0.95-1.47	.15
Use of amiodarone	1.65	1.00-2.72	.051
Depression	1.96	1.26-3.07	**.003**
Block 3 – with anxiety symptoms	**HR**	**95% CI**	**p**
QRS duration	1.14	0.70-1.88	.60
Secondary prevention indication	1.19	0.74-1.90	.48
CCI	1.34	1.21-1.47	**<.001**
Hypertension	0.74	0.23-2.38	.62
Shocks during follow-up †	1.23	1.06-1.43	**.007**
Use of beta-blocker	1.17	0.93-1.45	.18
Use of amiodarone	1.82	1.12-2.96	**.017**
Anxiety	1.39	0.86-2.22	.18

* Analyses were separately performed with patient depression and anxiety as covariates, respectively. † Appropriate and inappropriate shocks. Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; ICD, implantable cardioverter-defibrillator

DISCUSSION

In the current study, we investigated the relationship between two electrocardiographic measures influenced by cardiovascular physiological functioning – heart rate and QRS duration – and risk of all-cause mortality up to 6 years of follow-up in patients with an ICD. Increased heart rate, both when assessed continuously and using a cut-off of ≥80 bpm, was associated with a higher mortality risk. QRS duration, however, was only associated with increased mortality risk when comorbidity burden, measured with the age-adjusted CCI, was not taken into account.

Our results match the results of the only previous study among ICD patients on this topic, in which a strong relationship between increased mean heart rate and mortality and heart failure hospitalization was found,[10] and the results in other cardiac populations.[7,8,31] In patients with heart failure, who comprise a large subgroup within the ICD population, the association between heart rate and prognosis seems less straightforward than in other cardiac patients. Indeed, tachycardia acts as a compensatory response to impaired cardiac output up to a certain point, after which it also becomes a marker of excessive autonomic activation.[8] Optimal cut-off levels thus may differ across different subtypes of heart disease, which should be further investigated with respect to optimizing risk stratification. Since heart failure is common among ICD patients, we chose a relatively high cut-off of HR ≥80 bpm to evaluate the impact of heart rate on mortality and also used continuous measures of heart rate.

Prior studies have shown a significant relationship between prolonged QRS duration and prognosis in ICD patients.[11-13] In our sample, QRS duration did not uniquely contribute to patients' mortality risk, although there was a shared prognostic value of QRS duration and the presence of comorbidities in relation to mortality.

Several mechanisms may explain the relationship between heart rate and prognosis.[32] Higher heart rate increases vascular oxidative stress, and is associated with decreased restoration of endothelial function, a key event in the development of atherosclerosis, through increasing levels of circulating inflammatory markers. Furthermore, increasing heart rate promotes arterial stiffness and hampers angiogenesis, a natural defense mechanism to compensate for arterial occlusion. Moreover, arterial plaques tend to be less stable at increased heart rate. Increased heart rate also affects the myocardium, as coronary blood flow mainly occurs during diastole, which is firmly decreased with increasing heart rate.[32]

The current study is the first to include emotional distress as potential confounder in the relationship between heart rate and mortality. This is important, as emotional distress is independently related to risk of ventricular arrhythmias and mortality in ICD patients.[4] Although depression was associated with poorer prognosis, it did not substantially affect the relationship between heart rate and prognosis. Future research is warranted that focuses on the simultaneous presence of multiple clinical and psychological risk factors for mortality in this patient population, as they may interact to exacerbate patient risk.

Treatment should thus focus on reduction of resting heart rate. However, the vast majority of patients in the current sample have been prescribed one or more heart rate reducing agents. Interestingly, the use of beta-blockers and amiodarone was associated with an increased risk of mortality. Patients who are prescribed heart rate lowering agents likely constitute a high-risk group with poorer prognosis, despite the use of these agents. Insufficient medication adherence or incorrect use may also play a role, with approximately 30% of heart failure patients not complying with the prescribed treatment.[33] Less traditional methods of reducing heart rate, such as biofeedback, have shown encouraging results in terms of heart rate control in healthy persons, although sustained effects are unknown and research among cardiac patients is yet lacking.[34,35] Future research should reveal whether this behavioral approach is effective in reducing heart rate in ICD patients.

This study has some limitations. Due to incomplete data on cause of death, we were only able to focus on all-cause mortality as primary endpoint. Second, due to limited availability of other related autonomic measures, such as heart rate variability and baroreflex sensitivity measures, creation of a more comprehensive autonomic prediction model remains a future ambition. Moreover, we have not been able to assess changes in autonomic functioning during follow-up and its relation with prognosis due to availability of only pre implantation data. The relatively large follow-up range is also a limitation of the current study.

Strengths of the current study include the relatively long mean follow-up period, and the use of both dichotomous and continuous measures of heart rate and QRS duration, pointing towards the same conclusion. Furthermore, we adjusted for several aspects of physical and psychological functioning in statistical analyses, which might serve as potential confounders.

In conclusion, we found that heart rate was associated with an increased risk of all-cause mortality up to 6 years follow-up in a consecutive cohort of ICD patients with a first-time implant. The relationship between QRS duration and risk of all-cause mortality was explained by the presence of comorbid conditions. Although heart rate seems a relatively crude measure of autonomic functioning, it also appears to be an easy to assess, inexpensive marker of poor prognosis, which is broadly available as one of the standard measurable parameters in clinical practice. For this reason, application of heart rate as a measure for risk stratification should be encouraged in clinical practice.

REFERENCES

1. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-883.
2. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-237.
3. The Antiarrrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337:1576-1584.
4. Pedersen SS, Brouwers C, Versteeg H. Psychological vulnerability, ventricular tachyarrhythmias and mortality in implantable cardioverter defibrillator patients: Is there a link? Expert Rev Med Devices 2012;9:377-388.
5. Goldberg RJ, Larson M, Levy D. Factors associated with survival to 75 years of age in middle-aged men and women: The Framingham study. Arch Intern Med 1996;156:505-509.
6. Cooney MT, Vartiainen E, Laakitainen T, Juolevi A, Dudina A, Graham IM. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. Am Heart J 2010;159:612-619.e613.
7. Lang CC, Gupta S, Kalra P, Keavney B, Menown I, Morley C, Padmanabhan S. Elevated heart rate and cardiovascular outcomes in patients with coronary artery disease: Clinical evidence and pathophysiological mechanisms. Atherosclerosis 2010;212:1-8.
8. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): A subgroup analysis of a randomised controlled trial. Lancet 2008;372:817-821.
9. Volders PGA. Novel insights into the role of the sympathetic nervous system in cardiac arrhythmogenesis. Heart Rhythm 2010;7:1900-1906.
10. Ahmadi-Kashani M, Kessler DJ, Day J, Bunch TJ, Stolen KQ, Brown S, Sbaity S, Olshansky B. Heart rate predicts outcomes in an implantable cardioverter-defibrillator population. Circulation 2009;120:2040-2045.
11. Stecker EC, Zargarian M, Dogra V, John BT, Kron J, McAnulty JH, Chugh SS. Native QRS duration predicts the occurrence of arrhythmic events in ICD recipients. Europace 2006;8:859-862.
12. Bode-Schnurbus L, Böcker D, Block M, Gradaus R, Heinecke A, Breithardt G, Borggrefe M. QRS duration: A simple marker for predicting cardiac mortality in ICD patients with heart failure. Heart 2003;89:1157-1162.
13. Maciąg A, Przybylski A, Sterliński M, Lewandowski M, Gepner K, Kowalik I, Derejko P, Pytkowski M, Szumowski L, Szwed H. QRS complex widening as a predictor of appropriate implantable cardioverter-defibrillator (ICD) therapy and higher mortality risk in primary prevention ICD patients. Kardiol Pol 2012;70:360-368.
14. Charlson ME, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47(11):1245-1251.
15. Diaz A, Bourassa MG, Guertin M-C, Tardif J-C. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J 2005;26:967-974.
16. Kolloch R, Legler UF, Champion A, Cooper-DeHoff RM, Handberg E, Zhou Q, Pepine CJ. Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: Findings from the international verapamil-SR/trandolapril study (INVEST). Eur Heart J 2008;29:1327-1334.
17. Goldenberg I, Vyas AK, Hall WJ, Moss AJ, Wang H, He H, Zareba W, McNitt S, Andrews ML. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. J Am Coll Cardiol 2008;51:288-296.
18. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67:361-370.
19. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997;27:363-370.
20. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: An updated literature review. J Psychosom Res 2002;52:69-77.
21. Theuns DAMJ, Thornton AS, Klootwijk APJ, Scholten MF, Vantrimpont PJMJ, Balk AHMM, Jordaens LJ. Outcome in patients with an ICD incorporating cardiac resynchronisation therapy: Differences between primary and secondary prophylaxis. Eur J Heart Fail 2005;7:1027-1032.

22. Theuns DAMJ, Schaer BA, Soliman OII, Altmann D, Sticherling C, Geleijnse ML, Osswald S, Jordaens L. The prognosis of implantable defibrillator patients treated with cardiac resynchronization therapy: Comorbidity burden as predictor of mortality. Europace 2011;13:62-69.
23. Yap YG, Duong T, Bland M, Malik M, Torp-Pedersen C, Køber L, Connolly SJ, Gallagher MM, Camm AJ. Potential demographic and baselines variables for risk stratification of high-risk post-myocardial infarction patients in the era of implantable cardioverter-defibrillator - a prognostic indicator. Int J Cardiol 2008;126:101-107.
24. Poole JE, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH, Reddy RK, Marchlinski FE, Yee R, Guarnieri T, Talajic M, Wilber DJ, Fishbein DP, Packer DL, Mark DB, Lee KL, Bardy GH. Prognostic importance of defibrillator shocks in patients with heart failure. N Engl J Med 2008;359:1009-1017.
25. Powell BD, Saxon LA, Boehmer JP, Day JD, Gilliam Iii FR, Heidenreich PA, Jones PW, Rousseau MJ, Hayes DL. Survival after shock therapy in implantable cardioverter-defibrillator and cardiac resynchronization therapy-defibrillator recipients according to rhythm shocked: The ALTITUDE survival by rhythm study. J Am Coll Cardiol 2013;62:1674-1679.
26. Ellison KE, Hafley GE, Hickey K, Kellen J, Coromilas J, Stein KM, Lee KL, Buxton AE, Investigators ftM. Effect of β-blocking therapy on outcome in the multicenter unsustained tachycardia trial (MUSTT). Circulation 2002;106:2694-2699.
27. Kowey PR, Crijns HJGM, Aliot EM, Capucci A, Kulakowski P, Radzik D, Roy D, Connolly SJ, Hohnloser SH. Efficacy and safety of celivarone, with amiodarone as calibrator, in patients with an implantable cardioverter-defibrillator for prevention of implantable cardioverter-defibrillator interventions or death: The ALPHEE study. Circulation 2011;124:2649-2660.
28. Habibović M, Pedersen SS, van den Broek KC, Theuns DAMJ, Jordaens L, van der Voort PH, Alings M, Denollet J. Anxiety and risk of ventricular arrhythmias or mortality in patients with an implantable cardioverter defibrillator. Psychosom Med 2013;75:36-41.
29. Mastenbroek MH, Versteeg H, Jordaens L, Theuns DAMJ, Pedersen SS. Ventricular tachyarrhythmias and mortality in implantable cardioverter defibrillator (ICD) patients: Impact of depression in the MIDAS cohort. Psychosom Med 2014;76:58-65.
30. Hoogwegt MT, Pedersen SS, Theuns DAMJ, Kupper N. Relation between emotional distress and heart rate variability in patients with an implantable cardioverter-defibrillator. Psychophysiology 2014;51:187-196.
31. Habal MV, Liu PP, Austin PC, Ross HJ, Newton GE, Wang X, Tu JV, Lee DS. Association of heart rate at hospital discharge with mortality and hospitalizations in patients with heart failure. Circ Heart Fail 2014;7:12-20.
32. Custodis F, Schirmer SH, Baumhäkel M, Heusch G, Böhm M, Laufs U. Vascular pathophysiology in response to increased heart rate. J Am Coll Cardiol 2010;56:1973-1983.
33. Van der Wal MHL, Jaarsma T, van Veldhuisen DJ. Non-compliance in patients with heart failure; how can we manage it? Eur J Heart Fail 2005;7:5-17.
34. Alvarez Moleiro M, Villamaín Cid F. Effects of biofeedback training on voluntary heart rate control during dynamic exercise. Appl Psychophysiol Biofeedback 2001;26:279-292.
35. Peira N, Pourtois G, Fredrikson M. Learned cardiac control with heart rate biofeedback transfers to emotional reactions. PLoS One 2013;8:e70004.

PART THREE

Looking beyond the scope of the patient: The impact of partners of ICD patients

Interrelationship between emotional distress of implantable cardioverter-defibrillator patients and their partners: Influence on patients' health status the first 12 months post implantation

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ABSTRACT

Background: Partners' emotional distress is often ignored in clinical practice. We (1) focused on the relationship between anxiety and depression *within* implantable cardioverter-defibrillator (ICD) patients and partners; and the relationship between anxiety and depression *between* patients and partners, and (2) examined whether partner distress trajectory was associated with patient health status trajectory.

Methods: Consecutively implanted patients and their partners (N=433) recruited by an ICD nurse filled out the Hospital Anxiety and Depression Scale (HADS) on 5 occasions up to 12 months follow-up. Patients' health status was measured simultaneously with the Short Form Health Survey-36 (SF-36). Latent growth curve models were constructed.

Results: Individual differences in baseline distress and change in distress correlated between patients and partners. Patients' *baseline* and *change* in health status scores were largely explained by patients' own baseline and change in anxiety scores. Importantly, partner distress predicted better patient health status at baseline (partner anxiety: lower baseline patient social functioning (b=-0.07, p=.042); partner depression: more baseline patient bodily pain (b=-0.07, p=.024) and during follow-up (higher partner distress during follow-up: worse patient health status recovery during follow-up on all subscales except role limitations - emotional (b's ranging from -.11 to -.18).

Conclusions: Patient-partner distress patterns were highly similar, and although patients' own emotional distress largely predicted their health status at baseline and change therein during follow-up, on top of that, development of partner distress during follow-up was also predictive of how well patients' health status level recovered after implantation. Partners should not be neglected in the adaptation process post implantation.

INTRODUCTION

The implantable cardioverter-defibrillator (ICD) is the first line treatment for patients at risk of sudden cardiac death due to ventricular tachyarrhythmias, both as primary and secondary prevention.[1-3] Although the majority of patients reach acceptable levels of psychological functioning after implantation, a subgroup (25%) remains at high risk of developing emotional distress, directly after implantation or at a later stage.[4-8] Distress levels may in part be attributable to the uncontrollable and unpredictable course of ICD therapy and the associated uncertainty,[6,7] but also to the underlying heart disease (e.g. symptomatic heart failure)[9] and patients' pre implantation personality.[10]

The way patients cope with stress has traditionally been examined using individual-oriented stress models.[11] However, the presence of a partner may influence patients' appraisal of situational demands, and partners may also augment the available coping resources.[12] Dyadic coping models such as Bodenmann's systemic-transactional model of stress and coping[13] extend the individual-oriented stress model to a model in which the partner is involved in stress appraisal and coping. In this model, the process of stress-coping is perceived as a dyadic exchange of action (i.e. the stress signals of one partner) and reaction (i.e. dyadic coping of the other partner), as well as common dyadic coping efforts. In patients with acute or chronic illness, dyadic coping may be particularly important, as it has shown to positively influence not only psychological well-being[14] but also physical health.[15]

Instead of focusing on the ICD patient as an isolated individual, coping with an ICD should thus be understood as a dyadic concern, in which patients and partners affect each other's emotional well-being. Partners may play an essential role in adaptation to the ICD, and emotional distress in partners may lead to undesirable behaviour, such as overprotectiveness and discouragement of an active lifestyle of the patient.[16,17] On the other hand, in the context of the systemic-transactional model of dyadic coping, the patient's way of coping with the ICD may also impact on the partner's emotional well-being.[13] Furthermore, ICD implantation may affect shared aspects of the relationship, including emotional, social and sexual functioning.[18,19]

Specific to ICD patients, shock therapy occurs on an irregular and unpredictable basis. Patients and their partners are thus at increased risk of a state of permanently increased vigilance, with uncertainty and uncontrollability being important underlying themes in daily life. Dyadic coping theory has shown that perceived controllability in both patients and partners determines the appraisal of the stressor, the interaction between patient and partner, and the subsequent coping response.[13] Because of the uncontrollable nature of the permanently present threat, i.e. ventricular arrhythmia followed by shock delivery, the interrelationship of ICD patients' and their partners' well-being is a relevant topic for further examination.

Emotional distress levels of partners of ICD patients are at least as high if not higher than those of patients.[20-22] In addition, partners may experience difficulties with a change in role patterns from being a partner on equal terms to being a caregiver.[23] Emotional distress in partners has shown to be associated with poorer prognosis in cardiac patients.[24] A complete picture of the emotional well-being of partners of ICD patients and the association of emotional well-being between patients

and partners within the couple over time is thus important, and could provide us with targets for interventions aiming to improve both patients' and partners' quality of life and possibly even patients' prognosis.

In a recent study, patients' distress was found to be correlated with partners' distress (i.e. symptoms of anxiety and depression), with the type of distress corresponding within dyads (i.e. patients' anxiety was associated with partners' anxiety, and patients' depression with partners' depression).[25] However, in that study, using a multilevel approach, correlations of patient and partner distress were averaged over time, while the influence of change in distress across several points in time of both patients and partners and the influence of this on patients' health status remains unknown.

Therefore, the aim of the current study was (1) to longitudinally examine the relationship between anxiety and depression *within* patients and partners; and the relationship between anxiety and depression *between* patients and partners. Since health status has been associated with poorer prognosis,[26] we were also interested in (2) finding out whether partner distress (baseline distress and change in distress) was associated with patient health status at baseline and change in patient health status during follow-up.

METHODS

Patients and study design

Between August 2003 and February 2010, 448 consecutive patients implanted with a first-time ICD in the Erasmus Medical Center, Rotterdam, the Netherlands, with their partners, were enrolled in the Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter Defibrillator: A prospective Study (MIDAS). Exclusion criteria consisted of a life-expectancy of <1 year, being on the waiting list for heart transplantation, a history of psychiatric illness other than affective/anxiety disorders, and insufficient knowledge of the Dutch language. Having a partner was an explicit inclusion criteria for the study, although during the initial phase of the project some patients without a partner have been included (N=11). These patients were not included in the statistical analyses.

The study was conducted according to the Helsinki Declaration and approved by the Medical Ethics Committee of the Erasmus Medical Center. Prior to ICD implantation, an ICD nurse provided written and oral information on the study. After obtaining written informed consent from both patients and partners, the couples were asked to separately complete a similar set of standardized and validated questionnaires at baseline (i.e. one day prior to implantation), and at 10 days, 3, 6 and 12 months post implantation, resulting in a dyadic longitudinal design with 5 measurement points.

Measures

Demographic and clinical variables

Purpose-designed questions were used to obtain information on demographic characteristics (i.e. age, gender, marital status and educational level) of both patients and partners. Information on socio-economic status (SES) was obtained from Statistics Netherlands.

Information on clinical patient characteristics, including indication for ICD therapy (primary versus secondary prevention), treatment with cardiac resynchronization therapy (CRT), left ventricular ejection fraction (LVEF) ≤35%, QRS duration, the presence of coronary artery disease (CAD), symptomatic heart failure (defined as New York Heart Association (NYHA) functional class III+IV), atrial fibrillation, prior PCI or coronary artery bypass grafting (CABG), smoking, and use of cardiac (i.e. beta-blockers, statins, amiodarone, diuretics, ACE-inhibitors, and digoxin) and psychotropic medication, were captured from patients' medical records at the time of implantation. The prevalence of shock therapy, both appropriate and inappropriate, was captured during follow-up via device interrogation. In addition, information on comorbid medical disorders in patients was collected at the time of implantation. From this information, an age-adjusted version of the Charlson Comorbidity Index (CCI) was constructed.[27]

Anxiety and depression

Symptoms of anxiety and depression were assessed in patients and partners with the Hospital Anxiety and Depression Scale (HADS) at baseline, 10 days, 3, 6 and 12 months post implantation. This 14-item self-report questionnaire consists of 7 items measuring symptoms of anxiety (HADS-A) and 7 items measuring symptoms of depression (HADS-D). Items are scored on a 4-point Likert scale, with scores ranging from 0 to 3 (total score range of 0-21) and higher scores reflecting more symptoms.[28] Cronbach's alphas of 0.84 and 0.83 for the anxiety and depression subscales were found for the current study. The three-week test-retest reliability (0.89 and 0.86 for the HADS-A and HADS-D subscales) of the HADS is high.[29] The HADS has been developed to measure separate symptoms of anxiety and depression in a non-psychiatric hospital setting.[30] In the current study, continuous sum scores for anxiety and depression were used as markers of emotional distress.

Health status

The validated Dutch language version of the Short Form Health Survey 36 (SF-36) was used to measure patients' health status at baseline, 10 days, 3, 6 and 12 months post implantation.[31] The questionnaire consists of 36 items that contribute to eight subscales: physical functioning, role limitations - physical, bodily pain, social functioning, mental health, role limitations - emotional, vitality and general health. Scores range from 0 to 100 for each subscale, with higher scores indicating better health status.[32] Scale reliabilities as indicated by Cronbach's alphas range from 0.66 to 0.92.[31] Continuous sum scores for the eight subdomains of health status were calculated, and scores of the SF-36 were transformed by dividing the sum score of all scales by 10 for analytical purposes.

Statistical analyses

Latent growth curve analysis – To take full advantage of the longitudinal study design we used latent growth models.[33] These models can be seen as a direct extension of multilevel and structural equation models and allow for inter-individual variation in baseline (intercept) and change over time (slope), which makes them ideally suitable for modelling outcome trajectories across time. The

growth curves will be parameterized, such that the random intercept represents inter-individual differences at baseline and the random slope represents inter-individual variation in change during the 12 months post implantation. To allow for non-linear trajectories, the loadings on the random slope for in-between time points are unrestricted, allowing them to be interpreted as the proportional change relative to the total change from starting point to end point. In these models, variances can be explained at two levels: (1) the structural level, which reflects inter-individual differences in baseline values and change in distress and health status by means of a random intercept and random slope factor across time, and (2) the measurement level, which reflects further intra-individual variation by means of residual time-specific factors. The structural random factors (i.e. baseline and change) are allowed to correlate between patient and partner to further account for the dyadic structure; the same holds for the residuals for each measurement occasion. The random slope is regressed on the random intercept to control change for the variation in baseline.
All models were specified starting from the covariance matrix and estimated through the Lavaan library in the statistical software package R (http://www.r-project.org/). Full information maximum likelihood was used to make use of all available information for each individual under the missing at random assumption and in line with the intention-to-treat principle. Model fit was evaluated based upon commonly recommended goodness-of-fit indices,[34] including the χ^2 of exact model fit, the root mean square error of approximation (RMSEA) and the comparative fit index (CFI).

To assess the first aim of the study, a total of four parallel growth curves were constructed: a trajectory (1) assessing the relation between anxiety and depression within *patients*; (2) assessing the relation between anxiety and depression within *partners*; (3) the relation of *anxiety between patients and partners*; and (4) the relation of *depression between patients and partners*. Within patients/partners, the trajectories of anxiety and depression were highly similar in shape and the individual variation in intercept and slope was very strongly correlated (ranging from .79 to .94). Therefore, for the second aim of the study, eight latent growth curve models were constructed mapping out patient health status trajectories (one model for each scale) in relation to partner anxiety and partner depression *separately*. In this way, problems due to multicollinearity between the predictors anxiety and depression was avoided.

Hierarchical latent growth curve models were build, with stepwise inclusion of a priori selected covariates, based on the literature: (1) demographic and clinical covariates, including partner gender,[15] patient indication for ICD implantation,[21] symptomatic heart failure,[35] the occurrence of shock(s) during follow-up,[36] age-adjusted version of the CCI,[37] and a combined level of socio-economic status (SES) for patients and partners,[38] (2) baseline and change factors of patient levels of anxiety and depression in the separate anxiety and depression models, and (3) baseline and change factors of partner levels of anxiety and depression in the separate anxiety and depression models. Furthermore, in order to extract change distress levels from initial distress levels, for each growth curve, change in distress was adjusted for baseline influences of distress by including the random intercepts of the growth curves as predictors for the random slopes. Results for the latent growth curve models are presented as unstandardized regression coefficients (b). For continuous predictors, a b of -0.22 for partners' baseline anxiety for example means that for each extra point of

partners' anxiety at baseline, patients' health status decreases with 2.2 points (a decrease of 0.22*10 as a result of score transformation). For dichotomous predictors, contrast coding was used, meaning for example that for the presence of symptomatic heart failure a 1 was coded and for the absence of symptomatic heart failure a -1 was coded. A b of -0.64 for baseline health status in this case means that patients with symptomatic heart failure score 6.4 point lower on health status than average, while patients without symptomatic heart failure score 6.4 points higher on health status than average.

RESULTS

Patient and partner baseline characteristics

Overall, 448 patients were included in the study, of which 11 (2.5%) had no partner. In addition, 4 patients (1%) had missing data on a covariate, leaving 433 dyads of patient and partner in total for analysis. Included patients were compared with patients excluded from analyses. The latter were significantly more likely to have undergone CABG (46.7% versus 19.2%, p=.017) and to use psychotropic medication (38.5% versus 15.7%, p=.045). No other systematic differences between included and excluded patients were found, nor differences in baseline characteristics among included and excluded partners.

Table 1 displays baseline demographic characteristics of both patients and partners, as well as baseline clinical patient characteristics. The mean age of patients was 59±12 years, and 341 (79%) of the patients were male. Partners' mean age was 56±12 years and 94 (22%) of the partners were male. Fifty-seven patients (13.2%) received one or more shocks during the first year post implantation.

Distress trajectories for patients and partners

A model containing a total of four parallel growth curves were fitted on the HADS data: one trajectory for anxiety for patients and partners, respectively, and one for depression for patients and partners, respectively. The latent growth model provided an excellent fit to the data ($\chi^2_{(df=230)=}427$, p<.001, CFI=.975, RMSEA=.044), and was able to explain on average 75% and 80% of the variance in anxiety and 76% and 81% of the variance in depression at each time point for patients and partners, respectively. Results are presented in Table 2, in line with an example of the accompanying growth curve presentation in Figure 1. As indicated in the model, change in distress depended on the baseline distress level of the individual. To give an impression of the expected change, simple slopes were computed for an individual scoring average on baseline distress and all other predictors (anxiety patient: b=-0.64, Z=-2.53, p=.012; anxiety partner: b=-1.34, Z=-4.59, p<.001; depression patient: b=-0.20, Z=-0.81, p=.42; depression partner: b=-0.70, Z=-2.61, p=.009). These simple slopes showed that on average, distress decreased during follow-up. However, there is still a large amount of variation around these average change patterns, as indicated by the large variances of the random slopes (see Table 2). The shape of the trajectories was comparable for anxiety and depression, but slightly different between patients and partners. For both patients and partners, about 47-51% of the change to final level of distress already occurred after 10 days post implantation. However, whereas

for patients at 3 months post implantation almost all decline in distress had taken place with the trajectory stabilizing, for partners the trajectory was more gradually decreasing and flattened out after 6 months post implantation. This can be seen from the loadings on the random slope factors (L_1-L_5) which are shown in Figure 1 and Table 2.

Table 1. Baseline characteristics of patients and partners *

	Patients (N = 433)	**Partners (N = 433)**
Demographics		
Mean age (±SD)	58.54 (12.08)	56.20 (11.97)
Men	341 (78.8)	94 (21.7)
Lower SES †	203 (46.9)	203 (46.9)
Clinical factors		
Primary prevention indication	284 (65.6)	
CRT	121 (27.9)	
LVEF ≤35% ‡	320 (73.9)	
Mean QRS (±SD)	129.47 (36.32)	
CAD	251 (58.0)	
Previous PCI	114 (26.3)	
Previous CABG	83 (19.2)	
Symptomatic heart failure §	137 (31.6)	
Atrial fibrillation	101 (23.3)	
Diabetes	62 (14.3) #	
Mean score age-adjusted CCI	3.51 (2.37)	
Smoking	43 (9.9) ||	104 (24.0) **
Mean heart rate	68.15 (13.72) ||	
Medication		
Amiodarone	82 (18.9)	
Beta-blockers	345 (79.7)	
Diuretics	242 (55.9)	
ACE-inhibitors	310 (71.6)	
Statins	256 (59.1)	
Digoxin	67 (15.5)	
Psychotropic medication	65 (15.0) ††	65 (15.0) **

* Data are presented as N (%), unless otherwise indicated. † Based on ZIP-code and calculated per household by the Netherlands Institute for Social Research; ‡ N=62 (%) missing; § defined as NYHA functional class III+IV; # N=2 (%) missing; || N=17 (%) missing; ** N=21 (%) missing; †† N=19 (%) missing. Abbreviations: *ACE*, angiotensin-converting enzyme; *CABG*, coronary artery bypass grafting; *CAD*, coronary artery disease; *CCI*, Charlson Comorbidity Index; *CRT,* cardiac resynchronization therapy; *LVEF*, left ventricular ejection fraction; *N*, number; *PCI*, percutaneous coronary intervention; *QRS*, QRS duration; *SD*, standard deviation; SES, socio-economic status.

Table 2. Dyadic bivariate latent growth curve model for anxiety and depression for patients and partners †

		Patient		Partner	
		Anxiety	**Depression**	**Anxiety**	**Depression**
Baseline	Intercept [(1)]	5.689 ***	4.915 ***	6.835 ***	4.986 ***
	Prevention indication [(2)]	-.034	-.244	.299	.395
	Symptomatic heart failure [(3)]	.171	.204	.229	.596 **
	Gender partner [(4)]	.381	.270	-.601 *	-.272
	SES [(5)]	.185	-.014	-.148	-.247
	Shock(s) [(6)]	.123	.012	.003	-.106
	CCI [(7)]	-.045	.175 *	-.084	-.154
	Variance	11.484	11.624	14.613	12.852
	R^2	.018	.033 *	.026	.037 *
	F(6,427)	1.314	2.402	1.891	2.723
	p	.249	.027 *	.081	.013 *
Change	Intercept [(1)]	.492	.557	.280	.417
	Baseline patient	-.205 ***	-.153 **	-.010	.060
	Baseline partner	.004	-.001	-228 ***	-.283 ***
	Prevention indication [(2)]	.307 *	.370 *	.318	.115
	Symptomatic heart failure [(3)]	.143	-.032	.327	.037
	Gender partner [(4)]	-.195	-296	.072	.030
	SES [(5)]	-.030	-.019	.053	.005
	Shock(s) [(6)]	.893 ***	.747 ***	.376	.438 *
	CCI [(7)]	-.053	-.005	-.091	.067
	Variance	3.240	2.758	4.412	3.899
	R^2	.240	.232	.183	.224
	F(8,427)	22.472 ***	21.49 ***	15.884 ***	20.521 ***
	p	.012 *	.42	<.001 ***	.009 **
Trajectory §	L_1	0	0	0	0
	L_2	.470	.470	.510	.498
	L_3	1.027	.991	.782	.637
	L_4	.987	.954	.878	.952
	L_5	1	1	1	1
Residual	Variance	3.737	3.566	3.437	2.649
Overall	R^2	.748	.763	.798	.813

† Results are presented as b's as in regular regression analysis. [(1)] Predictor 1 in predictor box Figure 1; [(2)] predictor 2 in predictor box Figure 1, etc. Contrast coding was used for the dichotomous independent variables, with prevention indication: -1=primary indication, +1=secondary indication; symptomatic heart failure: -1=no, +1=yes; shock(s) during follow-up: -1=no, +1=yes; gender partner: -1=female, +1=male. Correlations between intercepts and slopes of the trajectories are displayed in the results section of the manuscript. * p<.05; ** p<.010; *** p<.001; # Indication of percentage change in distress score for each measurement occasion. Abbreviations: *CCI*, Charlson Comorbidity Index; *L*, loadings on random slope factor for each measurement occasion; *SES*, socio-economic status.

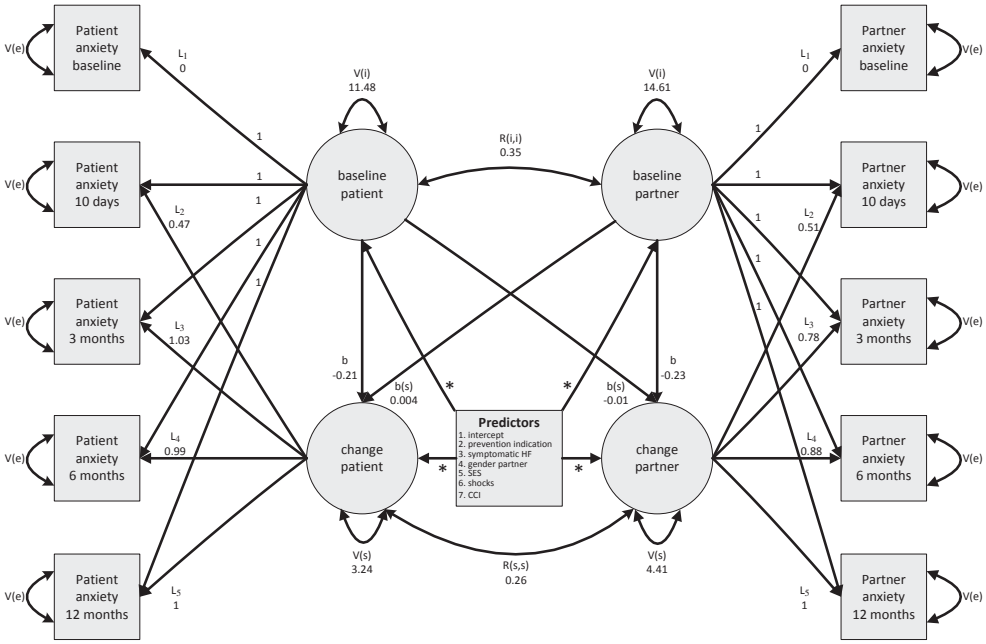

Figure 1. Dyadic bivariate latent growth curve model for patients' and partners' anxiety
* All predictors are included in the statistical model, but in order to preserve readability only regression coefficients of baseline patient and partner anxiety on change of patient and partner anxiety are shown. For regression coefficients of remaining predictors, see 'Baseline' and 'Change' sections of Table 2. The numbers following the predictors in Table 2 correspond to the predictor numbers in the predictor box of Figure 1. For the same reasons, residual correlations between patients and partners for each measurement occasion are omitted in the graphical representation of the model. Abbreviations: b(i): unstandardized regression coefficient in the regression equation for the random intercept (i.e. baseline); b(s): unstandardized regression coefficient in the regression equation for the random slope (i.e. change); L_x: loading on random slope factor; R(i,s): correlation random intercept and slope; V(e): residual variance; V(i): variance random intercept; V(s): variance random slope.

For all four trajectories, a significant negative effect of baseline on change was observed (b=-0.15 to -0.28). This means that people who reported relatively high distress levels at baseline, on average experienced a relatively larger reduction in distress over time. The residual correlation (i.e. after accounting for baseline distress and the covariates) in slope between patients and partners was .26 (Z=2.27, p=.023) for anxiety and .44 (Z=3.80, p<.001) for depression, which indicates that patients who experienced a relatively strong decrease in distress tended to have partners with also a relatively strong decrease in distress. With respect to the intercept (i.e. baseline distress) a similar pattern was observed: the patient-partner residual correlation in intercept was .35 (Z=5.29, p<.001) for anxiety and .32 (Z=5.18, p<.001) for depression. Thus, individual differences in baseline distress and change in distress correlated between patients and partners, with distress trajectories being relatively similar between patients and partners.

The included covariates - patient indication for ICD implantation, symptomatic heart failure, shock(s) during follow-up, partner gender, the age-adjusted version of the CCI and SES - were only able to explain a limited amount of the inter-individual variation in baseline distress (see R^2

for baseline in Table 2). However, some noteworthy effects were found. With respect to the inter-individual variation in baseline distress, partners of patients with symptomatic heart failure reported more baseline depressive symptoms than partners of patients without heart failure (b=0.60, Z=2.67, p=.008). Moreover, female partners tended to report significantly more anxiety at baseline than male partners (b=-0.60, Z=-2.42, p=.015), and patients with a higher CCI score tended to experience more depressive symptoms (b=.18, Z=2.09, p=.036). With respect to distress change, the key determinant was the occurrence of shock(s) during follow-up (see also R^2 for change in Table 2). Patients who did not receive a shock during follow-up showed a significantly larger decrease in anxiety (b=0.89, Z=4.41, p<.001) and depression (b=0.75, Z=3.65, p<.001) as compared to patients who did receive a shock during follow-up. Shocks were also associated with less reduction in depressive symptoms in partners (b=0.44, Z=-2.17, p=.030). Since these results do not provide insight into the direction (i.e. positive or negative) of the growth curves for the shocked versus non-shocked patients and with shock being an important predictor of distress in the current study, simple slopes were computed, again for an average individual with and without shock (anxiety: without shock: b=-1.54, Z=-6.99, p<.001; with shock: b=0.25, Z=0.61, p=.54 and depression: without shock: b=-0.95, Z=-4.43, p<.001; with shock: b=-0.38, Z=-1.37, p=.17). This shows that whereas absence of shocks during follow-up was associated with a reduction in distress over time, this reduction during follow-up did not occur in patients who experienced a shock. Finally, patients with a primary prevention indication showed a significantly larger decrease in anxiety (b=.31, Z=2.08, p=.038) and depression (b=0.37, Z=2.52, p=.012) than patients with a secondary prevention indication.

Linking dyadic anxiety trajectories to patients' health status

To examine whether partners' distress would have an additional influence on patients' health status, we built hierarchical models with cumulative addition of three blocks: (1) the six a priori selected covariates; (2) baseline and change factors of patient levels of emotional distress in the separate anxiety and depression models; and (3) baseline and change factors of partner levels of anxiety and depression in the separate anxiety and depression models. In Tables 3 and 4, the results of these latent growth models are presented. Overall, the models provided excellent fit to the data for all health status subscales (see top part Tables 3 and 4) and explained between 46-79% of the variance in patients' health status scores. Due to strong correlation between the mental health subscale and the anxiety scale of the HADS, it was not possible to incorporate the mental health subscale in the anxiety model. In the depression model, the subscales mental health, role limitations - emotional and vitality could not be included due to strong correlation between patient depression, partner depression and the concerning subscales.

Table 3. Patient health status trajectory linked to covariates and dyadic anxiety trajectories †

	Goodness of Fit	**PF**	**RL-P**	**BP**	**SF**	**MH**	**RL-E**	**VT**	**GH**
	χ^2(df=172)	372	333	397	415	-	354	411	358
	RMSEA	.052	.047	.055	.057	-	.049	.057	.050
	CFI	.956	.957	.938	.939	-	.951	.947	.961
Baseline	Intercept [(1)]	6.422 ***	5.314 ***	7.920 ***	8.222 ***	-	9.640 ***	7.206 ***	6.759 ***
Predictors	Prevention indication [(2)]	-.020	-.058	-.261 *	-.409 **	-	-.155	.027	.278 **
	Symptomatic heart failure [(3)]	-.573 ***	-.535 **	-.122	-.382 **	-	.197	-.458 ***	-.315 **
	Gender partner [(4)]	-.367 **	-.245	-.217	-.053	-	-.447 *	-.229 *	.012
	SES [(5)]	-.120	-.041	-.194 **	-.205 *	-	.023	-.128 *	-.088
	Shock(s) [(6)]	.175	.234	.133	-.038	-	.250	.265 *	.118
	CCI [(7)]	-.192***	.070	-.049	.022	-	-.158 *	-.065	-.157 ***
	Anxiety baseline patient	-.145 ***	.052 ***	-.230 ***	-.294 ***	-	-.598 ***	-.264 ***	-.253 ***
	Anxiety baseline partner	-.049	.046	-.041	-.069*	-	-.074	-.045	-.012
	Variance	4.076	5.477	1.905	3.586	-	4.420	2.182	2.359
covariates	R^2	.144	.063	.072	.069	-	.032	.113	.126
+patient	R^2	.201	.219	.311	.288	-	.523	.367	.343
+partner	R^2	.209	.243	.317	.297	-	.528	.374	.344
Change	Intercept	2.583 ***	2.813 **	3.013 **	5.971 ***	-	3.736 *	2.134 ***	.077
Predictors	Baseline health status	-.288 ***	-.192	-.240 *	-.607 ***	-	-.441 **	-.268 ***	-.031
	Prevention indication [(2)]	.081	-.180	.238 *	.295 **	-	.108	.084	-.011
	Symptomatic heart failure [(3)]	-.115	-.347	.030	-.037	-	-.256	.089	-.044
	Gender partner [(4)]	.103	.201	.369 **	.176	-	.438 *	.101	.059
	SES [(5)]	.057	-.090	.161	.032	-	.062	.010	.036
	Shock(s) [(6)]	.017	-.334	-.035	-.008	-	-.291	-.170	-.202
	CCI [(7)]	-.134 **	-.101	-.066	-.066	-	-.043	.011	.087 *
	Anxiety baseline patient	-.149 ***	-.190 *	-.166 ***	-.253 ***	-	-.218 *	-.130 ***	-.082 *

Table 3. Patient health status trajectory linked to covariates and dyadic anxiety trajectories † (Continued)

		PF	RL-P	BP	SF	MH	RL-E	VT	GH
Change	Anxiety change patient	-.420 ***	-.543 ***	-.351 ***	-.542 ***	-	-.827 ***	-.477 ***	-.401 ***
Predictors	Anxiety baseline partner	-.005	-.043	.058	-.017	-	.013	-.016	-.016
	Anxiety change partner	-.179 **	-.150	-.131 *	-.173 **	-	-.165 *	-.114 *	-.122 *
	Variance	1.609	4.631	.528	.893	-	.735	0.468	0.893
baseline	R^2	.107	.015	.092	.394	-	.354	.185	.016
+covariates	R^2	.162	.092	.235	.426	-	.433	.236	.093
+patient	R^2	.370	.249	.522	.724	-	.822	.687	.406
+partner	R^2	.434	.261	.658	.771	-	.868	.731	.460
Trajectory	L_1	0	0	0	0	-	0	0	0
	L_2	.46	.10	-.077	.353	-	.286	.450	.240
	L_3	.89	.78	.836	.848	-	.876	.932	.765
	L_4	.98	.93	.875	.939	-	.974	.963	.833
	L_5	1	1	1	1	-	1	1	1
Residual	Variance	1.614	7.452	3.387	2.471	-	8.182	1.185	1.045
Overall	R^2	.766	.552	.458	.604	-	.466	.732	.794

† For analytical purposes, scores were transformed by dividing the sumscore for each scale by 10. The mental health subscale was excluded due to very high correlations between anxiety scores and mental health subscale. Results are presented as unstandardized b's as in regular regression analysis. Contrast coding was used for the dichotomous independent variables, with prevention indication: -1=primary indication, +1=secondary indication; symptomatic heart failure: -1=no, +1=yes; shock(s) during follow-up: -1=no, +1=yes; gender partner: -1=female, +1=male. * $p \leq .050$; ** $p \leq .010$; *** $p \leq .001$. Abbreviations: *BP*, bodily pain; *CCI*, Charlson Comorbidity Index; *CFI*, comparative fit index; *GH*, general health; *L*, loadings on random slope factor for each measurement occasion; *PF*, physical functioning; *r*, correlation between random factors; *RL-E*, role limitations – emotional; *RL-P*, role limitations – physical; *RMSEA*, root mean square error of approximation; *SES*, socio-economic status; *SF*, social functioning; *VT*, vitality

Emotional distress and patients' baseline health status**.** The demographic and clinical covariates (step 1) explained between 3.2-14.4% of the variance. The presence of symptomatic heart failure and having a secondary prevention indication were the strongest predictors of lower health status at baseline (Table 3). Patients' own baseline anxiety scores explained an additional 6.7-49.1% of the variance, depending on the particular subscale (step 2). Patients' own anxiety scores were related to patients' health status score on all subscales (all p<.001). In the third step, partners' baseline anxiety scores were added, explaining 0.1-2.4% of the variance beyond the covariates and patients' own anxiety scores. Each point of increase in partners' baseline anxiety score was significantly associated with a 0.7 lower health status score on the social functioning subscale (b=-.07, Z=-2.03, p=.042). For the other subscales, partners' baseline anxiety did not significantly predict patients' baseline health status scores on top of the other included predictors. Similar results were found for the association between patients' and partners' depressive symptoms and patients' baseline health status. For details, see Table 4.

Emotional distress and patients' change in health status over time. The demographic and clinical covariates altogether explained 3.2-14.3% of the variance in the change of patient health status over time. ICD indication, gender of the partner and the CCI were the most important associates of patients' health status during follow-up, with patients with a secondary prevention indication, a male partner and lower CCI scores generally improving more on health status during follow-up (Table 3). In the second step patients' own baseline anxiety and change in anxiety were added, with an additional 15.7-45.1% of the variance being explained. Patients' own change in anxiety was the most important predictor of patients' change in health status (p<.001 for all subscales except physical functioning (p>.05)), followed by patients' baseline anxiety score. Partners' anxiety explained 1.2-13.6% of additional variance in the model. Each point of increase in partners' *baseline* anxiety was associated with a 4.2 point decrease in patient physical functioning during follow-up (b=-.42, Z=-5.38, p<.001). Moreover, increase in partner anxiety during *follow-up* was associated with impaired patient health status on all subscales except role limitations - physical (Table 3: b's ranging from -.11 to -.18). Change in partner anxiety was a predictor of changes in patients' health status on top of patients' and partners' baseline levels of anxiety, and on top of changes in patients' own health status.

Similar results were found for the association between patients' and partners' depressive symptoms and change in patients' health status. These results are shown in Table 4. Importantly, increase in partner depression during follow-up was associated with worse recovery in patients' health status with respect to physical functioning (b=-.25, Z=-3.25, p=.001), bodily pain (b=-.15, Z=-2.07, p=.039), social functioning (b=-.18, Z=-2.75, p=.006) and general health (b=-.19, Z=-2.87, p=.004), on top of baseline depression in patients and partners.

Table 4. Patient health status trajectory linked to covariates and dyadic depression trajectories

	Goodness of Fit	PF	RL-P	BP	SF	MH	RL-E	VT	GH
	χ^2(df=172)	464	410	428	483	-	-	-	456
	RMSEA	.063	.057	.059	.065	-	-	-	.062
	CFI	.941	.943	.935	.929		-	-	.945
Baseline	Intercept health status	6.663 **	5.409 **	7.738 **	8.804 **	-	-	-	6.846 ***
Predictors	Prevention indication	-.068 **	-.129	-.293 *	-.466 **	-	-	-	.241 **
	Symptomatic heart failure	-.562 *	-.511 *	-.110	-.371 *	-	-	-	-.306 **
	Gender partner	-.354	-.230	-.251 *	-.061	-	-	-	-.019
	SES	-.145	-.101	-.247 **	-.266 *	-	-	-	-.138 *
	Shock(s)	.193	.109	.112	-.058	-	-	-	.108
	CCI	-.139 *	-.033	-.007	.093	-	-	-	-.099 **
	Depression baseline patient	-.266 **	-.416 **	-.223 ***	-.351 **	-	-	-	-.295 ***
	Depression baseline partner	-.017	-.082	-.067 *	-.060	-	-	-	-.031
	Variance	3.551	4.473	1.884	3.187	-	-	-	2.049
covariates	R^2	.144	.063	.072	.069	-	-	-	.126
+patient	R^2	.294	.367	.327	.389	-	-	-	.411
+partner	R^2	.292	.374	.339	.390	-	-	-	.412
Change	Slope health status	2.456 ***	2.584 **	3.093 **	6.242 ***	-	-	-	.381
Predictors	Baseline health status	-.263 ***	-.164	-.231 *	-.622 ***	-	-	-	-.064
	Prevention indication	.122	-.128	.249 *	.284 **	-	-	-	-.001
	Symptomatic heart failure	-.170	-.393	.018	-.101	-	-	-	-.102
	Gender partner	.048	.131	.299 *	.095	-	-	-	.043
	SES	.036	-.107	.143 *	-.007	-	-	-	.028
	Shock(s)	.084	-.214	-.013	-.014	-	-	-	-.179
	CCI	-.087 *	-.036	-.027	.000	-	-	-	.115 **
	Depression baseline patient	-.150 ***	-.214 *	-.152 **	-.265 ***	-	-	-	-.109 **
	Depression change patient	-.886 ***	-1.140 ***	-.553 ***	-.772 ***	-	-	-	-.595 ***
	Depression baseline partner	-.011	-.019	.053	-.025	-	-	-	-.002
	Depression change partner	-.249 **	-.220	-.147 *	-.181 **	-	-	-	-.187 **
	Variance	0.164	1.976	.194	.134	-	-	-	.436
baseline	R^2	.107	.015	.092	.394	-	-	-	.016
+covariates	R^2	.162	.093	.235	.426	-	-	-	.094
+patient	R^2	.858	.639	.784	.928	-	-	-	.656
+partner	R^2	.940	.664	.868	.963	-	-	-	.732
Trajectory	L_1	0	0	0	0	-	-	-	0
	L_2	.457	.098	-.058	.357	-	-	-	.242
	L_3	.892	.791	.837	.850	-	-	-	.771
	L_4	.956	.934	.863	.925	-	-	-	.839
	L_5	1	1	1	1	-	-	-	1
Residual	Variance	1.612	7.444	3.396	2.473	-	-	-	1.045
Overall	R^2	.764	.551	.456	.608	-	-	-	.792

† For analytical purposes, scores were transformed by dividing the sumscore for each scale by 10. The subscales mental health, role limitations-emotional and vitality were excluded due to very high correlations between depression scores and these particular subscales. Results are presented as unstandardized b's as in regular regression analysis. Contrast coding was used for the dichotomous independent variables, with prevention indication: -1=primary indication, +1=secondary indication; symptomatic heart failure: -1=no, +1=yes; shock(s) during follow-up: -1=no, +1=yes; gender partner: -1=female, +1=male. * $p \leq .050$; ** $p \leq .010$; *** $p \leq .001$. Abbreviations: *BP*, bodily pain; *CCI*, Charlson Comorbidity Index; *CFI*, comparative fit index; *GH*, general health; *L*, loadings on random slope factor for each measurement occasion; *PF*, physical functioning; *r*, correlation between random factors; *RL-E*, role limitations – emotional; *RL-P*, role limitations – physical; *RMSEA*, root mean square error of approximation; *SES*, socio-economic status; *SF*, social functioning; *VT*, vitality

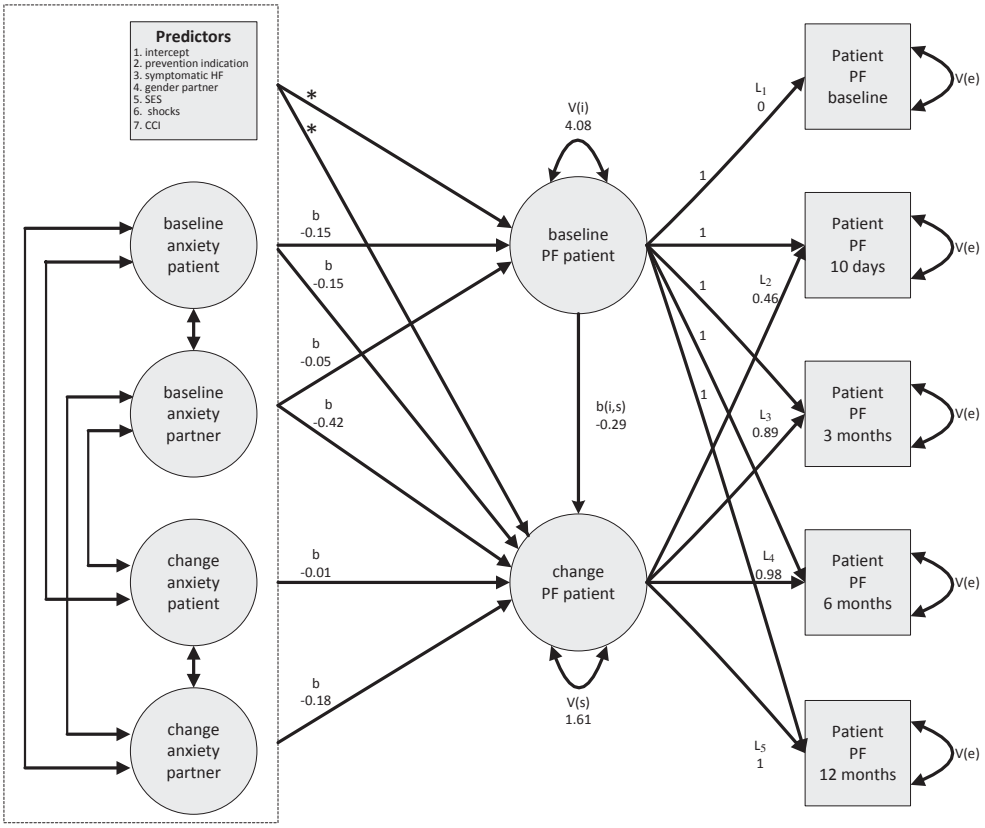

Figure 2. Dyadic anxiety linked to patients' health status (physical functioning as example)
* All predictors are included in the statistical model, but in order to preserve readability only regression coefficients of baseline patient and partner anxiety on change of patient and partner anxiety are shown. For regression coefficients of remaining predictors, see 'Baseline' and 'Change' sections in the physical functioning column of Table 3. All factors within the left dashed rectangle are correlated, but for reasons of intelligibility, we have only shown the associations between the anxiety factors and omitted the associations between the predictor box and the anxiety factors. The numbers following the predictors in Table 3 correspond to the predictor numbers in the predictor box of Figure 2. For the same reasons, residual correlations between patients and partners for each measurement occasion are omitted in the graphical representation of the model. Abbreviations: b(i): unstandardized regression coefficient in the regression equation for the random intercept (i.e. baseline); b(s): unstandardized regression coefficient in the regression equation for the random slope (i.e. change); V(e): residual variance; V(i): variance random intercept; V(s): variance random slope.

DISCUSSION

The findings of the current study showed that individual differences in baseline distress and change in distress correlated between patients and partners, with distress trajectories over time being relatively similar for patients and partners. Moreover, we found that patients' baseline health status scores and change in health status scores during follow-up were strongly related to patients' own baseline distress scores. On top of that, partners' baseline anxiety was associated with lower social

functioning of patients, while partners' baseline depression was associated with an increase in patients' bodily pain. With regard to change in patient health status, higher partner baseline anxiety predicted decreases in patient physical functioning during follow-up. Additionally, increases in partner anxiety during follow-up were related to decreased patient health status for the domains physical functioning, bodily pain, social functioning, emotional role limitations, vitality and general health during follow-up, and increases in partner depression during follow-up with worse recovery of physical functioning, bodily pain, social functioning and general health. Importantly, although the amounts of explained variance of partner distress were not particularly high, worsening of partner distress during follow-up remained a predictor of changes in patients' health status on top of patients' and partners' baseline levels of distress, with results being largely similar for anxiety and depression.

The included demographic and clinical covariates predicted only a small amount of variance in all models. Nevertheless, with respect to partners' baseline distress levels, we found that partners of patients with symptomatic heart failure were more distressed than partners of patients without symptomatic heart failure. This adds to the findings of previous studies showing that patients' clinical characteristics, including comorbid medical conditions, contribute to partners' risk of emotional distress.[21,23] Female partners were also more distressed than male partners. This finding is in line with previous results among chronically ill patients and their partners.[15] Increased distress in female partners could be attributed to several mechanisms, including greater psychosocial burden due to the condition of the spouse,[39] a perception of failing in the caregiver role,[39] increased attentiveness to emotions and use of less effective coping styles.[41]

In our study, patients with a primary prevention indication showed a more favorable course of psychological well-being, as anxiety and depressive symptoms more sharply decreased among these patients compared to patients with a secondary prevention indication. Previous research has found similar results.[23] Importantly, the current study found a hampering effect of shocks on the recovery of anxiety and depression of patients, and depression of partners during follow-up. The impact of shocks on emotional distress may partly depend on the interval between shock and assessment of emotional distress,[42] and as yet evidence on the impact of shocks on health status is mixed.[42-45]

Patients' and partners' emotional distress patterns were comparable in course, and partners' changes in emotional distress were associated with patients' health status recovery during the first 12 months post implantation, indicating that patients and partners go through a similar process of adaptation and emotion regulation after ICD implantation. Being part of a couple is highly effective when it comes to emotion regulation. Social baseline theory[46] explains that close proximity is the baseline assumption of the human brain, and that social proximity and interaction decrease physical and mental costs of environmental demands via two mechanisms: risk distribution and load sharing. While the former may mainly be of interest from an evolutionary perspective, the latter may be particularly interesting in this context, because load sharing makes the patient perceive the environment as less threatening and less difficult to cope with. This produces large savings in terms of neural and peripheral physiological reactions, which can be beneficial for the ability to

cope mentally with the challenging situation, but also for cardiac functioning. For example, the absence of social proximity could lead to impaired control of emotions as a result of reduced mesolimbic functioning and to the release of stress hormones in the peripheral system.[46] Thus, optimal psychological functioning of the partner increases the likelihood that the patient will be able to adapt to the new situation of living with an ICD both mentally and physically.

This study has some limitations. First, we were not able to include a measure of dyadic coping styles in the current study. Coping can influence the emotional distress pattern of patients and partners, and previous research has shown that patients with emotional distress are more likely to use ineffective coping strategies, such as avoidance and withdrawal,[47] which tend to be similar in both partners within the dyad.[48] Non-adaptive coping is thus a risk factor that runs within the dyad when emotional distress is present. A related concept that was not measured in the current study is relationship quality. Although there is evidence for a link between relationship quality and patient and partner outcomes, there is also evidence that being part of a relationship on its own is predictive of affect and health.[49] Furthermore, this study was conducted mainly amongst Caucasian patients living in a western society. Dyadic interaction and expression of emotions may be culture-dependent, making these results not necessarily generalizable to patients of other origins.

An important strength of this study is the sound statistical methodology, benefiting fully of the longitudinal design of the study. Furthermore, the focus on the interrelationship between both patients' and partners' distress on the one hand and on patients' health status on the other hand is new in arrhythmia research. In addition, the large sample size, particularly regarding the participating partners, and the high participation rate, are advantages of the study.

In conclusion, we found that distress patterns of patients and partners were highly similar, and that although patients' own emotional distress played an important role in predicting their health status at both baseline and change therein during follow-up, on top of that, the development of partner distress during follow-up was also predictive of how well patients' health status was able to recover after implantation. The influence of the distress recovery of partners was visible on a wide range of patient health status subscales during follow-up. Since partner distress is a risk factor for poor coping, and partners play a key role in the recovery of patients, interventions should not only be focused on psychological functioning of the patient but also that of the partner.

REFERENCES

1. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352(3):225-237.
2. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346(12):877-883.
3. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337(22):1576-1584.
4. Magyar-Russell G, Thombs BD, Cai JX, Baveja T, Kuhl EA, Singh PP, Montenegro Braga Barroso M, Arthurs E, Roseman M, Amin N, Marine JE, Ziegelstein RC. The prevalence of anxiety and depression in adults with implantable cardioverter defibrillators: A systematic review. J Psychosom Res 2011;71(4):223-231.
5. Matchett M, Sears SF, Hazelton G, Kirian K, Wilson E, Nekkanti R. The implantable cardioverter defibrillator: Its history, current psychological impact and future. Expert Rev Med Devices 2009;6(1):43-50.
6. Pedersen SS, Theuns DAMJ, Jordaens L, Kupper N. Course of anxiety and device-related concerns in implantable cardioverter defibrillator patients the first year post implantation. Europace 2010;12(8):1119-1126.
7. Sears SF, Conti JB. Quality of life and psychological functioning of ICD patients. Heart 2002;87(5):488-493.
8. Whang W, Albert CM, Sears Jr SF, Lampert R, Conti JB, Wang PJ, Singh JP, Ruskin JN, Muller JE, Mittleman MA. Depression as a predictor for appropriate shocks among patients with implantable cardioverter-defibrillators: Results from the Triggers Of Fentricular Arrhythmias (TOVA) study. J Am Coll Cardiol 2005;45(7):1090-1095.
9. Suzuki T, Shiga T, Kuwahara K, Kobayashi S, Suzuki S, Nishimura K, Suzuki A, Ejima K, Manaka T, Shoda M, Ishigooka JUN, Kasanuki H, Hagiwara N. Prevalence and persistence of depression in patients with implantable cardioverter defibrillator: A 2-year longitudinal study. Pacing Clin Electrophysiol 2010;33(12):1455-1461.
10. Pedersen SS, Hoogwegt MT, Jordaens L, Theuns DAMJ. Pre implantation psychological functioning preserved in majority of implantable cardioverter-defibrillator patients. Int J Cardiol 2011;166(1):215-220.
11. Lazarus RS, Folkman S, Stress, appraisal, and coping. New York, NY: Springer, 1984.
12. Meuwly N, Bodenmann G, Germann J, Bradbury TN, Ditzen B, Heinrichs M. Dyadic coping, insecure attachment, and cortisol stress recovery following experimentally induced stress. J Fam Psychol 2012;26(6):937-947.
13. Bodenmann G. A systemic-transactional conceptualization of stress and coping. Swiss J Psychol 1995;54(1):34-49.
14. Berg CA, Upchurch R. A developmental-contextual model of couples coping with chronic illness across the adult life span. Psychol Bull 2007;133(6):920-954.
15. Cutrona CE, Russel DW, Gardner KA, *The relationship enhancement model of social support*, in *Couples coping with stress: Emerging perspectives on dyadic coping*, Revenson TA, Kayser K, and Bodenmann G, Editors. 2005, American Psychological Association: Washington, DC. p. 73-95.
16. Dougherty CM, Thompson EA. Intimate partner physical and mental health after sudden cardiac arrest and receipt of an implantable cardioverter defibrillator. Res Nurs Health 2009;32(4):432-442.
17. Hazelton AG, Sears SF, Kirian K, Matchett M, Shea J. Coping with my partner's ICD and cardiac disease. Circulation 2009;120(10):e73-e76.
18. Hagedoorn M, Sanderman R, Bolks HN, Tuinstra J, Coyne JC. Distress in couples coping with cancer: A meta-analysis and critical review of role and gender effects. Psychol Bull 2008;134(1):1-30.
19. Vazquez LD, Sears SF, Shea JB, Vazquez PM. Sexual health for patients with an implantable cardioverter defibrillator. Circulation 2010;122(13):e465-e467.
20. Pedersen SS, Van den Berg M, Erdman RAM, Van Son J, Jordaens L, Theuns DAMJ. Increased anxiety in partners of patients with a cardioverter-defibrillator: The role of indication for ICD therapy, shocks, and personality. Pacing Clin Electrophysiol 2009;32(2):184-192.
21. Sowell LV, Sears SFJ, Walker RL, Kuhl EA, Conti JB. Anxiety and marital adjustment in patients with implantable cardioverter defibrillator and their spouses. J Cardiopulm Rehabil Prev 2007;27(1):46-49.

22. Van den Broek KC, Habibović M, Pedersen SS. Emotional distress in partners of patients with an implantable cardioverter defibrillator: A systematic review and recommendations for future research. Pacing Clin Electrophysiol 2010;33(12):1442-1450.
23. Five BL, Fausel CA, *Hematopoietic dyscrasias and stem cell/bone marrow transplantation*, in *Psychooncology*, Holland JC, et al., Editors. 2010, Oxford University Press: New York, NY. p. 191-195.
24. Moser DK, Dracup K. Role of spousal anxiety and depression in patients' psychosocial recovery after a cardiac event. Psychosom Med 2004;66(4):527-532.
25. Van den Broek KC, Heijmans N, Van Assen MA. Anxiety and depression in patients with an implantable cardioverter defibrillator and their partners: A longitudinal study. Pacing Clin Electrophysiol 2013;36(3):362-371.
26. Piotrowicz K, Noyes K, Lyness JM, McNitt S, Andrews ML, Dick A, Hall WJ, Moss AJ, Zareba W. Physical functioning and mental well-being in association with health outcome in patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial II. Eur Heart J 2007;28(5):601-607.
27. Theuns DAMJ, Schaer BA, Soliman OI, Altmann D, Stichterling C, Geleijnse ML, Osswald S, Jordaens L. The prognosis of implantable defibrillator patients treated with cardiac synchronization therapy: Comorbidity burden as a predictor of mortality. Europace 2011;13(1):62-69.
28. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67(6):361-370.
29. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997;27(2):363-370.
30. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: An updated literature review. J Psychosom Res 2002;52(2):69-77.
31. Aaronson NK, Muller M, Cohen PDA, Essink-Bot M-L, Fekkes M, Sanderman R, Sprangers MAG, te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 health survey in community and chronic disease populations. J Clin Epidemiol 1998;51(11):1055-1068.
32. Ware J, Kosinski M. Interpreting SF-36 summary health measures: A response. Qual Life Res 2001;10(5):405-413.
33. Bollen KA, Curran PJ, Latent curve models: A structural equation approach. Hoboken, New Jersey: Wiley, 2006.
34. Hu LT, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Struct Equ Modeling 1999;6(1):1-55.
35. Pedersen SS, Hoogwegt MT, Jordaens L, Theuns DAMJ. Relation of symptomatic heart failure and psychological status to persistent depression in patients with implantable cardioverter-defibrillator. Am J Cardiol 2011;108(1):69-74.
36. Pedersen SS, Tekle FB, Hoogwegt MT, Jordaens L, Theuns DAMJ. Shock and patient preimplantation Type D personality are associated with poor health status in patients with implantable cardioverter-defibrillator. Circ Cardiovasc Qual Outcomes 2012;5(3):373-380.
37. Hoogwegt MT, Kupper N, Jordaens L, Pedersen SS, Theuns DAMJ. Comorbidity burden is associated with poor psychological well-being and physical health status in patients with an implantable cardioverter-defibrillator. Europace 2013;15(10):1468-1474.
38. Steptoe A, Molloy GJ, Messerly-Bürgy N, Wikman A, Randall G, Perkins-Porras L, Kaski JC. Emotional triggering and low socio-economic status as determinants of depression following acute coronary syndrome. Psychol Med 2011;41(09):1857-1866.
39. Coyne JC, Fiske V, *Couples coping with chronic and catastrophic illness*, in *Family health psychology*, Stephens MAP, Hobfoll SE, and Crowther J, Editors. 1992, Hemisphere: Washington, D.C. p. 129-149.
40. Hagedoorn M, Sanderman R, Buunk BP, Wobbes T. Failing in spousal caregiving: The 'identity-relevant stress' hypothesis to explain sex differences in caregiver distress. Br J Health Psychol 2002;7(Part 4):481-494.
41. Lutzky SM, Knight BG. Explaining gender differences in caregiver distress: The roles of emotional attentiveness and coping styles. Psychol Aging 1994;9(4):513-519.
42. Pedersen SS, Van den Broek KC, Van den Berg M, Theuns DAMJ. Shock as a determinant of poor patient-centered outcomes in implantable cardioverter defibrillator patients: Is there more to it than meets the eye? Pacing Clin Electrophysiol 2010;33(12):1430-1436.
43. Borne RT, Varosy PD, Masoudi FA. Implantable cardioverter-defibrillator shocks: Epidemiology, outcomes, and therapeutic approaches. JAMA Intern Med 2013;173(10):859-865.

44. Morken IM, Isaksen K, Karlsen B, NorekvÅL TM, Bru E, Larsen AI. Shock anxiety among implantable cardioverter defibrillator recipients with recent tachyarrhythmia. Pacing Clin Electrophysiol 2012;35(11):1369-1376.
45. Sears SF, Kirian K. Shock and patient-centered outcomes research: Is an ICD shock still a critical event? Pacing Clin Electrophysiol 2010;33(12):1437-1441.
46. Beckes L, Coan JA. Social baseline theory: The role of social proximity in emotion and economy of action. Soc Personal Psychol Compass 2011;5(12):976-988.
47. O'Farrell P, Murray J, Hotz SB. Psychologic distress among spouses of patients undergoing cardiac rehabilitation. Heart Lung 2000;29(2):97-104.
48. Son H, Thomas SA, Friedmann E. The association between psychological distress and coping patterns in post-MI patients and their partners. J Clin Nurs 2012;21(15-16):2392-2394.
49. Taylor SS, Davis MC, Zautra AJ. Relationship status and quality moderate daily pain-related changes in physical disability, affect, and cognitions in women with chronic pain. Pain 2013;154(1):147-153.

Long-term mortality risk in patients with an implantable cardioverter-defibrillator: Influence of emotional distress of their partners

9

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Submitted

ABSTRACT

Background: Emotional distress levels in partners of implantable cardioverter-defibrillator (ICD) patients are even higher than in ICD patients. We investigated the influence of partner distress on long-term mortality risk in patients with an ICD.

Methods: Distress was measured in 418 first-time ICD patients and their partners with the Hospital Anxiety and Depression Scale (HADS) at baseline. Study endpoint was all-cause mortality (up to 6 years follow-up). Cox proportional hazard regression analyses were used to separately assess the impact of partners' depression and anxiety on time to mortality.

Results: In total, 78 patients (18.7%) died during follow-up (mean follow-up 4.9±1.5 years, range 0.1-6.0 years). Depression and anxiety, defined as a score of ≥8 on the HADS-D and HADS-A, were present in 24.4% and 27.3% of the patients, and 22.2% and 43.1% of the partners, respectively. Partner depression was associated with patients' mortality risk in unadjusted analysis (HR=1.64; 95% CI=1.01-2.65; p=.044). After inclusion of patients' own emotional distress in the analyses, this relationship became non-significant (HR=1.43, 95% CI=0.86-2.38, p=.17). There was no association between partner anxiety and patients' prognosis (HR=1.13, 95% CI=0.71-1.78, p=.61) in adjusted analysis.

Conclusion: Partner depression was associated with risk of patient mortality, but when adjusting for patient levels of distress this fell short of statistical significance. Partners' psychological well-being seems to affect patients' psychological well-being more than patients' physical prognosis. Future research should focus on the impact of persistent, long-term emotional distress in partners, and on comorbid distress within the patient-partner dyad in relation to patient prognosis.

INTRODUCTION

The implantable cardioverter-defibrillator (ICD) is the treatment of first choice for patients at risk for sudden cardiac death (SCD) due to life-threatening ventricular tachyarrhythmias, both as primary and secondary prevention.[1-3] Emotional distress, including symptoms of anxiety, depression and posttraumatic stress, is prevalent in about 25% of patients with an ICD and influences their quality of life[4-7] but also prognosis.[8,9] In addition to the patient's psychological profile, the partner's emotional functioning also plays an important role in their adaptation process.[10] Previous research has shown that emotional distress is at least as prevalent in partners of ICD patients as it is in patients.[11,12] Moreover, partner emotional distress is correlated with patient emotional status in terms of depressive and anxious symptoms.[11]

However, little is known about the association between partner emotional distress and patient clinical outcomes, both in the cardiac and non-cardiac population. Research on the relationship between marital quality and mortality risk in patients with heart failure has shown that reduced marital quality was predictive of a higher risk for mortality up to 8 years follow-up.[13] Behavioral factors, including the ability to discuss the disease with each other and observed positivity of the partner, were particularly important determinants of survival. However, this long-term predictive effect was only significant for women with heart failure.[13,14] Although some research has focused on marital status and marital quality in relation to patient prognosis, the association between partner *distress* and patient prognosis remains unknown in the cardiac population, and the ICD population in specific. Partner distress may play a role in patient prognosis beyond the well-established effect of patients' own emotional distress on their prognosis.[15,16] Therefore, the aim of the current study was to investigate the influence of partner emotional distress, defined as the presence of significant symptoms of depression and anxiety, on risk of long-term mortality (up to 6 years follow-up) in patients with an ICD.

METHODS

Patients and study design

The Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter Defibrillator: A prospective Study (MIDAS) was set up in the Erasmus Medical Center, Rotterdam, in collaboration with Tilburg University, the Netherlands, to examine the psychological functioning of patients with a first-time ICD implantation and their partners. Between August 2003 and February 2010, 448 consecutive patients and their partners were enrolled in the study. Patients with a life-expectancy of <1 year, on the waiting list for heart transplantation, a history of psychiatric illness other than affective/anxiety disorders, or insufficient knowledge of the Dutch language were excluded from participation.

The study was conducted according to the Helsinki Declaration, and the study protocol was approved by the Medical Ethics Committee of the Erasmus Medical Center. An ICD nurse provided written and oral information on the study to patients and their partners prior to ICD implantation, after which written informed consent was obtained from both patients and partners. The couples

were asked to complete a similar set of standardized and validated questionnaires at baseline (i.e. one day prior to implantation).

Measures

Demographic and clinical variables

Demographic characteristics (i.e. age, gender, marital status and educational level) of both patients and partners were collected via purpose-designed questions in the questionnaires. Information on patients' and partners' socio-economic status (SES) was obtained from the Central Bureau of Statistics Netherlands. Information on clinical patient characteristics including indication for ICD therapy (primary versus secondary prevention), treatment with cardiac resynchronization therapy (CRT), left ventricular ejection fraction (LVEF) ≤35%, QRS duration, the presence of coronary artery disease (CAD), symptomatic heart failure (defined as New York Heart Association (NYHA) functional class III+IV), atrial fibrillation, prior percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), smoking, and use of cardiac (i.e. beta-blockers, statins, amiodarone, diuretics, ACE-inhibitors, and digoxin) and psychotropic medication, were collected from patients' medical records at the time of implantation. Furthermore, the Charlson Comorbidity Index (CCI) was constructed using data indicating the presence of renal failure, previous MI, chronic heart failure, diabetes mellitus, peripheral arterial disease, cerebrovascular disease, chronic obstructive pulmonary disease and cancer. In order to obtain a comorbidity index that is in accordance with the original CCI, a weight of 2 was assigned to renal failure and any malignancy, and a weight of 1 to the other comorbid conditions. The sum score of this index was subsequently adjusted for age, with addition of 1 extra point for each decade above age 50.

Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) was used to measure symptoms of anxiety and depression in patients and partners at baseline. This is a 14-item self-report questionnaire consisting of 7 items measuring symptoms of anxiety (HADS-A) and 7 items measuring symptoms of depression (HADS-D).[17] Items are rated following a 4-point Likert scale ranging from 0 to 3 (total score range 0-21), with higher scores reflecting more symptoms.[17] A cut-off score of ≥8 reflects optimal balance between sensitivity and specificity[18] and was used in the current study to define patients with clinically significant levels of anxiety and depression. The HADS has good psychometric properties, with mean Cronbach's alphas of 0.83 and 0.82 and a three-week test-retest reliability of 0.89 and 0.86 for the HADS-A and HADS-D subscales, respectively.[19] The HADS is a valid instrument designed to measure separate symptoms of anxiety and depression in a non-psychiatric hospital setting.[18]

Endpoint

All-cause mortality was used as endpoint in this study. Information on survival status up to 6.0 years post implantation was obtained via the Dutch municipal register and patients' medical records. The administrative date for end-of-study was set at June 1st 2013, as this was the time of updating the mortality data from the Dutch municipal register.

Statistical analyses

Baseline demographic and clinical variables for patients with complete versus incomplete data were compared with the χ^2 test (Fisher's Exact test when appropriate) for nominal variables, and Student's t-test for continuous variables.

The assumption of proportional hazards was checked by inspection of the log-minus-log plots for nominal variables and partial residual plots for continuous variables. In case of violation of the assumption, that variable was transformed into a time-dependent variable, enabling inclusion in the analyses without violating the proportional hazards assumption. Cox proportional hazard regression analyses were used to separately assess the impact of dichotomous partner depression and anxiety on time to all-cause patient mortality. In multivariable analyses using the Enter method, indication for ICD implantation, the age-adjusted CCI as an index for comorbidity burden, the use of amiodarone, and the presence of appropriate and inappropriate shocks were included as covariates. In addition, patient depression was included as covariate in the analysis examining the relation of partner depression to patient mortality, and anxiety was included in the analysis of the association between partner anxiety and patient mortality in order to avoid the problem of multicollinearity. Covariates were a priori selected based on the literature. Results of the Cox regression analyses are reported using hazard ratios (HR) with their corresponding 95% confidence intervals (CI). Additionally, p-values are reported with a value <.05 (two-sided) indicating statistical significance. Cumulative survival curves for mortality risk predicted by the presence of anxiety and depression in partners were constructed using the Kaplan-Meier method. The log-rank test was used to compare the proportion of cumulative survival stratified by group. Patients who underwent heart transplantation during the study (N=21) were censored as alive at the time of heart transplantation in both unadjusted and adjusted analyses due to removal of their ICD system. Furthermore, patients who were transferred to another hospital and therefore lost to follow-up (N=4) were censored as alive because clinical variables could not be obtained from the moment of losing contact. Results were repeated with continuous scores of partner depression and anxiety. PASW Statistics 19 statistical software was used to analyze the data (PASW IBM Corp., Armonk, NY, USA).

RESULTS

Patient and partner baseline characteristics

Overall, 448 patients were included in the study, of whom 11 (2.5%) had no partner. In addition, 18 patients (4.0%) and 30 partners (6.8%) did not complete the questionnaires. In total, 418 (93.3%) dyads of patient and partner were included in the adjusted analyses. Patients with complete data were compared with patients who did not participate in the analyses due to incomplete data. Patients who were not included in analyses were more likely to have a low SES (defined as a SES ranking of 1 or 2 on a scale of 1-10; p=.030), to suffer from CAD (p<.001), symptomatic heart failure (p=.027) and diabetes (p=.017), and to use psychotropic medication (p=.012).

Baseline demographic and clinical characteristics of patients and demographic characteristics of partners are shown in Table 1. The mean age of patients was 58±12 years, and 321 (79%) of the patients were male. Partners' mean age was 56±12 years and 90 (22%) of the partners were male.

Table 1. Baseline characteristics for patients and partners *

	Patients (N=418)	Partners (N=418)
Demographics		
Mean age (±SD)	58.3 (12.1)	56.0 (12.0)
Men	328 (78.5)	92 (22.0)
Lower SES †	192 (45.9) ‡	192 (45.9) ‡
Clinical factors		
Primary prevention indication	275 (65.8)	
CRT	120 (28.7)	
LVEF ≤35% §	309 (73.9)	
Mean QRS (±SD)	129.4 (36.4)	
CAD	236 (56.5)	
Previous PCI	107 (25.6)	
Previous CABG	80 (19.1)	
Symptomatic heart failure #	136 (32.5) ‡	
Atrial fibrillation	94 (22.5)	
Diabetes	58 (13.9)	
Smoking	43 (10.3) ‖	106 (25.4) **
Mean heart rate	68.3 (13.6)	
Medication		
Amiodarone	79 (18.9)	
Beta-blockers	332 (79.4)	
Diuretics	237 (56.7)	
ACE-inhibitors	299 (71.5)	
Statins	248 (59.3)	
Digoxin	63 (15.1)	
Psychotropic medication	64 (15.3) ††	67 (16.0) **

* Data are presented as N (%), unless otherwise indicated. † Based on ZIP-code and calculated per household by the Netherlands Institute for Social Research, ‡ N=2 (0.5%) missing; § N=59 (14.1%) missing; # defined as NYHA functional class III+IV, N=2 (0.5%) missing; || N=4 (1.0%) missing; ** N=3 (0.7%) missing; †† N=6 (1.4%) missing. Abbreviations: *ACE*, angiotensin-converting enzyme; *CABG*, coronary artery bypass grafting; *CAD*, coronary artery disease; *CRT,* cardiac resynchronization therapy; *LVEF*, left ventricular ejection fraction; *N*, number; *PCI*, percutaneous coronary intervention; *QRS*, QRS duration; *SD*, standard deviation; SES, socio-economic status

All-cause mortality

In total, 78 patients (18.7%) died during follow-up (mean follow-up period 4.9 ±1.5 years, range 0.1-6.0 years). Patients who underwent heart transplantation before ending of the study (N=21, 5.0%) were censored, as their ICD was explanted. In adjusted analyses, 28 additional patients (6.7%) were censored due to hospital transfer (and absence of clinical follow-up), just as 22 (5.3%) patients who were lost to follow-up.

Emotional distress within the dyad

In Table 2, mean continuous scores of depression and anxiety for patients and partners are reported, as well as the Pearson correlation between patients' depression and anxiety, and partners' depression

and anxiety. Using the cut-off score of ≥8 on the HADS-D to identify patients and partners with clinically significant levels of emotional distress, in 61.7% of the cases, neither the patient nor the partner showed depressive symptoms, while in 8.4% of the cases both patients and partners reported significant depressive symptoms. For 13.7% we found that the patient was not depressed while the partner was depressed, and for 16.1% we found that the patient was depressed while the partner was not depressed.

With respect to anxiety, in 44.6% of the dyads neither the patient nor the partner was anxious, while in 14.9% of the dyads both the patient and the partner were anxious. In 28.0% of the cases, only the partner was anxious, while in 12.5% of the dyads only the patient experienced anxiety symptoms.

Table 2. Mean levels of and correlations between emotional distress of patients and partners *

	Depression patient	**Anxiety patient**	**Depression partner**	**Anxiety partner**
HADS-score	4.93 ± 3.95	5.48 ± 3.97	4.90 ± 3.86	7.16 ± 4.40
Correlation	**Depression patient**	**Anxiety patient**	**Depression partner**	**Anxiety partner**
Depression patient	1			
Anxiety patient	0.661**	1		
Depression partner	0.237**	0.261**	1	
Anxiety partner	0.198**	0.292**	0.714**	1

* Results are presented as mean score on the HADS-D and HADS-A ± standard deviation.
**Pearson correlation coefficient r is significant on a p<.001 level (two-tailed).

Relationship between partner distress and patient risk of all-cause mortality

Proportional hazards assumptions were checked and met for all variables, except for the occurrence of shocks during follow-up, which was therefore transformed into a time-dependent variable. Results of the Cox regression analyses are presented in Table 3.

Depression – Cumulative hazard functions were significantly different for patients with versus without a depressed partner (log-rank χ^2=4.13; p=.042) (Figure 1). In unadjusted Cox regression analysis, partner depression was associated with a cumulative increased risk for all-cause mortality (HR=1.64; 95% CI=1.01-2.65; p=.044). When adjusting for the a priori selected clinical covariates, the relationship between partner depression and risk of mortality was reduced to trend level (HR=1.63; 95% CI=1.00-2.67; p=.053), and when adding patients' own depression to the model, the relationship between partner depression and patient mortality became non-significant (HR=1.43; 95% CI=0.86-2.38; p=.17), with patient depression being a significant predictor of patient mortality (HR=1.67; 95% CI=1.03-2.70; p=.038).

Anxiety – Cumulative hazard functions did not differ significantly for patients with versus without an anxious partner (log-rank χ^2=1.68; p=.20) (Figure 2). Partner anxiety was not associated with an increased risk for patient all-cause mortality during follow-up in unadjusted Cox regression analysis (HR=1.34; 95% CI=0.86-2.09; p=.20). Inclusion of the covariates did not change the results.

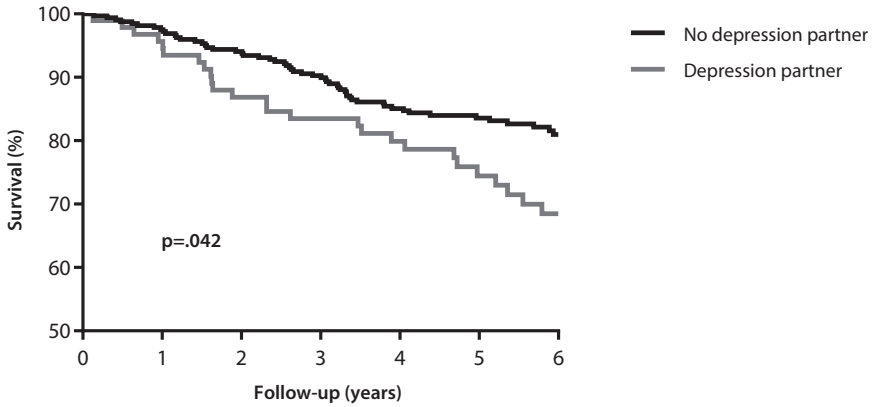
Repeating the results with continuous scores of partner emotional distress yielded similar

findings for both depression (unadjusted: HR=1.06; 95% CI=1.01-1.11; p=.037; adjusted: HR=1.05; 95% CI=0.99-1.12; p=.11) and anxiety (unadjusted: HR=1.03; 95% CI=0.98-1.08; p=.27; adjusted: HR=1.02; 95% CI=0.97-1.08; p=.40).

Table 3. Results of the Cox regression analyses*

	Partner depression		
Block 1	**HR**	**95% CI**	**p**
Depression partner	1.58	0.97-2.58	***.066***
Block 2	**HR**	**95% CI**	**p**
Depression partner	1.63	1.00-2.67	***.053***
Indication for ICD implantation	1.45	0.90-2.34	.13
Use of amiodarone	1.60	0.99-2.61	.06
CCI	1.39	1.27-1.53	**<.001**
Shocks during follow-up	1.16	0.99-1.35	.07
Block 3	**HR**	**95% CI**	**p**
Depression partner	1.43	0.86-2.38	.17
Indication for ICD implantation	1.50	0.92-2.42	.10
Use of amiodarone	1.49	0.90 -2.45	.12
CCI	1.38	1.25-1.52	**<.001**
Shocks during follow-up	1.16	0.99-1.35	.06
Depression patient	1.67	1.03-2.70	**.038**
	Partner anxiety		
Block 1	**HR**	**95% CI**	**p**
Anxiety partner	1.31	0.84-2.05	.24
Block 2	**HR**	**95% CI**	**p**
Anxiety partner	1.16	0.74-1.83	.52
Indication for ICD implantation	1.39	0.86-2.25	.18
Use of amiodarone	1.64	1.00-2.67	**.049**
CCI	1.39	1.26-1.52	**<.001**
Shocks during follow-up	1.16	0.99-1.36	.06
Block 3	**HR**	**95% CI**	**p**
Anxiety partner	1.13	0.71-1.78	.61
Indication for ICD implantation	1.43	0.88-2.33	.15
Use of amiodarone	1.59	0.97-2.61	.06
CCI	1.39	1.27-1.53	**<.001**
Shocks during follow-up	1.16	1.00-1.36	.06
Anxiety patient	1.29	0.79-2.12	.31

* Bold p-values indicate statistical significance, bold and italic p-values indicate significance on a trend level. Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio

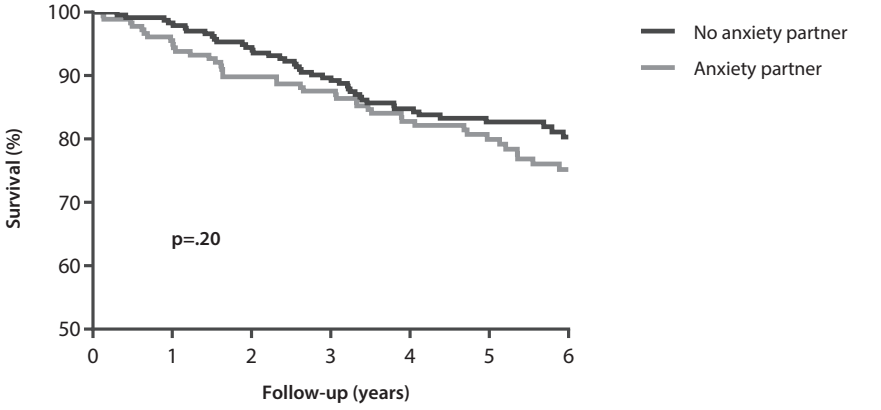


Number of patients at risk

	Baseline	1 year	2 years	3 years	4 years	5 years	6 years
No partner depression*	325	316	305	293	278	274	269
Partner depression*	93	88	80	78	74	70	67
Total # of patients	418	404	385	371	352	344	336

* A cut-off score of ≥8 on the HADS-D was used to define depression

Figure 1. Cumulative survival curve stratified by partners' depression



Number of patients at risk

	Baseline	1 year	2 years	3 years	4 years	5 years	6 years
No partner anxiety*	238	233	224	213	203	199	196
Partner anxiety*	180	171	161	158	149	145	140
Total # of patients	418	404	385	371	352	344	336

* A cut-off score of ≥8 on the HADS-A was used to define anxiety

Figure 2. Cumulative survival curve stratified by partners' anxiety

DISCUSSION

To our knowledge, this is the first study in ICD patients to examine the relationship between partner emotional distress and patient risk of mortality, using a large cohort of ICD patients and their partners and a long term follow-up period. Knowledge on a possible contribution of partners' psychological well-being to the patients' mortality risk is important, as it can provide us with targets for risk management and psychological treatment. The primary aim of this study was to investigate whether emotional distress in partners would be associated with an increased risk of long-term all-cause mortality in patients with a first-time ICD implant. We found that partner depression was associated with increased risk of patient mortality, but only in unadjusted analyses. When entering patients' own levels of emotional distress in the model, the relationship between emotional distress in partners and risk of mortality in patients became non-significant. We found no significant relationship between partner anxiety and patient risk of mortality. Clinical indicators of disease severity, including use of amiodarone and a higher CCI, were significant predictors of patient long-term all-cause mortality risk.

To date, the association between partner emotional distress and prognosis of patients with heart disease remains understudied. However, in previous research investigating the relationship between partner distress and patient emotional outcomes, we found that partners' emotional status was predictive of patients' health status on several subdomains, beyond patients' own own emotional status (Hoogwegt MT, Braeken J, Kupper N, Theuns DAMJ & Pedersen SS, unpublished data, 2013). The psychological status of partners is thus more likely to affect patients' psychological well-being instead of patients' physical status.

To our knowledge, no study has investigated the relationship between partner emotional distress and patient risk for morbidity and mortality in cardiovascular disease. Within the current literature though, several related concepts are frequently used in patient-partner research, including marital status, marital satisfaction or quality, and social support. Marital status refers to the question whether the patient has a partner or not, while marital quality is a marker of how satisfied patients and partners are about the relationship and the benefits that follow from that relationship. In both the general and cardiac population, marital status and marital quality have shown to be predictive of patient prognosis, with patients having a partner and being satisfied with this relationship displaying more favourable health outcomes than patients without a partner.[13,14,20-23] Social support is associated with a better prognosis of cardiac patients as well,[24] although there are also indications of this relationship being explained by lifestyle behaviors such as medication adherence and sedentary behaviour.[25,26] However, besides these related concepts as predictors of patient prognosis, to our knowledge, no research to date has examined the relationship between partner *distress* and patient mortality, neither in the cardiac, nor in the non-cardiac population.

We hypothesized that several mechanisms could explain a possible relationship between partner distress and patient mortality. First, partners with emotional distress are more likely to use inadequate coping strategies, such as avoidance and withdrawal.[27] Coping styles are known to be similar within the dyad, which means that ineffective coping of partners could affect patients' coping.[28] Adequate coping is crucial when it comes to health behaviors, which are strongly predictive

of patient prognosis.[29,30] With impaired coping resources in distressed partners, social support is also likely to be lower in these dyads, which again may increase the risk of poorer prognosis.[24] In the light of our null-finding, these mechanisms may more likely explain the correlation between partner and patient emotional distress instead of a relationship between partner distress and patient prognosis. Future research should focus on the question whether *persistent* emotional distress in the partner (i.e. significant symptoms of depression and/or anxiety over a longer period of time) might have a stronger impact on patient prognosis than emotional distress around the time of implantation. In addition, it would be interesting to examine whether comorbid emotional distress within the dyad (i.e. in both patients and partners) might increase patient risk of morbidity and mortality more than if distress is present only in the partner or the patient. Unfortunately, we were not able to examine these two aspects in our study due to the relatively low number of events.

The following limitations should be acknowledged. First, we have not been able to examine the association between partner emotional distress and cardiac-related mortality, because the cause of death was unclear from a considerable number of medical records. As a result, it is difficult to speculate about possible underlying mechanisms explaining the relationship between emotional distress and prognosis. Second, due to the limited number of patients who died during follow-up, we have not been able to include all factors that may impinge upon the relationship between partner distress and patient mortality. However, by including demographic and clinical covariates based on the literature, we have tried to incorporate as many relevant variables as possible. Furthermore, the design of the study permitted us to only use baseline measures of emotional distress in relation to patients' risk of mortality.

An important strength of the current study is the relatively long mean follow-up period of 4.9 years. This allowed us to study the long-term effect of partners' emotional distress around implantation on patients' risk of mortality. In addition, the partner sample size was particularly large, facilitating a reliable statistical evaluation. Third, the survival models were both performed with dichotomous and continuous measures of depression and anxiety. Finally, to our knowledge, no other study to date has examined the relationship between partner distress and patient prognosis in cardiovascular patients.

To conclude, the current study among ICD patients found no association between partner emotional distress and patient risk of mortality over a mean follow-up of 6 years. The psychological status of partners turns out to be more likely to affect patients' psychological well-being, instead of patients' physical status. More research on this important topic is warranted and should focus on persistent emotional distress in the partner and the presence of comorbid emotional distress within the dyad. Nevertheless, given that partners of ICD patients play a major role in the adaptation process around and after ICD implantation, partners should be involved in order to facilitate as adequate adaptation to the challenging treatment of the ICD as possible.

REFERENCES

1. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352(3):225-237.
2. The Antiarrhythmic sversus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337(22):1576-1584.
3. Epstein AE, DiMarco JP, Ellenbogen KA, Estes Iii NAM, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;51(21):e1-e62.
4. Sears SF, Conti JB. Quality of life and psychological functioning of ICD patients. Heart 2002;87(5):488-493.
5. Matchett M, Sears SF, Hazelton G, Kirian K, Wilson E, Nekkanti R. The implantable cardioverter defibrillator: Its history, current psychological impact and future. Expert Rev Med Devices 2009;6(1):43-50.
6. Pedersen SS, Theuns DAMJ, Jordaens L, Kupper N. Course of anxiety and device-related concerns in implantable cardioverter defibrillator patients the first year post implantation. Europace 2010;12(8):1119-1126.
7. Von Känel R, Baumert J, Kolb C, Cho E-YN, Ladwig K-H. Chronic posttraumatic stress and its predictors in patients living with an implantable cardioverter defibrillator. J Affect Disord 2011;131(1-3):344-352.
8. Ladwig K-H, Baumert J, Marten-Mittag B, Kolb C, Zrenner B, Schmitt C. Posttraumatic stress symptoms and predicted mortality in patients with implantable cardioverter-defibrillators: Results from the prospective living with an implanted cardioverter-defibrillator study. Arch Gen Psychiatry 2008;65(11):1324-1330.
9. Pedersen SS, Brouwers C, Versteeg H. Psychological vulnerability, ventricular tachyarrhythmias and mortality in implantable cardioverter defibrillator patients: Is there a link? Expert Rev Med Devices 2012;9(4):377-388.
10. Moser DK, Dracup K. Role of spousal anxiety and depression in patients' psychosocial recovery after a cardiac event. Psychosom Med 2004;66(4):527-532.
11. Van den Broek KC, Heijmans N, Van Assen MA. Anxiety and depression in patients with an implantable cardioverter defibrillator and their partners: A longitudinal study. Pacing Clin Electrophysiol 2013;36(3):362-371.
12. Van den Broek KC, Habibović M, Pedersen SS. Emotional distress in partners of patients with an implantable cardioverter defibrillator: A systematic review and recommendations for future research. Pacing Clin Electrophysiol 2010;33(12):1442-1450.
13. Rohrbaugh MJ, Shoham V, Coyne JC. Effect of marital quality on eight-year survival of patients with heart failure. Am J Cardiol 2006;98(8):1069-1072.
14. Coyne JC, Rohrbaugh MJ, Shoham V, Sonnega JS, Nicklas JM, Cranford JA. Prognostic importance of marital quality for survival of congestive heart failure. Am J Cardiol 2001;88(5):526-529.
15. Mastenbroek MH, Versteeg H, Jordaens L, Theuns DAMJ, Pedersen SS. Ventricular tachyarrhythmias and mortality in implantable cardioverter defibrillator (ICD) patients: Impact of depression in the MIDAS cohort. Psychosom Med 2014;76(1):58-65.
16. Habibović M, Pedersen SS, van den Broek KC, Theuns DAMJ, Jordaens L, Van der Voort PH, Alings M, Denollet J. Anxiety and risk of ventricular arrhythmias or mortality in patients with an implantable cardioverter defibrillator. Psychosom Med 2013;75(1):36-41.
17. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67(6):361-370.
18. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: An updated literature review. J Psychosom Res 2002;52(2):69-77.
19. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997;27(2):363-370.
20. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: A meta-analytic review. PLoS Med 2010;7(7):e1000316.

21. Jaffe DH, Manor O, Eisenbach Z, Neumark YD. The protective effect of marriage on mortality in a dynamic society. Ann Epidemiol 2007;17(7):540-547.
22. King KB, Reis HT. Marriage and long-term survival after coronary artery bypass grafting. Health Psychol 2012;31(1):55-62.
23. Barbash IM, Gaglia MAJ, Torguson R, Minha S, Satler LF, Pichard AD, Waksman R. Effect of marital status on the outcome of patients undergoing elective or urgent coronary revascularization. Am Heart J 2013;166(4):729-736.
24. Barth J, Schneider S, von Känel R. Lack of social support in the etiology and the prognosis of coronary heart disease: A systematic review and meta-analysis. Psychosom Med 2010;72(3):229-238.
25. Wu JR, Frazier SK, Rayens MK, Lennie TA, Chung ML, Moser DK. Medication adherence, social support, and event-free survival in patients with heart failure. Health Psychol 2013;32(6):637-646.
26. Brummett BH, Mark DB, Siegler IC, Williams RB, Babyak MA, Clapp-Channing NE, Barefoot JC. Perceived social support as a predictor of mortality in coronary patients: Effects of smoking, sedentary behavior, and depressive symptoms. Psychosom Med 2005;67(1):40-45.
27. O'Farrell P, Murray J, Hotz SB. Psychologic distress among spouses of patients undergoing cardiac rehabilitation. Heart Lung 2000;29(2):97-104.
28. Son H, Thomas SA, Friedmann E. The association between psychological distress and coping patterns in post-MI patients and their partners. J Clin Nurs 2012;21(15-16):2392-2394.
29. Knoops KB, de Groot LM, Kromhout D, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: The HALE project. JAMA 2004;292(12):1433-1439.
30. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med 2000;343(1):16-22.

PART FOUR

Inside the consulting room – helping the patient to get back on track

Information provision, satisfaction and emotional distress in patients with an implantable cardioverter-defibrillator

10

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Submitted

ABSTRACT

Background: Understanding the reasons for implantation with an implantable cardioverter-defibrillator (ICD) and possible implications for daily life is crucial for patients' adaptation. Few studies have examined the information ICD patients receive, their satisfaction, potential gaps in information provision, and patients' needs and preferences. We examined (1) the information provided around ICD implantation; (2) patients' satisfaction with the information; and (3) the association between information provision and satisfaction and emotional distress.

Methods: Patients (N=188) implanted with an ICD at two centers in the Netherlands completed a survey that included a purpose-designed vignette tapping into information provision and patient satisfaction, and standardized questionnaires on symptoms of depression and anxiety. The data were analyzed using descriptive statistics and linear regression analyses.

Results: The extent of adequate information provision differed per topic, with information on technical aspects of the ICD and patients' underlying heart disease being communicated to 85-99% of patients. Information about potential ICD-related psychological, social and sexual consequences was provided to ±60% of patients. Approximately 33% of patients expressed a wish for more information. Importantly, lower satisfaction with information on psychological consequences (β=-0.31, p=.001), physical limitations (β=-0.25, p=.005) and driving limitations (β=-0.22, p=.012) was associated with increased levels of anxiety.

Conclusions: Health-care professionals may omit discussing certain topics when informing patients around the time of implantation, which may influence not only patient satisfaction but also their emotional well-being. Training of staff responsible for information provision could be one step towards improving information provision to patients around the time of ICD implantation.

INTRODUCTION

The implantable cardioverter-defibrillator (ICD) is the best available treatment option for patients at risk of sudden cardiac death due to ventricular arrhythmias, both as primary and secondary prevention.[1-3] The majority of ICD patients adapt well to living with an ICD, while about 1 in 4 patients report significant levels of symptoms of anxiety and depression post implantation.[4-6] This may not necessarily be attributable to the device itself, but also to the underlying heart disease,[7] symptomatic heart failure,[8,9] and the patient's pre implantation psychological profile.[6,10]

Sufficient understanding of the reasons for ICD implantation, benefits and side effects of the ICD and its physical, mental and social implications for daily life play a major role in patients' adaptation post implantation. Previous research has shown that adequate information provision and psycho-education can help patients to adapt to life with an ICD and reduce emotional distress.[11-14] As such, health-care professionals play a key role in discussing the issues surrounding ICD implantation with patients and their families in order to facilitate optimal understanding and adaptation. Paradoxically, recent surveys among ICD patients have indicated that many patients have insufficient knowledge of why they were implanted with an ICD, its possible side effects and benefits.[15,16] In addition, involving the patient in the informed decision-making process around ICD implantation has shown to be a considerable challenge in clinical practice.[17]

Despite the importance of adequate patient education around ICD implantation, a paucity of studies have examined the actual amount of information patients receive, patients' needs and preferences, and patients' satisfaction with this information. In order to optimize the care and management patients with an ICD and their satisfaction with treatment, it is important to increase our knowledge of the information provision process in clinical practice. Therefore, the aims of the current study were to (1) map out the process of information provision around ICD implantation; (2) evaluate patients' satisfaction with the information provided in terms of amount, content, timing, and understanding of the information; and (3) examine whether level of information provision and patient satisfaction with this information are associated with symptoms of depression and anxiety.

METHODS

Patients and study design

All patients implanted with an ICD or ICD with cardiac resynchronization therapy (CRT-D) based on the current guidelines between May 2012 and October 2013 in the Erasmus Medical Center, Rotterdam, and the TweeSteden Hospital, Tilburg, the Netherlands, aged ≥18 years, and sufficiently proficient in the Dutch language to complete the questionnaire, were approached for participation in the current study. Exclusion criteria included insufficient knowledge of the Dutch language and being unable or unwilling to provide written informed consent. In addition, patients already participating in a clinical trial with patient-reported outcomes (e.g. quality of life, anxiety or depression) as endpoints were ineligible for study participation.

Patients were identified via the institutional databases of the Erasmus Medical Center and the TweeSteden Hospital and approached via a letter sent to their home address. The letter included written information about the study, a written informed consent form, a questionnaire package comprised of a vignette, a set of standardized and validated questionnaires together with a self-addressed, stamped envelope. If the questionnaire package was not returned within three weeks to the principal investigators at Tilburg University, a reminder letter and a new questionnaire package with a self-addressed, stamped envelope was sent.

The study protocol was approved by the Medical Ethics Committee of the Erasmus Medical Center, and the study was conducted according to the Helsinki Declaration. Written informed consent was obtained from all participating patients.

Measures

Demographic and clinical variables

Information on demographic characteristics (i.e. age, gender, marital status and educational level) was obtained via purpose-designed questions in the questionnaire. Information on clinical characteristics and patient's medical history was captured from their medical records, including indication for ICD therapy (primary versus secondary prevention), type of ICD (i.e. single chamber, dual chamber, CRT-D or subcutaneous ICD), left ventricular ejection fraction (LVEF) ≤35%, QRS duration, the presence of CAD, symptomatic heart failure (defined as New York Heart Association (NYHA) functional class III+IV), atrial fibrillation, prior percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), and use of cardiac medication (i.e. beta-blockers, statins, amiodarone, diuretics, ACE-inhibitors, and digoxin). Information on the occurrence of appropriate and inappropriate shocks was obtained via device interrogation during follow-up. Furthermore, information to construct the Charlson Comorbidity Index (CCI)[18] was gathered, including the presence of renal failure, previous myocardial infarction (MI), chronic heart failure, diabetes mellitus, peripheral arterial disease, cerebrovascular disease, chronic obstructive pulmonary disease and cancer. The sum score of this index was subsequently adjusted for age, with the addition of 1 extra point for each decade >50 years of age.[19]

Information provision and patient satisfaction

For the purpose of the current study, a vignette was designed, asking patients to recall the time around ICD implantation with respect to information received on specific topics (i.e. the patient's underlying heart disease, how the ICD works, which therapies the ICD can provide, what to do in case of a shock, psychological, social and sexual consequences of having an ICD, physical limitations due to the ICD and driving limitations) and how satisfied they were with the information in terms of quantity, content, timing and their understanding of the information. The vignette is displayed in Figure 1.

In order to collect additional data on information provision, we adapted the EORTC-INFO-25 questionnaire to ICD patients. The EORTC-INFO-25 was originally developed to measure information disclosure to cancer patients and has shown to be a reliable and valid self-report instrument.[20]

Figure 1. Vignette information provision and patient satisfaction [a]

Subject	Did you receive information about this topic?	Satisfaction with…			
		Amount of information	Content of the information	Timing of information provision	Understanding of the information
Underlying heart disease	YES / NO	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
How the ICD works	YES / NO	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
Which therapies the ICD can provide in case of an arrhythmia	YES / NO	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
What to do in case of an ICD shock	YES / NO	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
Psychological consequences of having an ICD (e.g. feelings of anxiety, depression)	YES / NO	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
Social consequences of having an ICD (e.g. incomprehension of friends/family)	YES / NO	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
Sexual consequences of having an ICD (e.g. anxiety regarding sexual intercourse)	YES / NO	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
Physical limitations as a result of the ICD (e.g. exercise, work)	YES / NO	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
Driving limitations	YES / NO	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5

[a] Please indicate (1) whether you received information about the topics shown on the left; and (2) how satisfied you were with the amount, content, timing and understanding of the information on a 1 to 5 scale. A score of 1 reflects no satisfaction, a score of 5 reflects full satisfaction.

Patients were asked to rate items on a 4-point Likert scale, with scores being linearly transformed via an algorhitm to a 0-100 scale. Four subscales can be derived from the EORTC-QLQ-INFO-25, including information about the *disease* (4 items), information about *medical tests* (3 items), information about *treatment* (6 items), and information about *other services* (i.e. out-of-hospital help, rehabilitation, dealing with the disease at home, psychological help, 4 items), as well as 8 single items which were not used in the current study.

Emotional distress: symptoms of depression and anxiety

The Patient Health Questionnaire (PHQ-9) was used to assess symptoms of depression. Based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria of depression, this questionnaire consists of 9 items rated on a Likert scale from 0 to 3 (score range 0 to 27). The PHQ-9 has shown to be a reliable and valid measure of depressive symptomatology, with a sensitivity and specificity of 88%.[21]

Anxiety symptoms were assessed with the Generalized Anxiety Disorder (GAD-7) scale, a 7-item questionnaire measuring generalized anxiety with items being scored on a 4-point Likert scale from 0 to 3 (score range 0 to 21).[22] The psychometric properties of the GAD-7 are adequate.[23]

Statistical analyses

Baseline demographic and clinical variables for responders versus non-responders and for patients from the Erasmus Medical Center versus the TweeSteden Hospital were compared with the Chi-square test (Fisher's Exact test when appropriate) for nominal variables, and Student's t-test for continuous variables. Frequency distributions and mean scores were computed in order to quantify self-reported information provision and patient satisfaction with information provision as collected with the vignette. The relationship between information provision and emotional distress was examined with unadjusted and adjusted linear regression analysis. Covariates were selected a priori based on the literature, with gender, the age-adjusted version of the CCI, center of implantation, and time since implantation being included as covariates in adjusted analyses using the Enter method. A p-value of <.05 (two-sided) was used to indicate statistical significance. PASW Statistics 20 statistical software was used to analyze the data (PASW IBM Corp., Armonk, NY, USA).

RESULTS

Patient baseline characteristics

A questionnaire package was sent to 324 patients, of which 227 patients were implanted in the Erasmus Medical Center and 97 patients in the TweeSteden Hospital. Of these, 5 patients (1.5%; N=2 from the Erasmus Medical Center and N=3 from TweeSteden Hospital) had moved and their new home address was unknown, and 3 patients (0.9%; N=2 from the Erasmus Medical Center and N=1 from TweeSteden Hospital) refused to participate. Furthermore, 128 patients (39.5%) neither responded to the initial questionnaire nor to the reminder, resulting in a response rate of 58.0%. Patients who were not included in the analyses due to refusal, loss to follow-up or non-response

(N=136) were compared with patients who were included (N=188) on demographic and clinical characteristics. No systematic differences between the two groups were found (all p>.05).

Table 1 provides an overview of the baseline demographic and clinical characteristics of the total sample, stratified by implanting center. The mean age of patients was 61±13 years, and 127 (68%) of the patients were male. A few systematic differences were found in demographic and clinical patient characteristics between the two hospitals. Patients from the Erasmus Medical Center were more likely to be younger (p<.001), to be male (p=.009) and to have undergone a previous PCI (p=.028), but less likely to suffer from symptomatic heart failure (p=.029) and to be prescribed diuretics (p=.002). No other systematic differences between patients from the two hospitals were found on baseline characteristics.

Table 1. Baseline characteristics for the total study sample and stratified by site*

	Total (N=188)	**Erasmus MC (N=126)**	**Twee-Steden (N=62)**	**p**
Demographics				
Mean age (±SD)	61.6 (13.3)	59.3 (14.6)	66.3 (8.6)	**<.001**
Men	127 (67.6)	93 (73.8)	34 (54.8)	**.009**
Clinical factors				
Primary prevention indication	143 (76.1)	94 (74.6)	49 (79.0)	.50
LVEF ≤35% †	108 (68.8)	65 (67.0)	43 (71.7)	.54
Mean QRS (ms ±SD) ‡	127.9 (31.2)	126.1 (30.9)	133.6 (31.7)	.19
CAD	99 (52.7)	65 (51.6)	34 (54.8)	.68
Previous PCI	56 (29.8)	44 (34.9)	12 (19.4)	**.028**
Previous CABG	27 (14.4)	17 (13.5)	10 (16.1)	.63
Symptomatic heart failure §	30 (16.7)	16 (12.7)	14 (25.9)	**.029**
Atrial fibrillation	45 (23.9)	33 (26.2)	12 (19.4)	.30
Diabetes	41 (21.8)	24 (19.0)	17 (27.4)	.19
Medication				
Amiodarone	22 (11.7)	14 (11.1)	8 (12.9)	.72
Beta-blockers	147 (78.2)	95 (75.4)	52 (83.9)	.19
Diuretics	100 (53.2)	57 (45.2)	43 (69.4)	**.002**
ACE-inhibitors	106 (56.4)	73 (57.9)	33 (53.2)	.54
Statins	106 (56.4)	66 (52.4)	40 (64.5)	.12
Digoxin	17 (9.0)	11 (8.7)	6 (9.7)	.83

* Data are presented as N (%), unless otherwise indicated. † N=31 (16.5%) missing; ‡ N=22 (11.7%) missing; § N=8 (4.3%) missing. Abbreviations: *ACE*, angiotensin-converting enzyme; *CABG*, coronary artery bypass grafting; *CAD*, coronary artery disease; *EMC,* Erasmus Medical Center; *LVEF*, left ventricular ejection fraction; *N*, number; *PCI*, percutaneous coronary intervention; *QRS*, QRS duration; *SD*, standard deviation; *site 1*, Erasmus Medical Center; *site 2*, TweeSteden Hospital

Of all patients who completed the questionnaire package, 17-18% did not complete the vignette but did complete the other questionnaires. These patients were not included in the prevalence of information provision and mean satisfaction scores as shown in Table 2. This subset of patients was also excluded from the unadjusted and adjusted linear regression analyses as shown in Table 3.

Information provision and patient satisfaction around implantation

When comparing information provision and patient satisfaction with information provision between the Erasmus Medical Center and the TweeSteden Hospital, patients from the TweeSteden Hospital received less information about which therapies the ICD can provide in case of an arrhythmia (p=.009) and about driving limitations (p=.024) as compared to patients from the Erasmus Medical Center. However, no differences were found with respect to patient satisfaction with the information provided by the two hospitals.

The results of the frequency of information provision and patient satisfaction with the provided information are shown in Table 2. Generally, information on more technical aspects related to the ICD and patients' underlying heart disease was provided, with 85-99% of patients reporting to be informed about these topics. The majority of patients also reported that they were notified of what to do in case of an ICD shock. Interestingly, patients reported that information on psychological, social and sexual aspects of being implanted with an ICD was less frequently provided. Approximately 60% of patients reported having received information on these topics. By contrast, information on physical limitations (81%) and driving limitations (88%) was more frequently provided. Not surprisingly, patient satisfaction with information provision was related to whether this information was provided. The highest satisfaction with amount, content, timing and understanding of information was found for information provision regarding the more technical aspects of the ICD and their underlying heart disease, whereas the lowest satisfaction was reported for information provision about psychological, social and sexual consequences of having an ICD. However, overall patient satisfaction on information provision was high as indicated by a mean satisfaction score of 3.9 on a scale from 1 to 5.

In an open-ended question, patients were also asked to list which topics they would have liked to receive more information about around the time of implantation. The topics most frequently mentioned were information about the ICD itself (N=24, i.e. placement, risks, underlying heart disease, life span of the ICD and what to do after having received a shock), physical limitations as a result of the implantation (N=18; i.e. healing process, physical rehabilitation, exercise, driving limitations and weight of the subcutaneous ICD), psychological consequences (N=13; i.e. how to deal with feelings of anxiety, how to receive psychological treatment, psychological consequences for the family), social consequences (N=8; i.e. return to work, traveling, care at home) and the wish for more information in general (N=5).

Association between information provision, satisfaction, and emotional distress

In order to examine the relationship between information provision and emotional distress, patients' answers on the yes/no question *'did you receive information on the following topics?'* were used for the topics psychological consequences, social consequences and sexual consequences of having an ICD, since these were the topics most likely not to have been addressed around the time of implantation. These results are presented in Table 3. No significant associations were found between information provision and emotional distress (i.e. depression and anxiety), neither in unadjusted analyses nor in adjusted analyses.

Table 2. Information provision and satisfaction with information provision *

Topic	Received information about this topic †		Satisfaction with… ‡				
	Yes (%)	No (%)	Amount of information	Content of information	Timing of information	Understanding of information	Mean satisfaction
Underlying heart disease	98.7	1.3	4.0 ± 0.9	4.0 ± 0.8	3.9 ± 0.9	4.2 ± 0.9	4.0 ± 0.9
How the ICD works	97.4	2.6	4.2 ± 0.8	4.0 ± 0.9	4.1 ± 0.9	4.2 ± 0.9	4.1 ± 0.9
Which therapies the ICD can provide in case of arrhythmia	85.1	14.9	3.9 ±1.0	3.8 ± 1.0	3.9 ± 0.9	4.0 ± 1.0	3.9 ± 1.0
What to do in case of an ICD shock	91.0	9.0	4.0 ± 1.0	4.0 ± 1.0	4.0 ± 1.0	4.1 ± 1.0	3.9 ± 1.0
Psychological consequences of having an ICD	63.9	36.1	3.5 ± 1.1	3.5 ± 1.1	3.6 ± 1.0	3.7 ± 1.2	3.6 ± 1.1
Social consequences of having an ICD	57.4	42.6	3.6 ± 1.1	3.6 ± 1.1	3.7 ± 1.0	3.8 ± 1.1	3.7 ± 1.1
Sexual consequences of having an ICD	60.6	39.4	3.6 ± 1.1	3.6 ± 1.1	3.7 ± 1.0	3.9 ± 1.1	3.7 ± 1.1
Physical limitations due to the ICD	80.6	19.4	3.9 ± 1.0	3.8 ± 1.0	3.9 ± 1.0	4.0 ± 1.1	3.9 ± 1.0
Driving limitations	87.7	12.3	4.2 ± 0.9	4.1 ± 1.0	4.1 ± 0.9	4.3 ± 0.9	4.2 ± 0.9

* Between 17.1-18.1% missing, data are presented with missings excluded. † Data are presented as N(%). ‡ Data are presented as mean score ± SD (score range 1-5)

In addition, for each topic, the mean satisfaction score from Table 2 was related to emotional distress. No significant associations between patient satisfaction and depression were found (all p>.05). However, lower patient satisfaction with the information provided about psychological consequences (β=-0.31, t=-3.37, p=.001), physical limitations (β=-0.25, t=-2.88, p=.005) and driving limitations (β=-0.22, t=-2.53, p=.012) was related to higher levels of anxiety. These relationships remained significant after adjusting for time since implantation, gender, the age-adjusted CCI and center of implantation.

Table 3. Association between information provision and symptoms of depression and anxiety (unadjusted and adjusted analyses)

Topic	β	t	p
Unadjusted - depression			
Psychological consequences of having an ICD	0.11	1.31	.19
Social consequences of having an ICD	0.12	1.50	.14
Sexual consequences of having an ICD	0.02	0.21	.83
Unadjusted - anxiety			
Psychological consequences of having an ICD	-0.09	-1.13	.26
Social consequences of having an ICD	-0.13	-.156	.12
Sexual consequences of having an ICD	-0.01	-0.09	.93
Adjusted - depression			
Psychological consequences of having an ICD	0.12	1.47	.14
Social consequences of having an ICD	0.12	1.48	.14
Sexual consequences of having an ICD	0.02	0.27	.79
Adjusted - anxiety			
Psychological consequences of having an ICD	-0.11	-1.36	.18
Social consequences of having an ICD	-0.15	-1.82	.07
Sexual consequences of having an ICD	0.002	0.02	.98

DISCUSSION

Given that adequate information provision around the time of ICD implantation can help patients to adjust to life with an ICD and reduce emotional distress,[11-14] it is paradoxical that information provision and patient satisfaction with this information remains understudied.[24-28] Available studies have used either a qualitative study design, examined a small sample of patients, or studied other cardiovascular populations than ICD patients.[24-26] Hence, our knowledge of information provision and patient satisfaction with this information is limited in the general cardiac population, and is lacking in ICD patients with a need to identify gaps in patients' potential needs and preferences.

To our knowledge, our study is one of the first in ICD patients to examine the process of information provision around the time of ICD implantation, patients' satisfaction with this information, and to relate these aspects to emotional distress. Generally, information on a wide range of topics was well covered, with particularly information on technical aspects of the ICD and patients' underlying heart

disease being conveyed to patients. Nevertheless, approximately 40% of the patients reported not having received information on potential psychological, social and sexual consequences of living with an ICD. Lower patient satisfaction with the information provided about these specific topics was related to higher levels of anxiety, also when adjusting for time since implantation, gender, the age-adjusted CCI and center of implantation.

The results of our study from the patients' perspective seem to largely correspond to health-care professionals' attitudes towards ICD therapy and issues that they discuss with patients.[29] In a recent survey, physicians reported that they are more inclined to discuss clinical issues, such as device- and shock-related matters, and less frequently broach psychosocial issues, including the impact of the device on quality of life, sexual functioning and the family. This survey also revealed that health-care staff, such as nurses, was more likely to discuss psychosocial issues.[29] It is possible that most physicians feel ill equipped to discuss these issues with patients, either due to time constraints, feelings of insecurity or other reasons. However, given that health-care staff other than physicians also do not always seem to cover the full range of topics that patients deem important, it is important to consider how this may be improved. One way would be to compile a checklist of topics that the physician or ICD nurse need to discuss with patients prior to implantation. Another way might be to add a psychologist to the multi-disciplinary team to support other health-care professionals, who may play an important role in training hospital staff how to communicate with patients and may be consulted for the diagnosis and treatment of psychological problems. Knowing that there is a mental health professional to refer to might alleviate the fears of some health care professionals of broaching particular topics.

On the whole, patient satisfaction was high, with slightly lower satisfaction scores on the topics that were less frequently provided. Importantly, this indicates that patient education around the time of implantation is generally well taken care of in these two hospitals in the Netherlands, with few differences found between the centers. There is room for improvement though, with about one third of patients still reporting that they wish to receive more information about the ICD itself, physical limitations, and psychological and social consequences. The finding that lower patient satisfaction with information provision about potential psychological consequences, physical limitations and driving limitations was associated with increased levels of anxiety highlights not only the importance of information provision itself, but also that patients' satisfaction with information provision may influence their emotional well-being.

The limitations of this study should be acknowledged. First, the response rate was somewhat low in comparison to other surveys.[27,30] Second, as the number of missing answers to the vignette was relatively high, this suggests that the lay-out chosen for the vignette might have been too complicated for several patients. In addition, the study design was retrospective, which may have biased the results. However, time since implantation was included as a covariate in the analyses but had no influence.

This study also has several strengths. Patients were included from two centers (one a university medical center and the other a peripheral teaching hospital), and few differences emerged between the centers. In addition, this is the first study with such a large sample size that has examined several

aspects of information provision and patients' satisfaction, while also providing detailed information on ICD patients' demographic and clinical profile.

In conclusion, we found that overall patients were well informed about a wide range of topics related to what to expect post ICD implantation. Information about technical aspects of the ICD and patients' underlying heart disease was particularly well covered. However, information about potential psychological, social and sexual consequences of having an ICD was less frequently discussed, with approximately one third of patients expressing a wish for more information. Less information provision about these topics was reflected in lower patient satisfaction scores, and importantly, lower satisfaction scores were associated with increased levels of anxiety. The current study thus highlights the importance of not only information provision itself, but also patients' satisfaction with the information provision process. Cardiologists, but also nurses and ICD technicians, have indicated that they might find it difficult to broach psychological, social and family matters with ICD patients,[29] while patients in the current study indicated that these are just the issues they are the least satisfied with in terms of the extent of information provided. Accordingly, training of the staff responsible for information provision by for example a psychologist could be one step forward towards further improving the information provision process around the time of ICD implantation, patient satisfaction and patient well-being.

REFERENCES

1. Moss A, Hall W, Cannom D, Daubert J, Higgins S, Klein H, Levine J, Saksena S, Waldo A, Wilber D. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med 1996;335(26):1933-1940.
2. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352(3):225-237.
3. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337(22):1576-1584.
4. Sears SF, Conti JB. Quality of life and psychological functioning of ICD patients. Heart 2002;87(5):488-493.
5. Ladwig K-H, Baumert J, Marten-Mittag B, Kolb C, Zrenner B, Schmitt C. Posttraumatic stress symptoms and predicted mortality in patients with implantable cardioverter-defibrillators: Results from the prospective living with an implanted cardioverter-defibrillator study. Arch Gen Psychiatry 2008;65(11):1324-1330.
6. Pedersen SS, Hoogwegt MT, Jordaens L, Theuns DAMJ. Pre implantation psychological functioning preserved in majority of implantable cardioverter-defibrillator patients. Int J Cardiol 2011;166(1):215-220.
7. Habibović M, Versteeg H, Pelle AJM, Theuns DAMJ, Jordaens L, Pedersen SS. Poor health status and distress in cardiac patients: The role of device therapy vs. underlying heart disease. Europace 2013;15(3):355-361.
8. Pedersen SS, Hoogwegt MT, Jordaens L, Theuns DAMJ. Relation of symptomatic heart failure and psychological status to persistent depression in patients with implantable cardioverter-defibrillator. Am J Cardiol 2011;108(1):69-74.
9. Suzuki T, Shiga T, Kuwahara K, Kobayashi S, Suzuki S, Nishimura K, Suzuki A, Ejima K, Manaka T, Shoda M, Ishigooka JUN, Kasanuki H, Hagiwara N. Prevalence and persistence of depression in patients with implantable cardioverter defibrillator: A 2-year longitudinal study. Pacing Clin Electrophysiol 2010;33(12):1455-1461.
10. Sears SF, Saia Lewis T, Kuhl EA, Conti JB. Predictors of quality of life in patients with implantable cardioverter defibrillators. Psychosomatics 2005;46(5):451-457.
11. Vazquez LD, Conti JB, Sears SF. Female-specific education, management, and lifestyle enhancement for implantable cardioverter defibrillator patients: The FEMALE-ICD study. Pacing Clin Electrophysiol 2010;33(9):1131-1140.
12. Dunbar SB, Dougherty CM, Sears SF, Carroll DL, Goldstein NE, Mark DB, McDaniel G, Pressler SJ, Schron E, Wang P, Zeigler VL. Educational and psychological interventions to improve outcomes for recipients of implantable cardioverter defibrillators and their families: A scientific statement from the American Heart Association. Circulation 2012;126(17):2146-2172.
13. Dunbar SB, Langberg JJ, Reilly CM, Viswanathan B, McCarty F, Culler SD, O'Brien MC, Weintraub WS. Effect of a psychoeducational intervention on depression, anxiety, and health resource use in implantable cardioverter defibrillator patients. Pacing Clin Electrophysiol 2009;32(10):1259-1271.
14. Eads AS, Sears SFJ, Sotile WM, Conti JB. Supportive communication with implantable cardioverter defibrillator patients: Seven principles to facilitate psychosocial adjustment. J Cardiopulm Rehabil 2000;20(2):109-114.
15. Cinar FI, Tosun N, Kose S. Evaluation of an education and follow-up programme for implantable cardioverter defibrillator-implanted patients. J Clin Nurs 2013;22(17-18):2474-2486.
16. Groarke J, Beirne A, Buckley UNA, O'Dwyer E, Sugrue D, Keelan TED, O'Neill J, Galvin JOE, Mahon N. Deficiencies in patients' comprehension of implantable cardioverter defibrillator therapy. Pacing Clin Electrophysiol 2012;35(9):1097-1102.
17. Joyce KE, Lord S, Matlock DD, McComb JM, Thomson R. Incorporating the patient perspective: A critical review of clinical practice guidelines for implantable cardioverter defibrillator therapy. J Interv Card Electrophysiol 2013;36(2):185-197.
18. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47(11):1245-1251.
19. Theuns DAMJ, Schaer BA, Soliman OII, Altmann D, Sticherling C, Geleijnse ML, Osswald S, Jordaens L. The prognosis of implantable defibrillator patients treated with cardiac resynchronization therapy: Comorbidity burden as predictor of mortality. Europace 2011;13(1):62-69.
20. Arraras JI, Greimel E, Sezer O, Chie W-C, Bergenmar M, Costantini A, Young T, Vlasic KK, Velikova G. An international validation study of the EORTC QLQ-INFO25 questionnaire: An instrument to assess the information given to cancer patients. Eur J Cancer 2010;46(15):2726-2738.

21. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606-613.
22. Spitzer RL, Kroenke K, Williams JW, Löwe B. A brief measure for assessing generalized anxiety disorder: The GAD-7. Arch Intern Med 2006;166(10):1092-1097.
23. Kroenke K, Spitzer RL, Williams JBW, Monahan PO, Löwe B. Anxiety disorders in primary care: Prevalence, impairment, comorbidity, and detection. Ann Intern Med 2007;146(5):317-325.
24. Van Driel AG, De Hosson MJJ, Gamel C. Sexuality of patients with chronic heart failure and their spouses and the need for information regarding sexuality. Eur J Cardiovasc Nurs 2014;13(3):227-234.
25. Pier C, Shandley KA, Fisher JL, Burstein F, Nelson MR, Piterman L. Identifying the health and mental health information needs of people with coronary heart disease, with and without depression. Med J Aust 2008;188(12 Suppl):S142-S144.
26. Harding R, Selman L, Beynon T, Hodson F, Coady E, Read C, Walton M, Gibbs L, Higginson IJ. Meeting the communication and information needs of chronic heart failure patients. J Pain Symptom Manage 2008;36(2):149-156.
27. Sarkar U, Schillinger D, Bibbins-Domingo K, Nápoles A, Karliner L, Pérez-Stable EJ. Patient–physicians' information exchange in outpatient cardiac care: Time for a heart to heart? Patient Educ Couns 2011;85(2):173-179.
28. Lesch W, Specht K, Lux A, Frey M, Utens E, Bauer U. Disease-specific knowledge and information preferences of young patients with congenital heart disease. Cardiol Young 2014;24(2):321-330.
29. Johansen JB, Mortensen PT, Videbæk R, Riahi S, Møller M, Haarbo J, Pedersen SS. Attitudes towards implantable cardioverter-defibrillator therapy: A national survey in Danish health-care professionals. Europace 2011;13(5):663-667.
30. Pedersen SS, Chaitsing R, Szili-Torok T, Jordaens L, Theuns DAMJ. Patients' perspective on deactivation of the implantable cardioverter-defibrillator near the end of life. Am J Cardiol 2013;111(10):1443-1447.

Undertreatment of anxiety and depression in patients with an implantable cardioverter-defibrillator: Impact on health status

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ABSTRACT

Background: Twenty-five to 33% of patients with an implantable cardioverter-defibrillator (ICD) experience anxiety and depression, but it is not known whether their symptoms are adequately treated. We investigated (1) whether patients with clinically relevant symptoms of distress received appropriate treatment, and (2) whether patients not treated for their emotional distress reported poorer health status using a prospective study design.

Methods: A consecutive cohort of 448 first-time patients with an ICD (21% women; mean age, 58±12 years) completed the Hospital Anxiety and Depression Scale (HADS) and the Short Form Health Survey 36 (SF-36). Information on psychological treatment was obtained via purpose-designed questions.

Results: At baseline, 35.5% of patients were emotionally distressed, of which 70.2% received no psychological treatment. At 12 months post-implantation, 24.3% of all patients had clinically significant levels of distress, of which 58.3% received no treatment. Patients experiencing distress but without treatment reported a significantly poorer health status than patients without distress and treatment (all $p<.001$) and compared to patients without emotional distress who did receive treatment (p varying between $p=.027$ and $p<.001$ for 6 subscales). Health status was better on four subscales than for patients with emotional distress and treatment (p varying between $p=.034$ and $p<.001$).

Conclusions: There was a serious gap between the need for psychological treatment and the actual delivery of treatment, with consequences to patients' health status. Detection and adequate treatment of distress in ICD patients remains an important target in this patient group in order to safeguard health status post-implantation.

INTRODUCTION

The implantable cardioverter-defibrillator (ICD) is the therapy of first choice for patients at risk for life-threatening ventricular arrhythmias, with mortality reductions up to 23% in both primary and secondary prophylaxis patients.[1-5] Although the majority of patients with an ICD reach acceptable levels of psychosocial functioning after ICD implantation,[4,6] a subgroup of 25-33% reports significant levels of anxiety, depression and posttraumatic stress.[7-11] In 50% of these patients, anxiety and depression remain at a clinically high level during the first year post implantation.[8,9] Distress in patients with an ICD not only influences daily functioning but has also been associated with an increased risk of ventricular arrhythmias[12,13] and mortality.[7,14]

The prevalence of emotional distress has been studied frequently over the last decade with distress receiving increasingly more attention in clinical cardiology practice,[15,16] although it is far from optimal.[16] However, identification of anxiety or depression does not automatically result in appropriate treatment, with a gap in the delivery of adequate care for patients with anxiety and depression. In epidemiological studies among the general population, with one-year prevalence rates of 8-17% and 5-11% for anxiety and mood disorders, respectively,[17,18] prescription patterns reveal that two-thirds of patients do not receive pharmacological treatment for their mental disorder.[17-19] An even smaller number of patients is treated by a mental health professional.[17,18] In post myocardial infarction (MI) patients, increases in the prescription of antidepressants have been reported, but these were attributed to a general trend of increased prescription rates rather than raised attention to the mental health of patients.[15] In patients with an ICD, a recent study found a considerable mismatch between patients with clinically significant levels of depression and pharmacological treatment, with only one out of 33 patients depressed at baseline and/or at 2 years post implantation receiving antidepressant therapy.[20]

To our knowledge, a paucity of studies in patients with an ICD have examined the level of emotional distress and whether patients with clinically significant levels receive adequate treatment. Furthermore, it remains unclear if distress left untreated leads to impaired health status, with health status being an independent predictor of morbidity and mortality in patients with an ICD.[21,22] Therefore, we examined (1) whether patients with clinically relevant symptoms of anxiety and depression received appropriate treatment (i.e. either psychotropic medication or treatment by a psychologist) and (2) whether patients not treated for their emotional distress report poorer health status.

METHODS

Patients and study design

The study cohort consisted of consecutive patients (N=448) who were implanted with a first-time ICD between August 2003 and February 2010 in the Erasmus Medical Center, Rotterdam, the Netherlands, and who were enrolled in the prospective Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter Defibrillator: A prospective Study (MIDAS). Exclusion criteria were a life-expectancy <1 year, being on the waiting list for heart transplantation,

history of psychiatric illness other than affective/anxiety disorders, or insufficient command of the Dutch language. Prior to ICD implantation, patients were approached by an ICD nurse, who provided written and oral information on the study, and asked patients to complete a set of standardized and validated questionnaires. Assessment took place at baseline (i.e. one day prior to implantation), and at 3, 6 and 12 months post implantation. The study protocol was approved by the Medical Ethics Committee of the Erasmus Medical Center, and the study was conducted according to the Helsinki Declaration. All patients provided written informed consent.

Measures

Demographic and clinical variables

All demographic and clinical variables were collected at baseline and were obtained from patients' medical records or from purpose-designed questions in the questionnaires. Information on demographic variables included age, gender, marital status and educational level. Information on clinical variables included indication for ICD therapy (primary versus secondary prevention), treatment with cardiac resynchronization therapy (CRT), left ventricular ejection fraction (LVEF) ≤35%, QRS duration, the presence of coronary artery disease (CAD), symptomatic heart failure (defined as New York Heart Association (NYHA) functional class III+IV), atrial fibrillation, diabetes mellitus, prior percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), smoking, and use of cardiac medication (i.e. beta-blockers, amiodarone, diuretics, ACE-inhibitors, statins, and digoxin). The occurrence of ICD therapy for ventricular tachyarrhythmias, both anti tachycardiac pacing episodes and shocks (both appropriate and inappropriate) was prospectively registered in our institutional database.

Anxiety and depression

Symptoms of anxiety and depression were measured at baseline, and at 3, 6 and 12 months follow-up using the Hospital Anxiety and Depression Scale (HADS), a 14-item self-report questionnaire consisting of 7 items measuring symptoms of anxiety (HADS-A) and 7 items measuring symptoms of depression (HADS-D).[23] All items are rated on a 4-point Likert scale, with scores ranging from 0 to 3 (total score range of 0-21); higher scores reflect more symptoms.[23] The psychometric properties of the HADS are good, with mean Cronbach's alphas of 0.83 and 0.82 and a three-week test-retest reliability of 0.89 and 0.86 for the HADS-A and HADS-D subscales, respectively.[24] The HADS is a valid instrument for screening for separate symptoms of anxiety and depression and was originally developed for assessment in non-psychiatric hospital settings.[25] A cut-off score of ≥8 indicates an optimal balance between sensitivity and specificity,[25] which we used in the current study to detect patients with clinically significant levels of anxiety and depression. Because of the high level of comorbidity between anxiety and depression and a large overlap in medication use for these conditions,[17,26] anxiety and depression were combined into one variable reflecting emotional distress, defined as a score of ≥8 on the HADS-A or HADS-D, or both.

Health Status

The Short Form Health Survey 36 (SF-36) was used to assess patients' health status at baseline, and at 3, 6 and 12 months post-implantation.[27] The questionnaire consists of 36 items that contribute to eight subscales: physical functioning (10 items), role limitations - physical (4 items), bodily pain (2 items), social functioning (2 items), mental health (5 items), role limitations - emotional (3 items), vitality (4 items) and general health (5 items). Scores on the individual subscales range from 0 to 100, with higher scores indicating better health status.[28] The SF-36 has adequate scale reliabilities, with Cronbach's alphas ranging from 0.78 to 0.92 in the general population and 0.66 to 0.90 in a group of cancer patients, respectively.[27]

Psychological treatment for emotional distress

Information on the use of psychotropic medication (predominantly anxiolytic and antidepressant medication) and treatment for emotional distress (defined as treatment either by a psychologist or the use of psychotropic medication, or both) was obtained at baseline, and at 3, 6 and 12 months follow-up via purpose-designed questions in the questionnaires. Previous research has shown moderate to high concordance between written self-report measures of medication use and other measures of medication adherence, including plasma drug concentrations.[29]

Statistical analyses

Baseline characteristics were compared with the χ^2 test (Fisher's exact test when appropriate) for nominal variables and one-way analysis of variance (ANOVA) with post hoc Bonferroni correction in case of a significant main effect for continuous variables. In order to compare patients in the different treatment conditions, four groups were defined: (1) no emotional distress and no treatment; (2) no emotional distress and treatment; (3) emotional distress and treatment; and (4) emotional distress and no treatment. The last group was used as reference group when comparing the first three groups on health status during follow-up. Cross-tabulations were performed to obtain information on treatment trends in emotionally distressed versus non distressed patients.

In order to examine whether patients who are not treated for their emotional distress report poorer health status, repeated measures analysis of variance (RM ANOVA) using general linear mixed modelling analysis was performed, using an unstructured covariance structure. This technique is suitable for analysis of repeated measurements, as it reckons with the possibility of correlated data. In addition, in contrast to traditional repeated measures ANOVA, one missing measurement occasion does not automatically lead to exclusion of that patient from analysis, limiting bias and preserving statistical power. First, intraclass correlations (ICCs), a measure of score dependencies within the patients, were computed for each subscale. A priori based on the literature, we decided to adjust for the following covariates: gender, age, educational level, indication for ICD therapy, presence of CAD, symptomatic heart failure, atrial fibrillation, diabetes mellitus, the use of beta-blockers and the occurrence of shocks (combined appropriate and inappropriate) during the 12 month follow-up period. All independent variables except group membership were set as fixed variables. Group membership was considered as time-varying, i.e. allowed to vary over time. The described effects in the results section are the effect of subgroup membership *at any time point* on the level of health

status over time, including all measurement occasions. Analyses were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, Ill, USA). For all tests, a p-value of <.05 was considered statistically significant.

RESULTS

Responders versus non-responders

From the 448 patients enrolled in the MIDAS study, 18 did not complete sufficient items on the HADS and/or the SF-36. In addition, 5 patients had missing data on treatment (either psychotropic or treatment by a psychologist) and were omitted. All remaining 425 patients (response rate 96.0%) provided sufficient data to be included in statistical analyses. Patients who were excluded from analyses were more likely to suffer from atrial fibrillation (p=.018). There were no other systematic differences on demographic and clinical baseline characteristics between study participants and non participants.

Baseline characteristics

Baseline characteristics of the remaining 425 patients are displayed in Table 1. The mean age was 58±12 years and 337 (79.3%) of the patients were male. Overall, 151 patients (35.5%) had clinically significant levels of emotional distress. Divided into the 4 different patient groups, 237 (55.8%) had no emotional distress and were not receiving treatment, 37 (8.7%) had no emotional distress but received treatment, 45 (10.6%) had emotional distress and were treated, and 106 (24.9%) experienced emotional distress but received no treatment. The various emotional distress and treatment groups did not differ significantly from each other on most variables. However, a few baseline differences were found. First, male patients were less likely to report emotional distress and to receive treatment for their distress than female patients. In addition, both distressed and non distressed single patients received more treatment (both p=.03). Patients having a lower educational level reported more emotional distress but did not receive treatment (p=.01). Finally, patients who smoked reported more emotional distress, both when treated and not treated (p=.04).

Course of group membership during follow-up

Because the time-varying nature of the distress and treatment condition, we investigated whether patients stayed in the same group during follow-up. On average, 55% of the patients stayed in the same group between baseline and 12 months follow-up. When the subgroups were examined separately, patients with no distress and no treatment were found to stay in this group during follow-up in 85% of the cases. Patients with no distress who did receive treatment, and patients with distress who did receive treatment, both stayed in the same group in 49% of the cases. Importantly, 39% of the patients in our reference group (distress but no treatment) remained untreated for their distress during the follow-up moments. In case of change, patients without distress and treatment were most likely to switch to the distress and no treatment group. Patients in the remaining 3 groups were all most likely to switch to the no distress and no treatment group.

Table 1. Baseline characteristics for the total study population and stratified by the different distress and treatment conditions *

	Total	No emotional distress & no treatment	No emotional distress & treatment	Emotional distress & treatment	Emotional distress & no treatment	p-value
N	425 (100)	237 (55.8)	37 (8.7)	45 (10.6)	106 (24.9)	
Demographics						
Mean age (±SD)	58.4 (12.1)	59.1 (12.1)	57.9 (11.5)	54.9 (13.5)	58.5 (11.6)	.21
Men	337 (79.3)	193 (81.4)	29 (78.4)	28 (62.2)	87 (82.1)	**.03**
Single/no partner †	27 (6.4)	8 (3.4)	4 (10.8)	6 (13.3)	9 (8.6)	**.03**
Lower education ‡	242 (57.9)	119 (50.6)	22 (61.1)	29 (64.4)	72 (70.6)	**.01**
Clinical risk factors						
Primary prevention Indication	279 (65.6)	155 (65.4)	25 (67.6)	31 (68.9)	68 (64.2)	.94
CRT	120 (28.2)	63 (26.6)	8 (21.6)	10 (22.2)	39 (36.8)	.12
Shocks during follow-up	58 (13.6)	34 (14.3)	5 (13.5)	6 (13.3)	13 (12.3)	.97
LVEF ≤35% §	314 (85.6)	175 (86.2)	28 (87.5)	32 (76.2)	79 (87.8)	.32
Mean QRS (±SD)	130.0 (36.4)	129.1 (33.9)	134.4 (42.1)	123.9 (36.0)	133.4 (39.9)	.41
CAD	246 (57.9)	135 (57.0)	20 (54.1)	27 (60.0)	64 (60.4)	.88
Previous PCI	111 (26.1)	62 (26.2)	7 (18.9)	15 (33.3)	27 (25.5)	.53
Previous CABG	87 (20.5)	50 (21.1)	7 (18.9)	10 (22.2)	20 (18.9)	.95
Symptomatic heart failure ||	135 (31.9)	66 (28.1)	14 (37.8)	18 (40.0)	37 (34.9)	.26
Atrial fibrillation	94 (22.1)	57 (24.1)	6 (16.2)	9 (20.0)	22 (20.8)	.68
Diabetes mellitus ¶	61 (14.4)	35 (14.9)	5 (13.5)	7 (15.6)	14 (13.2)	.97
Smoking #	46 (10.8)	18 (7.6)	3 (8.1)	8 (17.8)	17 (16.2)	**.04**
Medication use						
Amiodarone	78 (18.4)	40 (16.9)	4 (10.8)	7 (15.6)	27 (25.5)	.14
Beta-blockers	340 (80.0)	193 (81.4)	28 (75.7)	36 (80.0)	83 (78.3)	.82
Diuretics	242 (56.9)	131 (55.3)	21 (56.8)	31 (68.9)	59 (55.7)	.40
ACE-inhibitors	304 (71.5)	169 (71.3)	22 (59.5)	36 (80.0)	77 (72.6)	.23
Statins	252 (59.3)	139 (58.6)	22 (59.5)	23 (51.1)	68 (64.2)	.51
Digoxin	64 (15.1)	35 (14.8)	5 (13.5)	6 (13.3)	18 (17.0)	.92
Psychological treatment						
Psychotropic medication	70 (85.4)	-	31 (83.8)	39 (86.7)	-	.71
Treatment by psychologist	22 (26.8)	-	9 (24.3)	13 (28.9)	-	.64

* Data are presented as N (%), unless otherwise indicated. † 3/425 (0/7%) missing; ‡ education less than or equal to 13 years, 7/425 (1.6%) missing; § 58/425 (13.6%) missing; || defined as NYHA functional class III+IV, 2/425 (0.5%) missing; ¶ 2/425 (0.5%) missing; # 1/425 (0.2%) missing.
Abbreviations: *ACE*, angiotensin-converting enzyme; *CABG*, coronary artery bypass grafting; *CAD*, coronary artery disease; *CRT*, cardiac resynchronization therapy; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *N*, number; *PCI*, percutaneous coronary intervention; *QRS*, QRS duration; *SD*, standard deviation.

Table 2. Mean scores on anxiety and depression for the different distress and treatment groups at 12 months follow-up *

N=352	No emotional distress & no treatment (N=225)		No emotional distress & treatment (N=41)		Emotional distress & treatment (N=36)			Emotional distress & no treatment (N=50)			p-value
Emotional distress	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**% †**	**Mean**	**SD**	**% †**	
Anxiety	2.20	2.12	3.39	2.43	10.39	3.45	16.7	7.36	2.99	14.0	**<.001**
Depression	2.00	1.89	2.95	2.22	9.94	3.86	16.7	8.90	2.53	52.0	**<.001**
Comorbid anxiety and depression	-	-	-	-	11.48	2.55	66.7	10.03	1.19	34.0	**.02**

* A score of ≥8 on anxiety or depression or both is considered as a clinically significant level of emotional distress. † Percentage of patients with a score of ≥8 having anxiety, depression or comorbid anxiety and depression. Abbreviations: *N*, number; *SD*, standard deviation

As our main goal was to investigate the effect of distress and treatment group on health status, examining the effect of changing from distress and treatment group on health status is beyond the scope of this article.

Psychological treatment of emotional distress in ICD patients at 12 months post implantation

During the 12-months follow-up, information on treatment was lacking in 96 patients. Mean scores on anxiety and depression at 12 months post implantation of the remaining 352 patients are displayed in Table 2, which differed significantly between the 4 groups ($p<.001$). At 12 months post implantation, 86 patients (24.3% of all patients) had clinically significant levels of distress, of which 41 (47.7%) had comorbid anxiety and depression. Divided into 4 groups, 225 (63.9%) had no emotional distress and received no treatment, 41 (11.6%) had no emotional distress but received treatment, 36 (10.2%) had emotional distress and received treatment, and 50 (14.2%) experienced emotional distress but received no treatment.

Course of health status over time

Mean health status scores for each subscale at all measurement occasions for the total patient population are displayed in Figure 1. A small improvement in health status was seen during the first 3 months post implantation for each subscale (all $p<.001$). After this, scores tended to remain stable up to 12 months follow-up (all $p>.05$). Mean health status scores on the 4 measurement occasions for each subscale and stratified by group are shown in Figure 2.

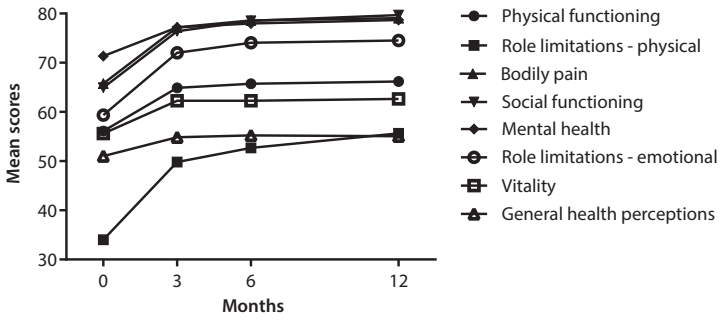

Figure 1. Mean scores on health status during the 12-month follow-up period

Health status in patients treated and not treated for emotional distress

Intraclass correlations (ICCs), describing the correlations between the different measurement occasions within patients, were computed. ICCs ranged from 0.37 for role functioning - emotional to 0.73 for general health, indicating moderate to high correlations, as was expected in this repeated measures design. In Table 3, acquired estimates, t- and p-values are displayed. At any time point, patients experiencing emotional distress but not receiving psychological treatment reported significantly poorer health status on all subscales than patients without distress and treatment (all $p<.001$).

Table 3. Comparison between the different distress and treatment conditions on the levels of health status over time *

	No emotional distress & no treatment			No emotional distress & treatment			Emotional distress & treatment		
SF-36 subscale	**Estimate**	**t**	**p**	**Estimate**	**t**	**p**	**Estimate**	**t**	**p**
Physical functioning	16.98	6.78	**<.001**	9.75	2.93	**.004**	0.25	0.07	.94
Role Functioning-Physical	25.24	4.81	**<.001**	10.32	1.47	.14	-11.39	-1.57	.12
Bodily Pain	16.03	5.16	**<.001**	6.44	1.55	.12	-9.15	-2.13	**.034**
Social Functioning	20.50	7.89	**<.001**	11.79	3.41	**.001**	-11.58	-3.23	**.001**
Mental Health	19.98	11.73	**<.001**	13.10	5.74	**<.001**	-8.89	-3.74	**<.001**
Role Functioning-Emotional	25.19	5.02	**<.001**	14.89	2.22	**.027**	-29.55	-4.25	**<.001**
Vitality	19.94	9.84	**<.001**	11.04	4.10	**<.001**	-2.80	-0.99	.32
General Health	12.40	5.73	**<.001**	7.30	2.54	**.012**	-2.15	-0.72	.48

* Analyzed by a repeated measures analysis of variance (RM ANOVA) using general linear mixed modelling analysis with 'Emotional distress & no treatment' as the reference group. This table reflects the effect of distress and treatment groups *at any time point* on the level of health status over time. Abbreviations: *SF-36,* Short Form Health Survey 36

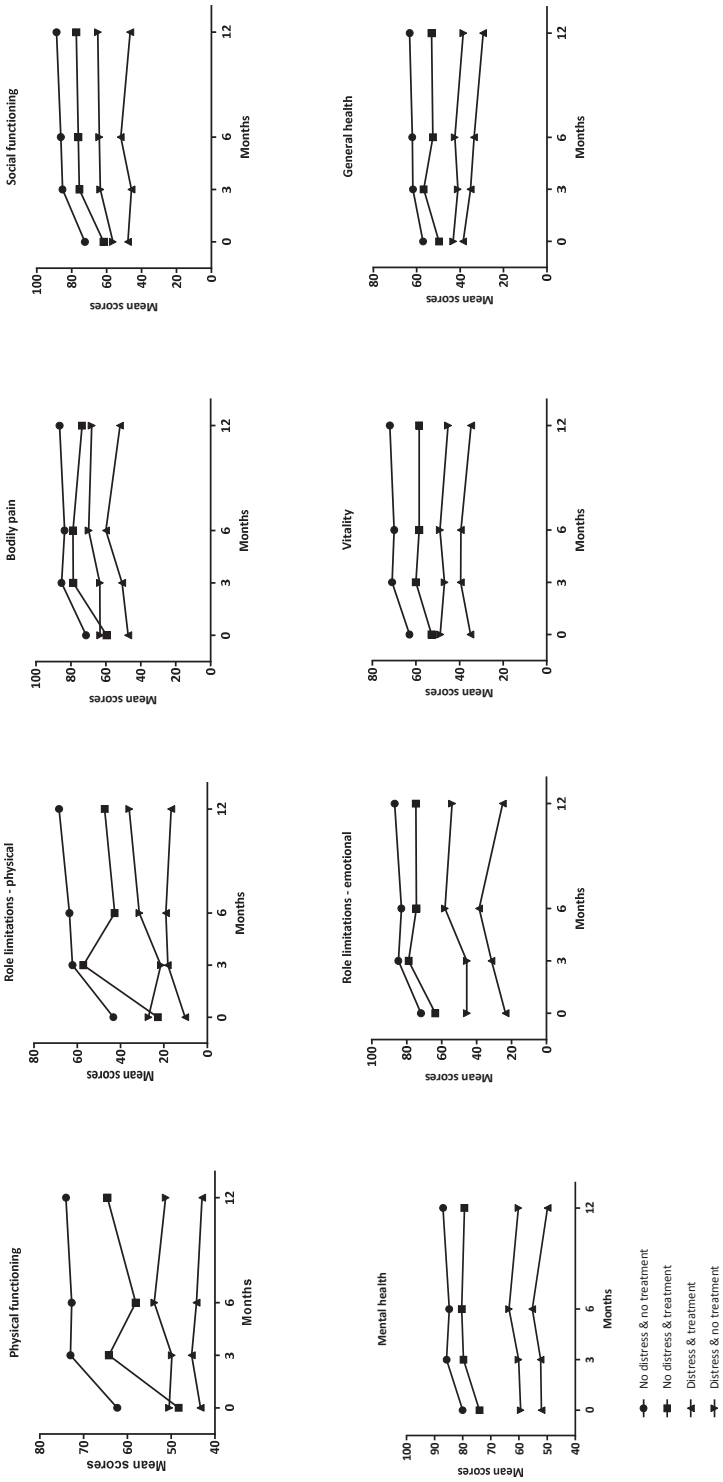

Figure 2. Mean health status scores on the 4 measurement occasions for each subscale and stratified by group

In addition, they reported inferior scores on physical functioning (p=.004), social functioning (p=0.001), mental health (p<.001), role functioning - emotional (p=.027), vitality (p<.001) and general health (p=.012) as compared to patients without emotional distress but receiving treatment. However, patients with emotional distress but without treatment experienced better health status with respect to bodily pain (p=.034), social functioning (p=.001), mental health and role functioning - emotional (both p<.001) than patients with emotional distress receiving treatment.

Interaction effects

Interaction effects between emotional distress and treatment on the one hand and time on the other hand were also examined for each subscale. In line with the main analysis, patients who suffered from emotional distress but who did not receive treatment were used as reference group. Interaction effects between time and subgroups were found on 2 subscales. With regard to bodily pain, patients without emotional distress and treatment improved significantly more during the first 3 months than the reference group (p=.004). On the subscale vitality, patients with no emotional distress and no treatment showed significantly more improvement during the first 3 months than patients in the reference group (p<.001). The same applied to patients with emotional distress receiving treatment (p=.020). Finally, patients without emotional distress and with treatment reported more improvement on vitality than patients in the reference group (p=.004) between 6 and 12 months follow-up.

DISCUSSION

In the current study, there was a serious gap between the prevalence of psychological distress and need for *and* the actual delivery of such treatment, with approximately two thirds of patients in need of treatment receiving none. In the subset of patients who were distressed and received treatment, the treatment response was poor, as reflected by these patients reporting the most impaired health status. Although patients treated for their distress reported poorer health status than patients with high levels of distress who were not treated, the latter group demonstrated significantly less improvement in health status at 12 months follow-up on the vitality subscale of the SF-36. As impaired health status has been found to be an independent predictor of morbidity and mortality in patients with an ICD,[21,22] the need for adequate psychological treatment is evident. Highly distressed patients treated for their distress reported the poorest health status across all health status domains and at all follow-up occasions as compared to the other groups. At first sight, this finding may seem counterintuitive, but due to greater impairments in daily functioning, this subset of patients may be prone to consult their physician or mental health professional more rapidly. Alternatively, it is possible that the treatment offered to this subset of patients is not sufficient considering the specific needs of patients with an ICD. In terms of type of treatment, in our sample the majority of patients receiving treatment were prescribed psychotropic medication, while only a small part consulted a psychologist. Yet, emotional problems occurring in this patient group can be very complex and specific (i.e. excessive fear for ICD firing and the unpredictability and

uncontrollability of receiving shocks),[30,31] such that being treated with psychotropic medication may not suffice and more specialized treatment by an experienced medical psychologist is warranted. This could explain the finding that distressed patients receiving treatment report the poorest health status in our sample. In addition, patients being treated for their emotional distress were more often single and women. Although the evidence is not conclusive, women with an ICD might be at heightened risk of psychological distress, in particular anxiety.[32]

Approximately half of the patients stayed in the same subgroup during 12 months follow-up. When patients crossed over to another distress and treatment group during follow-up, they were all most likely to report low levels of distress and not to be treated. Thus, we can conclude that a substantial part of the patients remained free of distress or recovered from their distress during follow-up, which is supported by previous research in this patient population.[33] However, a small subgroup of patients (approximately 8%) with no distress and receiving no treatment at inclusion is at risk for experiencing distress during follow-up, while not being treated for it. In addition, about 40% of untreated distressed patients remained in this condition during the 12 months of follow-up. This emphasizes the need for adequate monitoring and treatment, not solely around the implantation procedure but also during the first year(s) of follow-up.

The findings of this study match the conclusions of previous studies investigating psychological treatment and psychopharmacological prescription rates in the general population, as well as in primary and secondary care. However, the current study also extends our knowledge of the prevalence of treatment for psychological distress in patients with an ICD, identifying a clear mismatch. Two studies among the general population highlight the discrepancy between the prevalence of mental health problems and receiving treatment.[17,18]

Several barriers exist that may prevent individuals from obtaining adequate mental health care. Not only underdiagnosis and lack of awareness on the part of the health care provider contribute to this problem, but also individual patient factors, including willingness to disclose problems and having negative stereotypes of psychological treatment, as well as systemic factors, such as access to medical care.[18] Alonso and Lépine (2007) have indicated that only 36.8% of patients with a mood disorder and 20.6% of patients with anxiety seek help for these problems. Of these, still 20% received no psychological treatment, indicating that help seeking does not always result in adequate care.[17] In primary care patients, less than half of patients with any mood disorder receive any type of psychotropic drug.[19] A substantial part of patients with a 12-month diagnosis of pure depression receive only anxiolytics, indicating inadequate treatment in addition to undertreatment.[19] Several studies have reported that in particular patients with anxiety are at risk for undertreatment.[17,18] Although not specifically examined in this study, this is important to patients with an ICD, as anxiety is one of the most prevalent and disturbing symptoms among these patients, often with a chronic course.[9,10,34]

One could argue that all patients with clinically significant levels of anxiety and depression should be treated with psychotropic drugs or be referred to a mental health professional. The importance of symptom reduction is evident, given the negative impact on quality of life, ventricular tachyarrhythmias and mortality.[7,14,35] A recent meta-analysis indicates that selective serotonin

reuptake inhibitors (SSRIs) are safe to use in patients with depression and CAD.[36] In addition, SSRIs have proven to favour clinical outcomes, including improvement in heart rate variability (HRV), decrease of ventricular extrasystoles and number of shocks, and patient-reported outcomes, including symptoms of depression, anxiety and quality of life in both non depressed and depressed patients with an ICD.[37,38] The effectiveness of behavioral interventions in patients with an ICD has also been confirmed, as indicated by reduced symptoms of anxiety and depression and improved exercise capacity.[39-41]

The current study has several strengths. These include the high response rate, the relatively large sample size and the prospective study design with several measurement occasions. In addition, the moderate to high intraclass correlations underline the importance of reckoning with correlated data, with the relatively new statistical approach used in the current study meeting this requirement. Furthermore, information on emotional distress and treatment were present during the entire follow-up period.

The limitations of the present study should also be acknowledged. First, the small number of patients treated by a psychologist made it necessary for us to combine the use of psychotropic medication with treatment by a psychologist into one treatment variable. In addition, information on pharmacotherapy and treatment by a psychologist was based on self-report, which could lead to an underestimation of actual treatment rates. Third, we had no information on the type of specific psychotropic agents used at the different measurement occasions. However, Lecrubier (2007) has demonstrated that we still do not know what constitutes optimal psychopharmacological therapy for specific psychological symptoms.[19]

In conclusion, the current study indicates that there is serious gap between the prevalence of psychological distress and need for treatment, and the actual delivery of such treatment in patients with an ICD. Importantly, emotional distress that is untreated may have a detrimental influence on health status, which in turn may increase the risk of morbidity and mortality in this subset of patients. Closing the gap between the common symptoms of emotional distress and access to effective pharmacological and psychological treatment remains an important target in both primary and secondary prevention in this patient group. This could be accomplished by enhancing awareness in both physicians and patients, incorporating standard screening of psychosocial functioning in clinical practice, paying more attention to cross-talk between the responsible physician and mental health care provider in patients' medical records, and implementing specific psychological treatment programs targeting the specific issues and needs of patients with an ICD.

REFERENCES

1. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352(3):225-237.
2. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337(22):1576-1584.
3. Epstein AE, DiMarco JP, Ellenbogen KA, Estes Iii NAM, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;51(21):e1-e62.
4. Mark DB, Anstrom KJ, Sun JL, Clapp-Channing NE, Tsiatis AA, Davidson-Ray L, Lee KL, Bardy GH. Quality of life with defibrillator therapy or amiodarone in heart failure. N Engl J Med 2008;359(10):999-1008.
5. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346(12):877-883.
6. Passman R, Subacius H, Ruo B, Schaechter A, Howard A, Sears SF, Kadish A. Implantable cardioverter defibrillators and quality of life: Results from the defibrillators in nonischemic cardiomyopathy treatment evaluation study. Arch Intern Med 2007;167(20):2226-2232.
7. Ladwig K-H, Baumert J, Marten-Mittag B, Kolb C, Zrenner B, Schmitt C. Posttraumatic stress symptoms and predicted mortality in patients with implantable cardioverter-defibrillators: Results from the prospective living with an implanted cardioverter-defibrillator study. Arch Gen Psychiatry 2008;65(11):1324-1330.
8. Pedersen SS, Van den Broek KC, Theuns DAMJ, Erdman RAM, Alings M, Meijer A, Jordaens L, Denollet J. Risk of chronic anxiety in implantable defibrillator patients: A multi-center study. Int J Cardiol 2011;147(3):420-423.
9. Pedersen SS, Theuns DAMJ, Jordaens L, Kupper N. Course of anxiety and device-related concerns in implantable cardioverter defibrillator patients the first year post implantation. Europace 2010;12(8):1119-1126.
10. Sears SF, Conti JB. Quality of life and psychological functioning of ICD patients. Heart 2002;87(5):488-493.
11. Versteeg H, Theuns DAMJ, Erdman RAM, Jordaens L, Pedersen SS. Posttraumatic stress in implantable cardioverter defibrillator patients: The role of pre-implantation distress and shocks. Int J Cardiol 2011;146(3):438-439.
12. Dunbar SB, Kimble LP, Jenkins LS, Hawthorne M, Dudley W, Slemmons M, Langberg JJ. Association of mood disturbance and arrhythmia events in patients after cardioverter defibrillator implantation. Depress Anxiety 1999;9(4):163-168.
13. Van den Broek KC, Nyklícek I, Van der Voort PH, Alings M, Meijer A, Denollet J. Risk of ventricular arrhythmia after implantable defibrillator treatment in anxious Type D patients. J Am Coll Cardiol 2009;54(6):531-537.
14. Pedersen SS, Van den Broek KC, Erdman RAM, Jordaens L, Theuns DAMJ. Pre-implantation implantable cardioverter defibrillator concerns and Type D personality increase the risk of mortality in patients with an implantable cardioverter defibrillator. Europace 2010;12(10):1446-1452.
15. Benazon NR, Mamdani MM, Coyne JC. Trends in the prescribing of antidepressants following acute myocardial infarction, 1993-2002. Psychosom Med 2005;67(6):916-920.
16. Smolderen KG, Buchanan DM, Amin AA, Gosch K, Nugent K, Riggs L, Seavey G, Spertus JA. Real-world lessons from the implementation of a depression screening protocol in acute myocardial infarction patients. Circ Cardiovasr Qual Outcomes 2011;4(3):283-292.
17. Alonso J, Lépine JP. Overview of key data from the European Study of the Epidemiology of MEntal Disorders (ESEMED). J Clin Psychiatry 2007;68(Suppl 2):3-9.
18. Collins KA, Westra HA, Dozois DJA, Burns DD. Gaps in accessing treatment for anxiety and depression: Challenges for the delivery of care. Clin Psychol Rev 2004;24(5):583-616.
19. Lecrubier Y. Widespread underrecognition and undertreatment of anxiety and mood disorders: Results from 3 European studies. J Clin Psychiatry 2007;68(Suppl 2):36-41.

20. Suzuki T, Shiga T, Kuwahara K, Kobayashi S, Suzuki S, Nishimura K, Suzuki A, Ejima K, Manaka T, Shoda M, Ishigooka JUN, Kasanuki H, Hagiwara N. Prevalence and persistence of depression in patients with implantable cardioverter defibrillator: A 2-year longitudinal study. Pacing Clin Electrophysiol 2010;33(12):1455-1461.
21. Piotrowicz K, Noyes K, Lyness JM, McNitt S, Andrews ML, Dick A, Hall WJ, Moss AJ, Zareba W. Physical functioning and mental well-being in association with health outcome in patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial II. Eur Heart J 2007;28(5):601-607.
22. Steinberg JS, Joshi S, Schron EB, Powell J, Hallstrom A, McBurnie M. Psychosocial status predicts mortality in patients with life-threatening ventricular arrhythmias. Heart Rhythm 2008;5(3):361-365.
23. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67(6):361-370.
24. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997;27(2):363-370.
25. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: An updated literature review. J Psychosom Res 2002;52(2):69-77.
26. Martens EJ, de Jonge P, Na B, Cohen BE, Lett H, Whooley MA. Scared to death? Generalized anxiety disorder and cardiovascular events in patients with stable coronary heart disease: The Heart and Soul study. Arch Gen Psychiatry 2010;67(7):750-758.
27. Aaronson NK, Muller M, Cohen PDA, Essink-Bot M-L, Fekkes M, Sanderman R, Sprangers MAG, te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 health survey in community and chronic disease populations. J Clin Epidemiol 1998;51(11):1055-1068.
28. Ware J, Kosinski M. Interpreting SF-36 summary health measures: A response. Qual Life Res 2001;10(5):405-413.
29. Garber MC, Nau DP, Erickson SR, Aikens JE, Lawrence JB. The concordance of self-report with other measures of medication adherence: A summary of the literature. Med Care 2004;42(7):649-652.
30. Hegel M, Griegel L, Black C, Goulden L, Ozahowski T. Anxiety and depression in patients receiving implanted cardioverter-defibrillators: A longitudinal investigation. Int J Psychiatry Med 1997;27(1):57 - 69.
31. Pedersen SS, Van Domburg RT, Theuns DAMJ, Jordaens L, Erdman RAM. Concerns about the implantable cardioverter defibrillator: A determinant of anxiety and depressive symptoms independent of experienced shocks. Am Heart J 2005;149(4):664-669.
32. Brouwers C, Van den Broek KC, Denollet J, Pedersen SS. Gender disparities in psychological distress and quality of life among patients with an implantable cardioverter defibrillator. Pacing Clin Electrophysiol 2011;34(7):798-803.
33. Pedersen SS, Hoogwegt MT, Jordaens L, Theuns DAMJ. Pre implantation psychological functioning preserved in majority of implantable cardioverter-defibrillator patients. Int J Cardiol 2011;166(1):215-220.
34. Crössmann A, Schulz SM, Kühlkamp V, Ritter O, Neuser H, Schumacher B, Bauer W, Pauli P. A randomized controlled trial of secondary prevention of anxiety and distress in a German sample of patients with an implantable cardioverter defibrillator. Psychosom Med 2010;72(5):434-441.
35. Whang W, Albert CM, Sears Jr SF, Lampert R, Conti JB, Wang PJ, Singh JP, Ruskin JN, Muller JE, Mittleman MA. Depression as a predictor for appropriate shocks among patients with implantable cardioverter-defibrillators: Results from the Triggers Of Ventricular Arrhythmias (TOVA) study. J Am Coll Cardiol 2005;45(7):1090-1095.
36. Pizzi C, Rutjes AWS, Costa GM, Fontana F, Mezzetti A, Manzoli L. Meta-analysis of selective serotonin reuptake inhibitors in patients with depression and coronary heart disease. Am J Cardiol 2011;107(7):972-979.
37. Kuijpers PMJC, Honig A, Wellens HJJ. Effect of treatment of panic disorder in patients with frequent ICD discharges: A pilot study. Gen Hosp Psychiatry 2002;24(3):181-184.
38. Leftheriotis D, Flevari P, Ikonomidis I, Douzenis A, Liapis C, Paraskevaidis I, Iliodromitis E, Lykouras L, Kremastinos DT. The role of the selective serotonin re-uptake inhibitor sertraline in nondepressive patients with chronic ischemic heart failure: A preliminary study. Pacing Clin Electrophysiol 2010;33(10):1217-1223.
39. Chevalier P, Cottraux J, Mollard E, Sai N, Brun S, Burri H, Restier L, Adeleine P. Prevention of implantable defibrillator shocks by cognitive behavioral therapy: A pilot trial. Am Heart J 2006;151(1):191.e191-191.e196.
40. Kohn C, Petrucci R, Baessler C, Soto D, Movsowitz C. The effect of psychological intervention on patients' long-term adjustment to the ICD: A prospective study. Pacing Clin Electrophysiol 2000;23(4 Pt 1):450 - 456.
41. 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(12):1546-1554.

General discussion and summary of the results

12

The implantable cardioverter-defibrillator (ICD) is the treatment of first choice for the primary and secondary prevention of sudden cardiac death (SCD) in patients at high risk of life-threatening ventricular arrhythmias, with mortality risk reductions of 37% for all-cause mortality and 57% for sudden cardiac death when compared to antiarrhythmic drugs.[1-3] Expansion of the indications for ICD implantation throughout the years owing to encouraging results of primary prevention trials has led to an increasing number of patients living with an ICD.[4] Despite the unequivocal medical benefits of the ICD, a subset of ICD patients experiences emotional distress, including symptoms of depression, anxiety, and posttraumatic stress, as well as reduced quality of life.[5-7]

Due to cumulative evidence that the patient's psychological profile and level of distress are associated with risk of morbidity and mortality[8] and affect compliance,[9] recent European Guidelines on cardiovascular disease prevention in clinical practice emphasize the need to manage patients' distress.[10] According to these guidelines, adequate management of these factors via individual or group counselling has proven to have additional beneficial effects on biomedical risk factors and emotional distress, beyond cardiac rehabilitation. The sole focus on the management of the underlying somatic condition has thus shifted towards treating the patient as a whole, with the recognition that biological, psychological and social factors all interact to contribute to the patient's well-being and survival.

Although attention to more diverse risk stratification in ICD patients clearly has increased and models using multiple clinical risk markers have shown promising results regarding prediction of SCD risk,[11] there still remains a need for more optimal identification of vulnerable patients within the ICD population, in which there might also be a role for psychological factors.

The main objectives of this thesis were therefore to (1) expand the knowledge on clinical associates of emotional distress; (2) investigate autonomic nervous system (ANS) functioning as a potential associate of psychological and clinical outcomes; (3) further elucidate the influence of the partner on psychological and clinical outcomes of the patient; and (4) explore which information and psychological care are available to ICD patients in standard clinical practice and the needs and preferences of patients with this respect.

Emotional distress in patients with complications and more complex disease

Despite the unequivocal benefits of ICD therapy in terms of survival, research has also pinpointed the possible 'side effects' of ICD therapy in terms of a potentially negative impact on patient well-being.[12] Complications, including procedure- (e.g. lead dislodgement, infection) and device-related (inadequate sensing, inappropriate shocks) issues, may affect psychological adaption post implantation. Since it is known that the patient's emotional distress level tends to be at its highest within the first months post implantation, **Chapter 2** examined the association of procedure- and device related complications with emotional distress. We found that the occurrence of procedure- and device-related complications around and post implantation was associated with increased symptoms of anxiety and ICD-related concerns, while no relationship was found with depressive symptoms. The association of complications with general and ICD-specific anxiety instead of

depression seems logical, since complications may more likely infringe on patients' confidence in the ICD as a 'life-saver', which in turn may induce anxiety and insecurity. The observation that one in six patients experienced a complication throughout the first year emphasizes the importance of careful clinical and psychological monitoring of patients around and post implantation.

Comorbidities, including myocardial infarction (MI), chronic heart failure (CHF), renal failure and diabetes, are highly prevalent among ICD patients,[13] with multiple comorbidities often hampering patients' daily living and functioning. **Chapter 3** investigated the relationship between comorbidities assessed with an age-adjusted version of the Charlson Comorbidity Index (CCI) and emotional distress. In contrast to the findings in **Chapter 2**, where procedure- and device-related complications were associated with increased anxiety, we found that comorbidity burden was associated with depressive symptomatology and impaired physical health status. Since comorbidities may impinge on patients' activity levels, sleeping pattern, and social life, and thus overall lead to impaired physical functioning, this likely induces depressed mood and feelings of hopelessness rather than anxiety. Due to overlap in for example somatic symptoms of depression (i.e. sleep disturbance, loss of energy and weight changes) and clinical conditions such as CHF or renal failure, it may be a challenge in clinical practice to accurately signal psychological symptoms and not only interpret them as a 'normal' reaction to or part of impaired physical functioning. Both **Chapters 2 and 3** extend our knowledge of the relation between somatic conditions, comorbidities and psychological distress by confirming a link between physical and psychological symptoms. This underlines the importance of attention to a holistic approach to patient care including both clinical and psychological factors. Notwithstanding, the question whether a clinical high-risk profile leads to impaired psychological well-being, or the other way around, remains unsolved. Instead of focusing on separate risk factors, future research should seek to identify the most optimal 'package' of risk factors to detect vulnerable patients in order to optimize the care of patients with an ICD and enhance their well-being, quality of life, and survival.

Association of beta-blocker and statin use with psychological well-being in ICD patients

Beta-blockers are commonly prescribed to patients with an ICD due to their anti ischemic, anti arrhythmic and anti hypertensive properties, and their beneficial effects on ejection fraction and prognosis.[14] For years, concerns have been raised about a possible association between beta-blocker use and depression, which might play a role in the underutilization of beta-blockers in ICD patients.[14] Several central and peripheral pathways are proposed that could underlie this relationship, involving among others central binding to beta-adrenergic and beta-serotonergic receptors, interfering with noradrenergic and serotonergic signal flow, as well as peripherally mediated mechanisms in which beta-blockers alter autonomic activity in the periphery, which feeds back to the central nervous system (CNS) potentially inducing depressed mood.[15] The cardiovascular literature so far is inconclusive with respect to potential psychological side effects of beta-blockers. Moreover, the majority of studies have focused on a link between beta-blockers and depression, while little attention has been given to symptoms of anxiety. The relation between beta-blocker use and

anxiety may work differently than the relation with depression, with beta-blockers possibly reducing anxiety symptoms due to their arousal-lowering effect. In **Chapter 4**, we examined the relationship between beta-blocker use, including type and dosage, and symptoms of depression, anxiety and ICD concerns prior to implantation. We found no indication that beta-blockers are associated with emotional distress, which is consistent with a number of recent studies on the association between beta-blocker use and depression in general cardiac populations (for reviews see[15,16]). Although a recent cross-sectional study in percutaneous coronary intervention (PCI) patients revealed less depressive symptoms 12 months post intervention in patients using beta-blockers, at 1 month post PCI no significant association was present. Besides, these latter findings were contradicted in a large prospective study among post MI patients.[17] In conclusion, the majority of evidence so far suggests that beta-blocker use is not associated with impaired psychological well-being, which we confirmed in ICD patients in **Chapter 4**. Studies demonstrating an association between beta-blocker use and depression tend to be dated and based on small sample sizes. Physicians should not be restrained to prescribe beta-blockers to ICD patients, since they have proven benefits in terms of prognosis.

Statin therapy is prescribed in the majority of ICD patients as well, but the relation between statin therapy and psychological well-being remains unexplored and was therefore assessed in **Chapter 5**. Several mechanisms may be involved in the association between statin use and psychological well-being. Possible actions that could plead for a positive relation are protective effects on cerebrovascular processes (i.e. decreasing endothelial dysfunction and oxidative stress, and anti-inflammatory effects),[18,19] prevention of physical disabilities[20] and increased health conscientiousness and adherence in statin users.[20] On the other hand, statin use may have unfavourable effects. Low membrane cholesterol has been associated with depressive symptoms by disrupting the serotonin system[21] and statin use has been associated with side-effects, including headache, gastrointestinal complaints and dizziness, which might influence patients' health status.[22] In general, statin use was associated with poorer health status with respect to dimensions of physical and emotional role limitations, and social functioning. No significant relationship with depression and anxiety was found. Recently two reviews[21,23] on the association between statin use and depression were published, with mixed evidence. Importantly, these reviews both have methodological limitations (i.e. absence of a systematic review of the literature[21], focus on effects of low cholesterol instead of statin use on mood,[21] absence of thorough randomized controlled trials (RCTs)[23], and exclusion of post hoc analyses from trials[23]). Moreover, evidence mainly focused on non cardiac patients, while inflammatory and oxidative mechanisms that could underlie a possible relation between statin use and impaired psychological well-being may differ between cardiac and non cardiac patients. Recapitulating the evidence, there seems no strong indication for statin use being associated with depression. The relation with health status has been understudied, and our finding of statin use being associated with impaired health status, particularly reflected on the domains of physical and emotional role limitations and social functioning, implies that possible side-effects of statin use on health status should be discussed with the patient in order to prevent non compliance.

In summary, we found no strong indications for cardiovascular medication use to be associated with impaired psychological functioning. Physicians should not hesitate to prescribe beta-blockers and statins if indicated in ICD patients, since the evidence on negative effects of cardiovascular

drugs on psychological functioning is rather dated and of less robust methodology. Nevertheless, physicians should always be aware of possible interactions between medications, since ICD patients are often prescribed a complex multi-drug treatment regimen and for example, interactions between antidepressant use and beta-blockers have been reported.[24,25] Importantly, attention to side-effects obviously still remains a target in clinical practice.

In search of a psychophysiological link between emotional distress and clinical outcomes: The autonomic nervous system

Emotional distress is known to be associated with impaired clinical outcomes in ICD patients, including increased risk of ventricular arrhythmias and mortality.[8] Knowledge of the mechanisms explaining this link is important, as they can point towards treatment targets in clinical practice that may not only improve mood, but also improve cardiovascular prognosis. Of particular importance to the pathophysiology of ICD patients, the autonomic nervous system (ANS) has an important share in the development of ventricular arrhythmias, with a shift towards sympathetically dominated cardiac control.[26] **Chapter 6** examined the relationship between emotional distress (i.e. depression, ICD concerns and Type D personality) and heart rate variability (HRV), a measure of autonomic regulation of the heart. Although the sample size was small, there was an indication for lower overall autonomic control over 24 hours and lower parasympathetic control during rest in emotionally distressed patients.

The concepts of allostasis and allostatic load may provide us with insight into the way that (emotional) stress may lead to progression of heart disease. Allostasis is the process whereby an organism maintains physiological stability by changing parameters of its internal milieu by matching them appropriately to environmental demands.[27] Allostatic responses continuously occur throughout daily life, and allostatic load refers to the wear and tear that the body experiences when repeated allostatic responses are activated during stressful situations.[28] Chronic stress increases allostatic load and results in alterations in bodily systems functioning, including over-activation of the neuronal and hormonal sympathetic axes, as well as the HPA-axis (see also the level II response of the psychophysiological stress reactivity model by Lovallo and Gerin[29]). This is related to changes in cellular function and ultimately, due to an ever-shifting allostatic setpoint, leads to allostatic overload. Allostatic overload increases the risk of physiological dysfunction, disease and mortality.[30] Emotional distress, including depression, anxiety and more stable traits like Type D personality, can act as long-lasting stressors. The reduced overall HRV in distressed Type D patients (**Chapter 6**) may be a reflection of an *inadequate* response[30] in which the ANS is in a hypoactive state, while the reduced parasympathetic control in Type D and depressed patients during rest may indicate a *prolonged* stress response.[30] This inadequate stress response and increase in allostatic load may explain the increased risk of ventricular arrhythmias and prognosis that is observed in emotionally distressed ICD patients.

In **Chapter 7**, the associations of respectively heart rate and QRS duration with mortality were investigated. In accordance with existing literature in other cardiac populations, in our ICD

population a heart rate of ≥80 bpm conferred an increased mortality risk, while the relation between QRS duration (both when using a cut-off of >120 ms and a continuous measure of QRS duration) and mortality risk was non significant and mainly explained by the presence of comorbidities. Interestingly, emotional distress did not seem to affect the relationship between heart rate and mortality (i.e. act as confounder), as indicated by the relatively unaffected hazard ratio and confidence interval when including depression and anxiety as covariates in the analyses.

A number of potential mechanisms have been proposed to explain the relationship between increased heart rate and mortality, including increased oxidative stress, decreased restoration of endothelial function and arterial stiffness, hampering of angiogenesis, increased likelihood of plaque disruption and decreased myocardial blood flow.[31] More specifically looking at the autonomic nervous system, tachycardia may have various causes. Lower overall autonomic control, which we demonstrated to be associated with emotional distress (**Chapter 6**), speeds up heart rate towards the intrinsic automaticity level (or spontaneous pacemaker rhythm). On the other hand, sympathetic cardiac dominance facilitates automaticity, thereby increasing heart rate as well as the chance of ventricular arrhythmias.[32] The increased mortality risk associated with increased heart rate, which we confirmed in **Chapter 7**, may be a consequence of a sympatho-vagal imbalance which is characterized by sympathetic dominance and reduction of vagal control.

Chapters 6 and 7 give important impressions of the interrelationships between emotional distress, autonomic functioning and mortality, although the question whether the ANS may act as a pathophysiological pathway between emotional distress and clinical outcomes remains unanswered. Therefore, we performed additional analyses examining whether heart rate acts as a mediator in the relation between emotional distress and mortality. The results of the analyses are included as an addendum to this dissertation. In order for heart rate to be considered as a mediator, (1) the relationship between emotional distress and mortality should be statistically significant; (2) the relationship between emotional distress and heart rate should be statistically significant; (3) heart rate should be related to mortality, and (4) the relation between depression and mortality should become smaller or ideally non significant after adjusting for heart rate.[33] More extensively shown in the Addendum, the mortality risk associated with depression was not mediated via heart rate. This finding is also supported by previous research within this patient cohort, demonstrating an absence of a relationship between depression and the risk of ventricular tachyarrhythmias.[34] The pathway explaining the relation between depression and all-cause mortality risk is more likely to be multifactorial, with a combination of ANS functioning, stress hormones, inflammation, endothelial dysfunction, comorbidities and behavioral factors playing a role,[35] while the relation between heart rate and mortality may more easily be explained by ANS functioning and physical effects on the vasculature and myocardium (i.e. plaque damage and diminished perfusion). Future research should further elucidate which biobehavioral pathophysiological pathways may explain the heart rate-mortality and depression-mortality links. One major prerequisite in these future studies would be to also better differentiate between causes of death, because the link with all-cause mortality gives no directions towards specific mechanisms involved.

Risk stratification in ICD patients

This dissertation has revealed important predictors of prognosis in ICD patients. In **Chapter 7**, we found that heart rate was a significant predictor of long-term mortality, independent of several other clinical and psychological risk factors, just as the age-adjusted version of the Charlson Comorbidity Index (CCI), the occurrence of shocks during follow-up, the use of amiodarone and the presence of depressive symptoms. Inclusion of variables that are easy to assess and accurately predict risk enhances the chances of successful implementation of risk stratification models in clinical practice. Heart rate and the CCI may be examples of such variables. Since emotional distress has been shown to predict prognosis in ICD patients as well, inclusion of the patient's psychological profile in future algorithms used for risk stratification may be warranted.

The importance of the partner for patient well-being and prognosis

To date, research has mainly focused on the patient's psychological well-being, while recently attention has been called to the partner's emotional state. Partners of ICD patients may be confronted with a wide range of challenges, including caring for the patient, feelings of helplessness and uncertainty about the ICD giving a shock, changes in role patterns, fear of sexual activities, overprotective behavior and, more practical, driving restrictions to the patient.[36] Any of these challenges may be similar for patients and partners, with research indicating that emotional distress levels are equally high in patients and partners,[37] and also that the type of distress corresponds within the dyad.[38]

The knowledge on the influence of the partner's emotional state on the patient's well-being has been expanded in the current dissertation, as demonstrated in **Chapter 8**. We confirmed that patient and partner distress patterns during the first year post implantation are largely similar. However, we also demonstrated that although the patients' health status was largely predicted by their own levels of emotional distress, partner distress predicted baseline health status and course of health status during follow-up beyond patients' emotional functioning. Thus, patients experienced poorer baseline health status and poorer health status recovery during follow-up if their partners were emotionally distressed. These findings are supported by several theories, including dyadic coping theories, which assume that the process of stress-coping is perceived as a dyadic exchange of action (i.e. stress signals of one partner), reaction (dyadic coping of the other partner), and common dyadic coping efforts, with the patient and partner thus mutually influencing each other.[39] Within this context, the social baseline theory assumes that social proximity and interaction decrease physical and mental costs of environmental demands. Absence of social proximity may lead to impaired control of emotions due to reduced mesolimbic functioning and the release of stress hormones, which explains why having a partner may be supportive for both psychological and physical functioning.[40]

In addition to partner distress having an influence on patients' distress levels and health status, preliminary research in heart failure patients has shown that distress in partners may affect the course of heart failure symptoms during follow-up, independently of the level of the patient's own

distress level.[41] In continuation of this finding, the impact of partner distress on patient mortality risk was examined in **Chapter 9**, controlling for relevant clinical patient characteristics and the patients' own distress level. We found that the relationship between partner distress and patient mortality risk was non significant, mainly due to the patient's own level of distress explaining the majority of variance in mortality. Although the literature is scarce when it comes to the impact of partner distress on patient prognosis, several related concepts, including marital status, marital satisfaction or quality, and social support, have been investigated in relation to patient mortality risk, indicating a protective effect of the presence of a partner and/or a relationship of good quality.[42,43] A reason for the non significant results in **Chapter 9** could be the timing of assessment, with emotional distress in patients and partners being measured at baseline (i.e. one day prior to implantation). It is well-known that distress levels of both patients and partners decline during the first three months post implantation, and the group of partners with high distress levels at baseline may consist for a large part of partners who successfully adapt to ICD implantation on the short-term and thus constitute a low-risk group regarding prognosis. Future research should explore whether persistent distress in partners and comorbid distress within the patient-partner dyad may lead to more disadvantageous outcomes for both patients and partners.

Importantly, although so far the patient's mortality risk mainly seems to depend on the patient's own level of distress and clinical risk profile, the importance of the partner as a supportive anchor for the patient has been demonstrated in **Chapter 8**. To summarize, the partner thus seems more important for the psychological well-being of the patient than for the patients' physical state and prognosis. Due to equally high distress levels in partners and in patients, the partner should be involved in the treatment process in order to increase the chance of optimal adaptation for both patient and partner.

Screening patients for emotional distress in clinical practice

There is sufficient evidence showing that emotional distress is associated with a wide range of negative physical and psychological outcomes in cardiac patients, including reductions in quality of life,[44] decreased adherence[45] and participation in cardiac rehabilitation[46] and increased risk of morbidity and mortality.[34,47,48] This led the American Heart Association (AHA) to publish an advisory in 2008 calling for systematic screening for depression in patients with coronary heart disease (CHD) using a 2-step approach, with initial administration of the 2-item version of the Patient Health Questionnaire (PHQ), and immediate administration of the full PHQ-9 in patients scoring ≥1 at the PHQ-2 as a second screening step.[49] However, criticism rose shortly after publication of the advisory. The accuracy of depression screening instruments, the effect of screening on depression and cardiac outcomes and the effect of depression treatment on depression in patients in cardiovascular care settings were challenged in a subsequent review,[50] and inappropriate labeling, premature exposure of patients to antidepressant medications and increasing risk of stigma were raised as additional concerns.[51] Several recent, large-scale studies have investigated the feasibility of implementation of the AHA screening protocol in clinical cardiology practice. These studies also raised important

limitations, but ultimately point towards a more positive evaluation of the advisory. Having adopted a similar depression screening protocol in post MI patients, Smolderen et al. (2011) demonstrated that approximately 75% of eligible patients were screened, with 90% of those patients who underwent the routine depression screening protocol and who suffered from depression having their depression recognized after which further action was being taken.[52] A second study using the 2-step PHQ screening approach to identify depression among 4783 cardiac patients, with nurses performing the depression screening, revealed similar results.[53]

Screening should ideally take place in the inpatient hospital setting shortly after admission, which has shown to lead to better screening results in patients with cardiac illness when compared to screening afterwards the primary care setting.[53,54] Standard cardiac units seem to be the most suitable screening setting, since patients in the coronary intensive care unit are more likely to be confused, sedated or in poor physical state.[53] Ideal timing may differ across ICD patients, as primary indication patients often stay in the hospital for a very short period of time around implantation (which may be a suitable timing for screening), while secondary indication patients may be brought to the hospital in a life-threatening, urgent condition and are thus more likely to end up in an intensive care setting (in which case later screening may be more appropriate). Clinical practice should be aware of barriers that hamper the implementation of psychological screening, including money and time constraints and screening protocols with too many steps. Facilitation of staff education, short and uncomplicated referral pathways and improving visibility of the screening protocol in the workplace likely increase the chances of successful implementation of psychological screening in the cardiac setting. Female patients and patients with comorbid disorders should be extra carefully monitored, since these patients are at higher risk of not being screened.[52]

Although to date there is no evidence that screening for emotional distress leads to better prognosis, conquering these implementation barriers may lead to improved recognition of emotional distress. For effective continuation of care, in-hospital screening for emotional distress should be continued with follow-up screening since the course of distress can fluctuate over time,[55,56] and psychological treatment should be delivered if necessary.[52,57]

Future research should further investigate the efficacy, safety and cost-effectiveness of screening for emotional distress,[58] examine which instruments are the most sensitive and specific,[50] and investigate which professionals could best perform and evaluate the screening and what the most suitable timing for distress assessment would be. In particular, specific attention should be paid to screening for other psychological constructs than depression, since the psychological screening debate has only touched upon depression screening so far. Needless to say screening does not resolve patient's distress but only identifies those who are afflicted. Hence, screening should be combined with appropriate treatment in the subset of patients who need it, which will be discussed in detail in the following section.

Psychological treatment of ICD patients

In **Chapter 11**, we have shown that approximately two thirds of patients in need of psychological treatment around the time of implantation did not receive help. Moreover, approximately 40% of patients were persistently distressed throughout the first year post implantation, but were not treated for their distress during that period.[59] **Chapter 11** also showed that when treated, this treatment mainly consisted of prescription of psychotropic medication, while only a few patients were referred to a specialized mental health care professional such as a clinical psychologist. Probably partly for this reason, treatment was not entirely effective, as patients who did receive treatment, still reported the highest levels of emotional distress.[59]

Although missed by a considerable number of ICD patients, treatment of emotional distress has shown to improve several important aspects of daily functioning. The effect of cognitive behavioral therapy (CBT) has most frequently been investigated. The core principle of CBT explains that irrational, dysfunctional thoughts (i.e. *'my device prevents me to safely go out with friends'*) are leading to dysfunctional behavior (i.e. avoidance of public places). During CBT, automatic negative patterns of thinking are challenged and replaced by more functional thoughts and behaviors during individual or group sessions.[60] CBT interventions have shown significant effects on anxiety, depression, ICD concerns and quality of life.[61] CBT is often combined with an exercise program within the cardiac rehabilitation setting. Resuming healthy activity levels is particularly challenging for ICD patients, because patients may be uncertain about the level of activity that is safe to perform without being shocked by the ICD.[61] While exercise training alone has shown to be effective in improving psychological functioning in ICD patients,[61] a combined approach of CBT and exercise training seems to provide additional benefits.[62,63]

The cardiac rehabilitation setting also provides scope for a more detailed psycho-educational program targeted to ICD patients. While it is known that adequate information provision and psycho-education can reduce emotional distress,[64,65] knowledge of the actual information that patients receive and their satisfaction with this information is lacking. **Chapter 10** adds to this knowledge by showing that information about more technical aspects of the ICD and its therapies was adequately communicated to patients, while information about possible ICD-related psychological, social and sexual consequences was less frequently provided. Although in general patient satisfaction was high, about 1 in 3 patients expressed a wish for more information around the time of implantation. Importantly, lower patient satisfaction with information provision was associated with increased symptoms of anxiety. Thus, providing information to patients that suit their needs may increase their satisfaction with treatment and their ICD and reduce anxiety. Obviously, this remains an important target in clinical practice. Given that partners have also expressed their wish for more information[66,67] and that we showed that partners' distress levels influence patients' health status, involving the partner in the treatment process may be appropriate during cardiac rehabilitation, as this provides a unique setting to combine educational, physical, mental and social aspects of ICD treatment. Future research should focus in more detail on information provision wishes of partners of ICD patients, on the most appropriate timing and frequency of information provision, and on the

question how continuity of care, for example via a follow-up phone call, can ideally be facilitated.
CBT is also frequently combined with psychopharmacological treatment. Since tricyclic antidepressants (TCAs) may exert toxic effects on the heart by provoking conductance disorders,[68] SSRIs seem to be the psychopharmacological drugs of first choice in ICD patients. Further advantage of SSRIs is that they have both antidepressant and anxiolytic effects.[69] Although meta-analyses and reviews on the effectiveness of SSRIs to treat depression in patients with CHD have shown clear beneficial effects on depression,[70,71] large-scale trials have also reported non-significant results.[72] Besides, recent animal research has shown that long-term intake of fluoxetine, a SSRI, may reduce the responsiveness to autonomic control of the heart rhythm.[73] This is pertinent with respect to the psychological treatment of ICD patients, since autonomic cardiac control may already be deregulated in these patients.[74] Evidence on the safety and effectiveness of pharmacological treatment in ICD patients is scarce, and more research is warranted.

A small subset of ICD patients suffers from post-traumatic stress disorder (PTSD) (symptoms),[75] which may be treated with eye movement desensitization and reprocessing (EMDR). During treatment, the patient's attention is drawn to an external stimulus via eye movements, auditory tones or hand taps, while simultaneously focusing on the source of the trauma in order to process the trauma in an accelerated way.[76] The effectiveness of EMDR in reducing PTSD symptoms has been demonstrated in the general population,[77] while research in cardiac patients in general and ICD patients in particular is lacking. Extra caution and consultation of a cardiologist's expertise is warranted here, because mentally activating the traumatic event could lead to sudden increases in stress and autonomic arousal, which may be harmful to the ICD patient.

In **Chapter 6**, we found support for lower autonomic control in patients with increased levels of emotional distress.[78] Biofeedback training may be an effective treatment option in ICD patients, with several studies among cardiac patients having found encouraging effects of parasympathetic drive stimulating biofeedback on depressive symptoms[79] and on HRV.[80] Although these results are promising, they should be interpreted with prudence, since study samples are generally small, long-term effects on both psychological and medical outcomes are yet unclear and non significant results have also been published.[81]

Recent research has also revealed some interesting initial results on mindfulness and yoga on (bio)psychological functioning in ICD patients. Meditation practices, an important component of mindfulness therapy, have been associated with reductions in adrenergic arousal, with decreases in premature ventricular contractions in patients with ischemic heart disease.[82] Mindfulness training has previously shown to improve depression and clinical outcomes in heart failure patients,[83] and a recent study has revealed that a phone-delivered mindfulness training was effective in reducing anxiety and improve mindfulness skills in ICD patients.[84] Yoga, another arousal-reducing training, appears to be associated with reductions in anxiety as well, next to reductions in device-treated ventricular events.[85]

Even though the evidence of psychological interventions being effective in reducing emotional distress and improving quality of life is accumulating, it is not known yet whether and how these effects can translate into effects on clinical outcomes, such as morbidity and mortality. To date, the

majority of studies have failed to detect effects of psychological treatment on clinical outcomes. This may partly be explained by methodological limitations of current psychosocial intervention studies, including small samples, heterogeneous interventions, lack of randomization, a relatively high mean age, a wide range of timespan between implantation and start of intervention, lack of information on treatment adherence and lack of screening for patients at risk of emotional distress.[86] Furthermore, an a priori fixed length of treatment without distinguishing effective treatment strategies for subgroups is common in clinical trials, while this may not connect to the patients' needs.[87] However, effects of psychological treatment on patients' well-being have been established, which should be sufficient to justify the value of incorporating psychological treatment in clinical cardiology practice.

Future considerations with respect to psychological treatment

Several other factors that may impact on the success of psychological intervention (studies) in ICD patients should receive attention in future research. First, it is important to consider the patient's needs and preferences for treatment, as positive outcomes of psychological interventions strongly depend on whether the patient is willing to receive help and actually has a question for help. Second, the most optimal timing of treatment start should be examined. Emotional distress of ICD patients tends to decline particularly during the first 3 months post implantation.[88] Linden and colleagues have shown that psychological treatment in cardiac patients may be more effective when started at least 2 months post event, probably due to the natural decline in distress during this initial post event phase.[87] Other factors in relation to treatment accessibility and success, such as resources (i.e. travel distance, health insurance), differences between subgroups of patients and psychological factors other than depression and anxiety, should be topics for further investigation.

Methodological considerations

The results presented in this dissertation should be interpreted with the following limitations in mind. Initial distress was measured only one day prior to implantation, and we have no knowledge of the distress pattern in the period prior to implantation. However, the nature of cardiac disease leading to an indication for ICD implantation makes it impossible to assess distress earlier in at least 35% of patients, who received an ICD due to secondary prevention prophylaxis, which is often suddenly indicated. Furthermore, we only focused on all-cause mortality as an endpoint, as information on cause of death was lacking. Knowledge on cause of death is vital in order to explore which psychobiological mechanisms account for the found relationship, as this could provide us with targets for prevention and treatment. Future research should thus include cause of death. In addition, our results were based on self-report measures of emotional distress and not on clinical diagnoses based on the Diagnostic and Statistical Manual of Mental Disorders (DSM). However, we expect that in general, the relationships that we found would have been stronger in case of clinical diagnoses of emotional distress as compared to self-reported symptoms of anxiety and depression. Furthermore, even minimal symptoms of emotional distress are found to be predictive of prognosis

in cardiac patients and thus to be important.[89] Finally, the results of the current dissertation may not be fully generalizable to all ICD patients. Since our sample predominantly consisted of male patients with a mean age of around 60 years, outcomes may differ for example in younger patients and female patients.

The studies presented in this dissertation also have several strengths. For all chapters except Chapter 6, a relatively large sample of ICD patients (N=448) was used, which promotes the likelihood of sufficient power to detect significant relationships if present. Moreover, the number of partners included simultaneously in this study exceeds that of many other studies investigating the well-being of partners of ICD patients, and the response rate ranging from 96% at baseline to 81% at 12 months follow-up is rather high.[38,90] The availability of an extensive demographic and clinical patient profile in the current study enabled us to control for important potential confounders on top of it. Finally, we used a longitudinal study design, with one distress measurement one day prior to ICD implantation, and four follow-up occasions throughout the first year post implantation. This enabled us to describe how ICD patients and their partners adapt to the implantation throughout the first year post implant.

Box 1. What the current dissertation adds

- ICD patients experiencing complications around and post implantation and patients suffering from comorbid diseases report more emotional distress and poorer physical health status than patients without complications or comorbidities. These patients may require additional cardiac and psychological monitoring and care.
- Cardiac medication use is not associated with symptoms of anxiety and depression and only with some subdomains of health status in ICD patients.
- ICD patients with emotional distress and Type D personality show impaired functioning of the autonomic nervous system.
- Increased heart rate, a marker of autonomic functioning, is associated with poorer prognosis and could be added as an easy-to-measure risk marker in clinical practice.
- Partners of ICD patients experience a similar pattern of emotional distress around and post implantation. Partner emotional distress is related to patient distress, and partner distress partly determines patients' evaluation of their own health status. Involvement of the partner in the adaptation process thus seems to have additional benefits for both patients and partners.
- Information on psychological, social and sexual consequences post implantation is not adequately provided, which is associated with impaired patient satisfaction. This in turn is associated with increased levels of anxiety.
- A substantial number (25%) of ICD patients report emotional distress during the first year post implantation, but paradoxically the majority of these patients are not treated for their distress with potential consequences to health status, morbidity, and mortality.

Concluding remarks

The current dissertation adds to our knowledge of factors that may contribute to the well-being and prognosis of patients with an ICD, which is the current state-of-the-art and first line treatment for the prevention of sudden cardiac death due to life-threatening arrhythmias both as primary

and secondary prophylaxis. Complications around and post implantation and the presence of a higher comorbidity burden increased the risk of emotional distress. Further, we demonstrated that the use of beta-blockers and statins did not contribute substantially to psychological distress in patients. This is important, since underuse of cardiac medication still exists, which could impede the recovery of patients. Furthermore, ANS components, including heart rate variability and heart rate, were shown to be associated with emotional distress and to contribute to poor prognosis. To broaden the scope from the patient as an individual to the patient as part of a dyad, the correlation between patient and partner distress, and the impact of partner distress on patient health status, were also investigated. Distress patterns between patients and partners were largely similar, and partners' distress exerted an effect on patient health status beyond patients' own distress. Future consideration should be given to involving the partner in the treatment process. Finally, as a transition to psychology practice, the relation between delivery of information about the ICD and its possible consequences, patient satisfaction and emotional distress was investigated. Information around the time of implantation was generally well-provided, but information on potential psychological, social and sexual issues post implant were less often discussed. Importantly, decreased patient satisfaction with the provided information was associated with increased anxiety, which underlines the importance of adequate psycho-education around the time of implantation. Unfortunately, our results also demonstrated undertreatment for psychological distress in the ICD population, with a negative association with health status. The implementation of screening for psychological functioning in ICD patients in clinical practice followed by patient-tailored treatment should be given due consideration, in order to identify the subgroup of patients at risk for decreased psychological functioning and optimize the clinical care and management of ICD patients and their partners.

REFERENCES

1. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346(12):877-883.
2. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352(3):225-237.
3. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337(22):1576-1584.
4. Camm J, Nisam S. Implantable cardioverter-defibrillator utilization. Europace 2011;13(3):448.
5. Magyar-Russell G, Thombs BD, Cai JX, Baveja T, Kuhl EA, Singh PP, Montenegro Braga Barroso M, Arthurs E, Roseman M, Amin N, Marine JE, Ziegelstein RC. The prevalence of anxiety and depression in adults with implantable cardioverter defibrillators: A systematic review. J Psychosom Res 2011;71(4):223-231.
6. Sears SF, Conti JB. Quality of life and psychological functioning of ICD patients. Heart 2002;87(5):488-493.
7. Ladwig K-H, Baumert J, Marten-Mittag B, Kolb C, Zrenner B, Schmitt C. Posttraumatic stress symptoms and predicted mortality in patients with implantable cardioverter-defibrillators: Results from the prospective living with an implanted cardioverter-defibrillator study. Arch Gen Psychiatry 2008;65(11):1324-1330.
8. Pedersen SS, Brouwers C, Versteeg H. Psychological vulnerability, ventricular tachyarrhythmias and mortality in implantable cardioverter defibrillator patients: Is there a link? Expert Rev Med Devices 2012;9(4):377-388.
9. Ziegelstein RC, Fauerbach JA, Stevens SS, Romanelli J, Richter DP, Bush DE. Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. Arch Intern Med 2000;160(12):1818-1823.
10. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WMM, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvänne M, Scholte Op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F, guidelines Oewctpot, Cooney MT, Guidelines ECfP, Bax J, Baumgartner H, Ceconi C, Dean V, Fagard R, Funck-Brentano C, Hasdai D, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Ž, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Reviewers D, Aboyans V, Ezquerra EA, Baigent C, Brotons C, Burell G, Ceriello A, De Sutter J, Deckers J, Del Prato S, Diener HC, Fitzsimons D, Fras Z, Hambrecht R, Jankowski P, Keil U, Kirby M, Larsen ML, Mancia G, Manolis AJ, McMurray J, Pająk A, Parkhomenko A, Rallidis L, Rigo F, Rocha E, Ruilope LM, van der Velde E, Vanuzzo D, Viigimaa M, Volpe M, Wiklund O, Wolpert C. 'European guidelines on cardiovascular disease prevention in clinical practice (version 2012)' the fifth joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2012;33(13):1635–1701.
11. Exner DV, Kavanagh KM, Slawnych MP, Mitchell LB, Ramadan D, Aggarwal SG, Noullett C, Van Schaik A, Mitchell RT, Shibata MA, Gulamhussein S, McMeekin J, Tymchak W, Schnell G, Gillis AM, Sheldon RS, Fick GH, Duff HJ. Noninvasive risk assessment early after a myocardial infarction: The REFINE study. J Am Coll Cardiol 2007;50(24):2275-2284.
12. Tung R, Zimetbaum P, Josephson ME. A critical appraisal of implantable cardioverter-defibrillator therapy for the prevention of sudden cardiac death. J Am Coll Cardiol 2008;52(14):1111-1121.
13. Theuns DAMJ, Schaer BA, Soliman OII, Altmann D, Sticherling C, Geleijnse ML, Osswald S, Jordaens L. The prognosis of implantable defibrillator patients treated with cardiac resynchronization therapy: Comorbidity burden as predictor of mortality. Europace 2011;13(1):62-69.
14. Hauptman PJ, Swindle JP, Masoudi FA, Burroughs TE. Underutilization of β-blockers in patients undergoing implantable cardioverter-defibrillator and cardiac resynchronization procedures. Circ Cardiovasc Qual Outcomes 2010;3(2):204-211.
15. Verbeek DEP, Van Riezen J, De Boer RA, Van Melle JP, De Jonge P. A review on the putative association between beta-blockers and depression. Heart Fail Clin 2011;7(1):89-99.
16. Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. JAMA 2002;288(3):351-357.
17. Van Melle JP, Verbeek DEP, Van den Berg MP, Ormel J, Van der Linde MR, De Jonge P. Beta-blockers and depression after myocardial infarction: A multicenter prospective study. J Am Coll Cardiol 2006;48(11):2209-2214.

18. Otte C, Zhao S, Whooley MA. Statin use and risk of depression in patients with coronary heart disease: Longitudinal data from the Heart and Soul study. J Clin Psychiatry 2012;73(5):610-615.
19. Prinz V, Endres M. The acute (cerebro)vascular effects of statins. Anesth Analg 2009;109(2):572-584.
20. Yang CC, Jick SS, Jick H. Lipid-lowering drugs and the risk of depression and suicidal behavior. Arch Intern Med 2003;163(16):1926-1932.
21. You H, Lu W, Zhao S, Hu Z, Zhang J. The relationship between statins and depression: A review of the literature. Expert Opin Pharmacother 2013;14(11):1467-1476.
22. Davidson MH, Robinson JG. Lipid-lowering effects of statins: A comparative review. Expert Opin Pharmacother 2006;7(13):1701-1714.
23. Parsaik AK, Singh B, Hassan Murad M, Singh K, Mascarenhas SS, Williams MD, Lapid MI, Richardson JW, West CP, Rummans TA. Statins use and risk of depression: A systematic review and meta-analysis. J Affect Disord 2013; E-pub ahead of print. doi:10.1016/j.jad.2013.11.026
24. Goryachkina K, Burbello A, Boldueva S, Babak S, Bergman U, Bertilsson L. Inhibition of metoprolol metabolism and potentiation of its effects by paroxetine in routinely treated patients with acute myocardial infarction (AMI). Eur J Clin Pharmacol 2008;64(3):275-282.
25. McCollum DL, Greene JL, McGuire DK. Severe sinus bradycardia after initiation of bupropion therapy: A probable drug-drug interaction with metoprolol. Cardiovasc Drugs Ther 2004;18(4):329-330.
26. Tomaselli GF, Zipes DP. What causes sudden death in heart failure? Circ Res 2004;95(8):754-763.
27. Sterling P, Eyer J, *Allostasis: A new paradigm to explain arousal pathology*, in *Handbook of life stress, cogntition and health*, Fisher S and Reason J., Editors. 1988, New York: John Wiley & Sons.
28. McEwen BS, Stellar E. Stress and the individual: Mechanisms leading to disease. Arch Intern Med 1993;153(18):2093-2101.
29. Lovallo WR, Gerin W. Psychophysiological reactivity: Mechanisms and pathways to cardiovascular disease. Psychosom Med 2003;65(1):36-45.
30. Juster R-P, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci Biobehav Rev 2010;35(1):2-16.
31. Custodis F, Schirmer SH, Baumhäkel M, Heusch G, Böhm M, Laufs U. Vascular pathophysiology in response to increased heart rate. J Am Coll Cardiol 2010;56(24):1973-1983.
32. Korshunov VA, Dyachenko IA, Murashev AN (2013) Genetic determinants of heart rate variation and cardiovascular diseases. 89-103 doi:10.5772/53642.
33. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51(6):1173-1182.
34. Mastenbroek MH, Versteeg H, Jordaens L, Theuns DAMJ, Pedersen SS. Ventricular tachyarrhythmias and mortality in implantable cardioverter defibrillator (ICD) patients: Impact of depression in the MIDAS cohort. Psychosom Med 2014;76(1):58-65.
35. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: A clinical review. Eur Heart J 2013.
36. Van den Broek KC, Habibović M, Pedersen SS. Emotional distress in partners of patients with an implantable cardioverter defibrillator: A systematic review and recommendations for future research. Pacing Clin Electrophysiol 2010;33(12):1442-1450.
37. Pedersen SS, Van Domburg RT, Theuns DAMJ, Jordaens L, Erdman RAM. Type D personality is associated with increased anxiety and depressive symptoms in patients with an implantable cardioverter defibrillator and their partners. Psychosom Med 2004;66(5):714-719.
38. Van den Broek KC, Heijmans N, Van Assen MA. Anxiety and depression in patients with an implantable cardioverter defibrillator and their partners: A longitudinal study. Pacing Clin Electrophysiol 2013;36(3):362-371.
39. Bodenmann G. A systemic-transactional conceptualization of stress and coping. Swiss J Psychol 1995;54(1):34-49.
40. Beckes L, Coan JA. Social baseline theory: The role of social proximity in emotion and economy of action. Soc Personal Psychol Compass 2011;5(12):976-988.
41. Rohrbaugh MJ, Shoham V, Cleary AA, Berman JS, Ewy GA. Health consequences of partner distress in couples coping with heart failure. Heart Lung 2009;38(4):298-305.
42. Rohrbaugh MJ, Shoham V, Coyne JC. Effect of marital quality on eight-year survival of patients with heart failure. Am J Cardiol 2006;98(8):1069-1072.

43. King KB, Reis HT. Marriage and long-term survival after coronary artery bypass grafting. Health Psychol 2012;31(1):55-62.
44. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: The Heart and Soul study. JAMA 2003;290(2):215-221.
45. Gehi A, Haas D, Pipkin S, Whooley MA. Depression and medication adherence in outpatients with coronary heart disease: Findings from the Heart and Soul study. Arch Intern Med 2005;165(21):2508-2513.
46. Glazer KM, Emery CF, Frid DJ, Banyasz RE. Psychological predictors of adherence and outcomes among patients in cardiac rehabilitation. J Cardiopulm Rehabil 2002;22(1):40-46.
47. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure: A meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol 2006;48(8):1527-1537.
48. Habibović M, Pedersen SS, Van den Broek KC, Theuns DAMJ, Jordaens L, Van der Voort PH, Alings M, Denollet J. Anxiety and risk of ventricular arrhythmias or mortality in patients with an implantable cardioverter defibrillator. Psychosom Med 2013;75(1):36-41.
49. Lichtman JH, Bigger JT, Blumenthal JA, Frasure-Smith N, Kaufmann PG, Lespérance F, Mark DB, Sheps DS, Taylor CB, Froelicher ES. Depression and coronary heart disease: Recommendations for screening, referral, and treatment: A science advisory from the American Heart Association prevention committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Psychiatric Association. Circulation 2008;118(17):1768-1775.
50. Thombs BD, De Jonge P, Coyne JC, Whooley. MA, Frasure-Smith N, Mitchell AJ, Zuidersma M, Eze-Nliam C, Lima BB, Smith CG, Soderlund K, Ziegelstein RC. Depression screening and patient outcomes in cardiovascular care: A systematic review. JAMA 2008;300(18):2161-2171.
51. Ziegelstein RC, Thombs BD, Coyne JC, De Jonge P. Routine screening for depression in patients with coronary heart disease: Never mind. J Am Coll Cardiol 2009;54(10):886-890.
52. Smolderen KG, Buchanan DM, Amin AA, Gosch K, Nugent K, Riggs L, Seavey G, Spertus JA. Real-world lessons from the implementation of a depression screening protocol in acute myocardial infarction patients. Circ Cardiovasc Qual Outcomes 2011;4(3):283-292.
53. Sowden G, Mastromauro CA, Januzzi JL, Fricchione GL, Huffman JC. Detection of depression in cardiac inpatients: Feasibility and results of systematic screening. Am Heart J 2010;159(5):780-787.
54. Larsen KK, Vestergaard M, Søndergaard J, Christensen B. Screening for depression in patients with myocardial infarction by general practitioners. Eur J Preve Cardiol 2013;20(5):800-806.
55. Koenig HG. Depression outcome in inpatients with congestive heart failure. Arch Intern Med 2006;166(9):991-996.
56. Pedersen SS, Hoogwegt MT, Jordaens L, Theuns DAMJ. Pre implantation psychological functioning preserved in majority of implantable cardioverter-defibrillator patients. Int J Cardiol 2011;166(1):215-220.
57. Elderon L, Smolderen KG, Na B, Whooley MA. Accuracy and prognostic value of American Heart Association–recommended depression screening in patients with coronary heart disease: Data from the Heart and Soul study. Circ Cardiovasc Qual Outcomes 2011;4(5):533-540.
58. Hasnain M, Vieweg WVR, Lesnefsky EJ, Pandurangi AK. Depression screening in patients with coronary heart disease: A critical evaluation of the AHA guidelines. J Psychosom Res 2011;71(1):6-12.
59. Hoogwegt MT, Kupper N, Theuns DAMJ, Zijlstra WP, Jordaens L, Pedersen SS. Undertreatment of anxiety and depression in patients with an implantable cardioverter-defibrillator: Impact on health status. Health Psychol 2012;31(6):745-753.
60. Beck AT. Thinking and depression: II. Theory and therapy. Arch Gen Psychiatry 1964;10(6):561-571.
61. Dunbar SB, Dougherty CM, Sears SF, Carroll DL, Goldstein NE, Mark DB, McDaniel G, Pressler SJ, Schron E, Wang P, Zeigler VL. Educational and psychological interventions to improve outcomes for recipients of implantable cardioverter defibrillators and their families: A scientific statement from the American Heart Association. Circulation 2012;126(17):2146-2172.
62. Fitchet A, Doherty P, Bundy C, Bell W, Fitzpatrick A, Garratt C. Comprehensive cardiac rehabilitation programme for implantable cardioverter-defibrillator patients: A randomised controlled trial. Heart 2003;89(2):155 - 160.
63. Lewin R, Coulton S, Frizelle D, Kaye G, Cox H. A brief cognitive behavioural pre-implantation and rehabilitation programme for patients receiving an implantable cardioverter defibrillator improves physical health and reduces psychological morbidity and unplanned re-admissions. Heart 2009;95(1), 63-69.

64. Dunbar SB, Langberg JJ, Reilly CM, Viswanathan B, McCarty F, Culler SD, O'Brien MC, Weintraub WS. Effect of a psychoeducational intervention on depression, anxiety, and health resource use in implantable cardioverter defibrillator patients. Pacing Clin Electrophysiol 2009;32(10):1259-1271.

65. Eads AS, Sears SFJ, Sotile WM, Conti JB. Supportive communication with implantable cardioverter defibrillator patients: Seven principles to facilitate psychosocial adjustment. J Cardiopulm Rehabil 2000;20(2):109-114.

66. Harding R, Selman L, Beynon T, Hodson F, Coady E, Read C, Walton M, Gibbs L, Higginson IJ. Meeting the communication and information needs of chronic heart failure patients. J Pain Symptom Manage 2008;36(2):149-156.

67. Van Driel AG, De Hosson MJJ, Gamel C. Sexuality of patients with chronic heart failure and their spouses and the need for information regarding sexuality. Eur J Cardiovasc Nurs 2013; E-pub ahead of print. doi:10.1177/1474515113485521.

68. Glassman AH, Roose SP, Bigger J, Jr. The safety of tricyclic antidepressants in cardiac patients: Risk-benefit reconsidered. JAMA 1993;269(20):2673-2675.

69. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JT Jr., Krishnan KR, Van Zyl LT, Swenson JR, Finkel MS, Landau C, Shapiro PA, Pepine CJ, Mardekian J, Harrison WM, Barton D, McIvor M. Sertraline Antidepressant Heart Attack Randomized Trial (SADHEART) Group. Sertraline treatment of major depression in patients with acute mi or unstable angina. JAMA 2002;288(6):701-709.

70. Pizzi C, Rutjes AWS, Costa GM, Fontana F, Mezzetti A, Manzoli L. Meta-analysis of selective serotonin reuptake inhibitors in patients with depression and coronary heart disease. Am J Cardiol 2011;107(7):972-979.

71. Parissis J, Fountoulaki K, Paraskevaidis I, Kremastinos DT. Sertraline for the treatment of depression in coronary artery disease and heart failure. Expert Opin Pharmacother 2007;8(10):1529-1537.

72. O'Connor CM, Jiang W, Kuchibhatla M, Silva SG, Cuffe MS, Callwood DD, Zakhary B, Stough WG, Arias RM, Rivelli SK, Krishnan R. Safety and efficacy of sertraline for depression in patients with heart failure: Results of the SADHART-CHF (sertraline against depression and heart disease in chronic heart failure) trial. J Am Coll Cardiol 2010;56(9):692-699.

73. Henze M, Tiniakov R, Samarel A, Holmes E, Scrogin K. Chronic fluoxetine reduces autonomic control of cardiac rhythms in rats with congestive heart failure. Am J Physiol Heart Circ Physiol 2013;304(3):H444-H454.

74. Jankowska EA, Ponikowski P, Piepoli MF, Banasiak W, Anker SD, Poole-Wilson PA. Autonomic imbalance and immune activation in chronic heart failure – pathophysiological links. Cardiovasc Res 2006;70(3):434-445.

75. Versteeg H, Theuns DAMJ, Erdman RAM, Jordaens L, Pedersen SS. Posttraumatic stress in implantable cardioverter defibrillator patients: The role of pre-implantation distress and shocks. Int J Cardiol 2011;146(3):438-439.

76. Shapiro F. Eye movement desensitization and reprocessing (EMDR): Evaluation of controlled PTSD research. J Behav Ther Exp Psychiatry 1996;27(3):209-218.

77. Van der Kolk BA, Spinazzola J, Blaustein ME, Hopper JW, Hopper EK, Korn DL, Simpson WB. A randomized clinical trial of eye movement desensitization and reprocessing (EMDR), fluoxetine, and pill placebo in the treatment of posttraumatic stress disorder: Treatment effects and long-term maintenance. J Clin Psychiatry 2007;68(1):37-46.

78. Hoogwegt MT, Pedersen SS, Theuns DAMJ, Kupper N. Relation between emotional distress and heart rate variability in patients with an implantable cardioverter-defibrillator. Psychophysiology 2014;51(2):187-196.

79. Patron E, Messerotti Benvenuti S, Favretto G, Valfrè C, Bonfà C, Gasparotto R, Palomba D. Biofeedback assisted control of respiratory sinus arrhythmia as a biobehavioral intervention for depressive symptoms in patients after cardiac surgery: A preliminary study. Appl Psychophysiol Biofeedback 2013;38(1):1-9.

80. Del Pozo JM, Gevirtz RN, Scher B, Guarneri E. Biofeedback treatment increases heart rate variability in patients with known coronary artery disease. Am Heart J 2004;147(3):545.

81. Wheat AL, Larkin KT. Biofeedback of heart rate variability and related physiology: A critical review. Appl Psychophysiol Biofeedback 2010;35(3):229-242.

82. Benson H, Alexander S, Feldman CL. Decreased premature ventricular contractions through use of the relaxation response in patients with stable ischaemic heart-disease. Lancet 1975;2(7931):380-382.

83. Sullivan MJ, Wood L, Terry J, Brantley J, Charles A, McGee V, Johnson D, Krucoff MW, Rosenberg B, Bosworth HB, Adams K, Cuffe MS. The support, education, and research in chronic heart failure study (SEARCH): A mindfulness-based psychoeducational intervention improves depression and clinical symptoms in patients with chronic heart failure. Am Heart J 2009;157(1):84-90.

84. Salmoirago-Blotcher E, Crawford S, Carmody J, Rosenthal L, Yeh G, Stanley M, Rose K, Browning C, Ockene I. Phone-delivered mindfulness training for patients with implantable cardioverter defibrillators: Results of a pilot randomized controlled trial. Ann Behav Med 2013;46(2):243-250.

85. Toise SCF, Sears SF, Schoenfeld MH, Blitzer ML, Marieb MA, Drury JH, Slade MD, Donohue TJ. Psychosocial and cardiac outcomes of yoga for ICD patients: A randomized clinical control trial. Pacing Clin Electrophysiol 2014;37(1):48-62.
86. Salmoirago-Blotcher E, Ockene I. Methodological limitations of psychosocial interventions in patients with an implantable cardioverter-defibrillator (ICD); A systematic review. BMC Cardiovascular Disorders 2009;9(1):56.
87. Linden W, Phillips MJ, Leclerc J. Psychological treatment of cardiac patients: A meta-analysis. Eur Heart J 2007;28(24):2972-2984.
88. Hoogwegt MT, Kupper N, Jordaens L, Pedersen SS, Theuns DAMJ. Comorbidity burden is associated with poor psychological well-being and physical health status in patients with an implantable cardioverter-defibrillator. Europace 2013;15(10):1468-1474.
89. Pedersen S, Denollet J, Jonge P, Simsek C, Serruys P, Domburg R. Brief depression screening with the PHQ-2 associated with prognosis following percutaneous coronary intervention with paclitaxel-eluting stenting. J Gen Intern Med 2009;24(9):1037-1042.
90. Sowell LV, Sears SFJ, Walker RL, Kuhl EA, Conti JB. Anxiety and marital adjustment in patients with implantable cardioverter defibrillator and their spouses. J Cardiopulm Rehabil Prev 2007;27(1):46-49.

Addendum
Mediation model depression, heart rate and mortality

ADDENDUM: Mediation model depression, heart rate and mortality

In secondary analyses, heart rate was formally tested as a mediator of the relationship between depression and mortality. In order for heart rate to be considered as a mediator, (1) depression should be significantly related to mortality; (2) depression should be significantly related to the proposed mediator heart rate; (3) heart rate should be related to mortality, and (4) the relation between depression and mortality should become non-significant after adjusting for heart rate.[1] Anxiety was left out of consideration, as the association between anxiety and mortality was non significant in the current sample. The association between depression and mortality risk was examined with Cox regression analysis, just as the primary analyses on the relation between heart rate and mortality risk as described in **Chapter 7**. The association between depression and heart rate was assessed with linear regression. For both depression and heart rate, continuous values were used, because depressive symptom levels were equally distributed across the heart rate range. In Cox regression, the relationship between emotional distress and mortality turned out to be significant (HR=1.11, 95% CI=1.06-1.17, p<.001), which has previously been demonstrated in the current sample.[2] Furthermore, the association between depression and heart rate was also significant (β=0.12, t=2.33, p=.020). Subsequently, the relationship between heart rate and mortality was assessed, indicating that heart rate was significantly associated with mortality risk (HR=1.02, 95% CI=1.01-1.03, p=.040). When heart rate was added as a predictor of mortality next to depression, the relation between depression and mortality was unaltered, and remained significant (HR=1.11, 95% CI=1.05 -1.16, p<.001), while continuous heart rate became a non-significant predictor of mortality (HR=1.01, 95% CI=0.99-1.03, p=.07). This leads us to conclude that heart rate does not act as a mediator in the relationship between depression and mortality risk in the current sample.

REFERENCES

1. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51(6):1173-1182.
2. Mastenbroek MH, Versteeg H, Jordaens L, Theuns DAMJ, Pedersen SS. Ventricular tachyarrhythmias and mortality in implantable cardioverter defibrillator (ICD) patients: Impact of depression in the MIDAS cohort. Psychosom Med 2014;76(1):58-65.

Summary in Dutch
Nederlandse samenvatting

SUMMARY IN DUTCH / NEDERLANDSE SAMENVATTING

Plotse hartdood komt voor bij ongeveer 1:1000 tot 1:2000 mensen in de algemene populatie, terwijl individuen met een bestaande coronaire hartziekte ongeveer 50% kans lopen om te overlijden aan plotse hartdood. Een van de oorzaken van plotse hartdood is het optreden van ritmestoornissen van de hartkamers (ventrikels). Deze ventriculaire ritmestoornissen kunnen leiden tot een snel en chaotisch samentrekken van de hartkamers, waardoor de vitale organen te weinig bloed ontvangen wat uiteindelijk kan resulteren in overlijden. De implanteerbare cardioverter-defibrillator (ICD) wordt gezien als de belangrijkste en meest succesvolle vorm van behandeling bij patiënten die een verhoogd risico hebben op plotse hartdood. De ICD wordt net onder de huid in de borst geïmplanteerd en registreert via een of meerdere elektronische draden continue het hartritme. Wanneer een levensbedreigende ventriculaire ritmestoornis optreedt, kan de ICD deze verhelpen door het leveren van antitachycardie pacing of door een elektrische shock. Daarnaast bestaan er ook biventriculaire pacemakers die zorgen voor een gelijktijdig samentrekken van de hartkamers bij patiënten met hartfalen (cardiale resynchronisatie therapie (CRT)) en die eveneens shocks kunnen afgeven bij ventriculaire ritmestoornissen. De ICD werd oorspronkelijk alleen geïmplanteerd bij patiënten die eerder een plotse hartstilstand hebben overleefd (secundaire preventie indicatie). Tegenwoordig zijn de indicatiecriteria echter verruimd en wordt de ICD ook geïmplanteerd bij patiënten die een hoog risico lopen op plotse hartdood, maar nog niet eerder een hartstilstand of ventriculaire ritmestoornissen hebben ervaren (primaire preventie indicatie).

Patiënten met een ICD worden rondom en na de implantatie geconfronteerd met medische en psychologische uitdagingen. Medische uitdagingen zijn onder andere complicaties ten gevolge van de implantatie, en het onderliggend lijden van de patiënt zoals hartfalen en andere gelijktijdige medische aandoeningen, zoals nierfalen, diabetes, perifeer vaatlijden of een aandoening aan de luchtwegen. Daarnaast rapporteert ongeveer 25% van de ICD-patiënten psychologische klachten, waaronder symptomen van depressie, angst, post-traumatische stress en aanpassingsproblemen in het sociale leven. Een aantal factoren dat geassocieerd is met het optreden van psychologische klachten is bekend, waaronder het optreden van shocks en het onderliggend hartlijden. De relatie tussen andere medische factoren enerzijds, zoals medicatiegebruik en de aanwezigheid van andere, gelijktijdige aandoeningen, en psychologisch functioneren anderzijds, was tot op heden echter niet eenduidig.

In dit proefschrift wordt daarom aandacht besteed aan de relatie tussen de medische behandeling en medische patiënt-gerelateerde factoren enerzijds, en het psychologisch functioneren anderzijds. Allereerst werd onderzocht of het optreden van procedure- en ICD-gerelateerde complicaties in de periode van vlak voor implantatie tot 12 maanden erna geassocieerd was met slechter psychologisch welbevinden. In totaal kreeg 17% van de patiënten te maken met een complicatie, waarvan het merendeel ICD-gerelateerd was. Er werd een significante relatie gevonden tussen het optreden van complicaties en symptomen van angst en zorgen om de ICD gedurende de eerste 12 maanden na

implantatie, terwijl er geen relatie werd gevonden tussen complicaties en depressie (**Hoofdstuk 2**). Daarnaast werd gedurende dezelfde periode eveneens onderzocht of er een relatie bestaat tussen de aanwezigheid van andere medische aandoeningen en het psychologisch functioneren (symptomen van depressie en angst en patiënt-gerapporteerde gezondheidstoestand). Hierbij werd gebruikt gemaakt van een aangepaste versie van de Charlson Comorbidity Index (CCI), een samenvattingsmaat voor het aantal andere aanwezige medische aandoeningen die ook rekening houdt met de ernst van de aandoeningen en waarin leeftijd ook als risicofactor werd meegenomen. In tegenstelling tot complicaties, die geassocieerd waren met meer angst, was de aanwezigheid van andere medische aandoeningen geassocieerd met meer depressie en een verslechtering in fysieke gezondheidstoestand. De aanwezigheid van chronisch hartfalen, chronisch obstructieve longziekten, cerebrovasculaire aandoeningen en nierfalen waren de belangrijkste voorspellers van depressie en een verslechterde gezondheidstoestand (**Hoofdstuk 3**). Uit dit hoofdstuk bleek eveneens dat de prevalentie van gelijktijdig voorkomende medische aandoeningen bij ICD-patiënten hoog is. Om deze aandoeningen te behandelen, gebruikt het grootste deel van de ICD patiënten meerdere cardiale en niet-cardiale medicijnen. De mogelijke relatie tussen dit medicijngebruik en de psychologische toestand van de patiënt heeft in het verleden veel stof doen opwaaien. In dit proefschrift werd daarom onderzocht of het gebruik van bètablokkers en statinen geassocieerd was met het psychologisch functioneren van de ICD-patiënt, waarbij rekening werd gehouden met het type bètablokker en statine. Er werd geen significante relatie gevonden tussen het gebruik van bèta-blokkers en symptomen van depressie, angst en ICD-gerelateerde zorgen (**Hoofdstuk 4**). Dit is in overeenstemming met een groot deel van de bestaande recente literatuur. Daarentegen rapporteerden patiënten die statinen gebruikten een slechtere gezondheidstoestand dan patiënten die geen statinen gebruikten, vooral op het gebied van fysieke en emotionele rolbeperkingen en sociaal functioneren. Er werd geen relatie gevonden tussen het gebruik van statinen en symptomen van depressie en angst (**Hoofdstuk 5**). Het uitbreiden van kennis over de relatie tussen medische factoren die te maken hebben met de implantatie en bijkomende (hart) aandoeningen, en het psychologisch functioneren van de patiënt is belangrijk, omdat op deze manier de patiënten die een hoog risico lopen op het ontwikkelen van psychologische problemen gemakkelijker herkend kunnen worden.

In het tweede deel van dit proefschrift is het functioneren van het autonome zenuwstelsel van ICD-patiënten onderzocht. Het autonome zenuwstelsel heeft een belangrijke regulerende functie in het lichaam en stuurt organen aan, waaronder het hart. Sympathische en parasympathische (vagale) zenuwtakken verbinden het centrale gedeelte van het autonome zenuwstelsel met het hart, waarmee geleiding, hartslag, en het samentrekken van het hart worden gereguleerd. Het autonome zenuwstelsel heeft een belangrijk aandeel in de ontwikkeling van ritmestoornissen, waarbij een verschuiving wordt gezien van de sympatho-vagale aansturing naar sympathisch gedomineerde aansturing. Goed functioneren van het autonome zenuwstelsel is dus een belangrijke voorspeller voor de prognose van de patiënt.

Hartslagvariabiliteit (HRV) is de schommeling in het tijdsinterval tussen twee opeenvolgende hartslagen en wordt veelvuldig gebruikt als maat van autonome controle. In dit proefschrift werd HRV gemeten met behulp van 24-uurs Holter monitoring. Psychologische klachten, zoals symptomen van depressie, angst en post-traumatische stress, zijn in eerder onderzoek in verband gebracht met HRV binnen de algemene en de cardiale populatie, waarbij een relatie werd gevonden tussen depressie en angst en een verlaagde HRV. Omdat autonoom functioneren van groot belang is bij de ontwikkeling van ritmestoornissen, werd deze relatie verder onderzocht. Bij ICD-patiënten met een Type D persoonlijkheid werd een lagere autonome sturing over het hele etmaal, en een lagere parasympathische sturing tijdens periodes van rust gevonden. Daarnaast werden bij patiënten met verhoogde depressiescores ook indicaties gevonden voor verstoorde hartregulatie door het parasympathische zenuwstelsel tijdens rust en slaap (**Hoofdstuk 6**). De gevonden verhoogde sympathische en verlaagde parasympathische sturing bij ICD-patiënten met meer psychologische klachten zou de ontwikkeling van ventriculaire ritmestoornissen kunnen bevorderen. Gezien de kleine steekproef die in dit onderzoek gebruikt werd, is meer onderzoek onder een groter aantal ICD-patiënten nodig om deze relaties te repliceren en goed onderbouwde conclusies te kunnen trekken.

Het belang van een goed functionerend autonoom zenuwstelsel voor de prognose van ICD-patiënten lijkt dus evident. In deze patiëntenpopulatie is hier echter nog weinig onderzoek naar verricht. In dit proefschrift werd daarom onderzocht of er een relatie bestaat tussen de hartslag en de QRS-duur (de depolarisatiefase van de hartkamers) enerzijds, en het risico op overlijden anderzijds. Een hogere hartslag, zowel bij een grenswaarde van ≥80 slagen per minuut, als continue gemeten, bleek geassocieerd te zijn met een slechtere prognose, onafhankelijk van een aantal belangrijke medische en psychologische factoren. De relatie tussen QRS-duur en het risico op overlijden bleek verklaard te worden door de aanwezigheid van gelijktijdig voorkomende andere medische aandoeningen. Deel 2 van dit proefschrift laat dus zien dat psychologische klachten gerelateerd zijn aan een minder goed werkend autonoom zenuwstelsel, en dat een minder goed functionerend autonoom zenuwstelsel een hoger overlijdensrisico met zich meebrengt.

Wetenschappelijk onderzoek heeft zich tot op heden voornamelijk gericht op de patiënt, terwijl de partner eventuele ICD-therapieën of een hartstilstand ook van dichtbij meemaakt. Uit eerder onderzoek is bekend dat partners evenveel of zelfs meer psychologische klachten rapporteren dan de patiënt zelf, waarbij met name angst een belangrijke rol lijkt te spelen bij de partner. Aandacht voor het psychologisch functioneren van de partner is belangrijk, omdat psychologische problematiek bijvoorbeeld kan leiden tot overbeschermend gedrag richting de patiënt. De relatie tussen het psychologisch functioneren van de patiënt en de partner werd daarom gedurende 12 maanden na ICD implantatie onderzocht, evenals de impact van psychologische klachten bij de partner op de subjectieve gezondheidstoestand van de patiënt. Het psychologische klachtenpatroon bleek overeen te komen tussen patiënten en hun partners, zowel rond implantatie als gedurende de 12 maanden erna. De gezondheidstoestand van de patiënten rond implantatie en gedurende de 12 maanden erna bleek voornamelijk bepaald te worden door hun eigen psychologische

klachtenpatroon, al waren symptomen van depressie en angst bij de partner daarbovenop ook voorspellend voor de subjectieve gezondheidstoestand van de patiënt (**Hoofdstuk 8**). Dit geeft aan dat de partner een belangrijke toegevoegde rol vervult in het aanpassingsproces van de patiënt. Het belang van het betrekken van de partner bij de begeleiding van de patiënt rond en na implantatie is hiermee onderstreept, evenals het feit dat psychologische klachten ook bij partners voorkomen en professionele aandacht verdienen.

Naast een aandeel van de partner in het psychologische functioneren van de patiënt, zou de partner ook van invloed kunnen zijn op medische uitkomsten. Het wel of niet getrouwd zijn en psychologische klachten bij de patiënt zelf zijn bekende risicofactoren voor overlijden van de patiënt, maar over de aanwezigheid van psychologische klachten bij de partner als voorspeller van overlijdensrisico is weinig bekend. In dit proefschrift is daarom onderzocht of psychologische klachten van de partner het overlijdensrisico van de patiënt konden voorspellen, bovenop de psychologische klachten die de patiënt zelf rapporteerde. Psychologische klachten van de partner leken de kans op overlijden van de patiënt te voorspellen, maar dit effect werd niet-significant wanneer de psychologische klachten van de patiënt werden meegenomen. Psychologische klachten van de partner bleken dus geen toegevoegde voorspellende waarde te hebben met betrekking tot het overlijdensrisico van de patiënt (**Hoofdstuk 9**). Desondanks hebben de resultaten van **Hoofdstuk 8** aangetoond dat het belangrijk blijft de partner te betrekken bij de behandeling van de ICD-patiënt. Hierdoor is de kans op een optimaal psychologisch herstel van zowel patiënt als partner en een hernieuwde, evenwichtige relatie tussen patiënt en partner groter.

Voor het aanpassingsproces van de patiënt zijn begrip van de redenen voor ICD implantatie, het onderliggende medische probleem en de mogelijke medische, psychologische en sociale implicaties voor het dagelijks leven belangrijk. Eerder onderzoek heeft uitgewezen dat adequate informatievoorziening en psycho-educatie het bestaan van psychologische klachten bij ICD patiënten kunnen verminderen. Er is echter nauwelijks onderzoek verricht naar de mate van informatievoorziening rondom implantatie, en wat de behoeften van de patiënt hierin zijn. Dit werd onderzocht in dit proefschrift. Naar voren kwam dat informatie over de meer technische aspecten van de ICD en de medische oorzaak voor implantatie, evenals informatie over fysieke beperkingen en beperkingen in het autorijden frequent met patiënten besproken werd (in zo'n 80-99% van de gevallen). Informatie over psychologische, sociale en seksuele gevolgen van ICD implantatie werd echter met slechts 57-64% van de patiënten besproken. Ongeveer een derde van de patiënten wenste rondom implantatie meer informatie over al deze onderwerpen te ontvangen. Daarnaast werd duidelijk dat patiënten die minder tevreden zijn over de informatievoorziening, meer angst ervaren. Een goede informatievoorziening rondom implantatie kan dus bijdragen aan een beter begrip van de noodzaak en eventuele gevolgen van de ICD-implantatie bij de patiënt, evenals een betere aanpassing aan het leven met een ICD. De klinisch psycholoog zou hierin een belangrijke rol kunnen spelen, omdat is aangetoond dat artsen, maar ook verpleegkundigen en ander zorgpersoneel, moeite kunnen hebben met het ter sprake brengen van dit soort voor de patiënt belangrijke onderwerpen.

Hoewel een aanzienlijk deel van de ICD-patiënten aangeeft last te hebben van depressie, angst of andere klachten die het dagelijks functioneren kunnen belemmeren, betekent dit niet automatisch dat deze patiënten op een adequate manier psychologisch worden begeleid. In dit proefschrift werd daarom onderzocht of de patiënten met verhoogde niveaus van depressie en angst in de praktijk psychologisch werden behandeld, en of het niet behandelen van deze kwetsbare groep zou samengaan met een slechtere subjectieve gezondheidstoestand. Een belangrijke bevinding van dit proefschrift was dat ongeveer twee derde van de patiënten met verhoogde niveaus van depressie en angst geen psychologische behandeling in de vorm van psychotrope medicatie of behandeling door een psycholoog onderging. Dit leek bovendien een negatieve weerslag te hebben op de gezondheidstoestand van deze patiënten. Daarnaast leek de behandeling die patiënten wel kregen, niet altijd aan te sluiten bij de behoeften van de patiënt, wat gereflecteerd werd door de laagste subjectieve gezondheidstoestand van patiënten die psychologische problemen hadden en hier wél voor werden behandeld (**Hoofdstuk 11**). Het feit dat psychologische behandeling bij de meeste patiënten werd gegeven in de vorm van psychotrope medicatie en niet in de vorm van gesprekstherapie bij een psycholoog, zou hiervoor een verklaring kunnen zijn. Het is dus van groot belang dat het signaleren van psychologische klachten in een vroeg stadium plaatsvindt, en de gekozen psychologische behandeling aansluit bij de behoeften van de patiënt en diens eventuele partner.

Dit proefschrift heeft bijgedragen aan de kennis op het gebied van factoren die een rol spelen bij het welzijn en de prognose van patiënten met een ICD. Complicaties rondom en na de implantatie en de aanwezigheid van andere medische aandoeningen zijn gerelateerd aan een verslechterd psychologisch functioneren van de patiënt. Het gebruik van twee belangrijke soorten cardiale medicatie, namelijk bètablokkers en statinen, bleek nauwelijks geassocieerd te zijn met het psychologisch functioneren van ICD-patiënten. Dit is een belangrijke bevinding, omdat er helaas nog steeds sprake is van ondergebruik van cardiale medicatie en dit een belangrijke beperking kan zijn voor zowel fysiek als mentaal herstel van de patiënt. Verder werd in dit proefschrift aangetoond dat HRV en hartslag, beide indicatoren van het functioneren van het autonome zenuwstelsel, gerelateerd waren aan psychologisch functioneren en prognose. In dit proefschrift werd ook getracht de samenhang tussen het psychologisch functioneren van patiënt en partner in kaart te brengen, en werd onderzocht of een slechter psychologisch functioneren van de partner van invloed was op de subjectieve gezondheidstoestand van de patiënt. Het psychologisch functioneren van patiënt en partner bleek voor een belangrijk deel samen te hangen, en psychologische problemen bij de partner bleken een negatieve weerslag te hebben op de gezondheidstoestand van de patiënt. In de toekomst zal onderzocht moeten worden hoe de partner het beste bij het begeleidingsproces na ICD-implantatie kan worden betrokken en zelf ook psychologische hulp zou kunnen krijgen, mocht dat nodig zijn .

Informatievoorziening is een belangrijk middel om het aanpassingsproces van de patiënt aan het leven met de ICD te vergemakkelijken. Met name informatie over psychologische, sociale en seksuele gevolgen van ICD implantatie bleek met een aanzienlijk deel van de patiënten niet te zijn besproken, met een lagere patiënttevredenheid als gevolg. Deze lagere patiënttevredenheid was

geassocieerd met meer angstklachten, wat aangeeft hoe belangrijk een goede informatievoorziening rondom implantatie is. Ten slotte werd in dit proefschrift aangetoond dat een groot deel van de patiënten met psychologische problemen geen adequate psychologische behandeling kreeg. Het implementeren van psychologische screening is dan ook een belangrijk doel voor de klinische praktijk, waarbij het ziekenhuis een geschikte plaats lijkt om deze screening uit te voeren. Wanneer deze screening gecombineerd wordt met een psychologische behandeling op maat die aansluit bij de wensen en behoeften van de patiënt, waarbij gedacht kan worden aan cognitieve gedragstherapie, psychotrope medicatie, eye movement desensitization and reprocessing (EMDR) therapie, een multidisciplinair hartrevalidatieprogramma, biofeedback of mindfulness, zou de zorg voor de ICD-patiënt en diens partner verbeterd kunnen worden.

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List of publications

PUBLICATIONS

Hoogwegt MT, Theuns DAMJ, Pedersen SS, Kupper N. Long-term mortality risk in patients with an implantable cardioverter-defibrillator: Influence of heart rate and QRS duration. Int J Cardiol 2014; doi:10.1016/j.ijcard.2014.06.030

Hoogwegt MT, Pedersen SS, Theuns DAMJ, Jordaens L, Kupper N. Association between Type D personality, depression, implantable cardioverter-defibrillator concerns and heart rate variability. Psychophysiol 2014;51(2):187-196.

Versteeg H, **Hoogwegt MT**, Hansen TB, Pedersen SS, Zwisler A-D, Thygesen LC. Depression, not anxiety, is independently associated with 5-year hospitalizations and mortality in patients with ischemic heart disease. J Psychosom Res 2013;75(6):518-525.

Hoogwegt MT, Versteeg H, Hansen TB, Thygesen LC, Pedersen SS, Zwisler AD. Exercise mediates the association between positive affect and mortality in patients with ischemic heart disease up to 5 years follow-up. Circ Cardiovasc Qual Outcomes 2013;6(5):559-566

Hoogwegt MT, Kupper N, Jordaens L, Pedersen SS, Theuns DAMJ. Comorbidity burden is associated with poor psychological well being and physical health status in patients with an implantable cardioverter-defibrillator. Europace 2013;15(10):1468-1474

Pedersen SS, **Hoogwegt MT**, Jordaens L, Theuns DAMJ. Procedure- and device related complications and psychological morbidity in implantable cardioverter-defibrillator patients. Int J Cardiol 2013;168(1):606-607

Hoogwegt MT, Theuns DAMJ, Kupper N, Jordaens L, Pedersen SS. Relation of statin therapy to psychological functioning in patients with an implantable cardioverter-defibrillator. Am J Cardiol 2013;111(8):1169-1174.

Pedersen SS, **Hoogwegt MT**, Jordaens L, Theuns DAMJ. Pre implantation psychological functioning preserved in majority of implantable cardioverter-defibrillator patients 12 months post implantation. Int J Cardiol 2013;166(1):215-220.

Hoogwegt MT, Schiffer AAJJ, Smolderen KG & Denollet J. Psychologie en Geneeskunde. Behavioural Medicine. Chapter 5: Ischemische hart- en vaatziekten (2012). Houten: Bohn Stafleu van Loghum.

Pedersen SS, Tekle FB, **Hoogwegt MT**, Jordaens L, Theuns DAMJ. Shock and patient preimplantation Type D personality are associated with poor health status in patients with implantable cardioverter-defibrillator. Circ Cardiovasc Qual Outcomes 2012;5(3):373-380.

Hoogwegt MT, Kupper N, Theuns DAMJ, Zijlstra WP, Jordaens L, Pedersen SS. Undertreatment of anxiety and depression in patients with an implantable cardioverter-defibrillator: Impact on health status. Health Psychol 2012;31(6):745-753.

Hoogwegt MT, Kupper N, Theuns DAMJ, Jordaens L, Pedersen SS. Beta-blocker therapy is not associated with symptoms of anxiety and depression in patients receiving an implantable cardioverter-defibrillator. Europace 2012;14(1):74-80.

Pedersen SS, **Hoogwegt MT**, Jordaens L, Theuns DAMJ. Relation of symptomatic heart failure and psychological status to persistent depression in patients with implantable cardioverter defibrillator. Am J Cardiol 2011;108(1):69-74.

Hoogwegt MT, Hoeks SE, Pedersen SS, Scholte op Reimer WJM, Van Gestel YRBM, Verhagen HJM, Poldermans D. Smoking cessation has no influence on quality of life in patients with peripheral arterial disease 5 years post-vascular surgery. Eur J Vasc Endovasc Surg 2010;40(3):355-362.

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Madelein Hoogwegt was born on July 17, 1985 in Venlo, the Netherlands. She finished high school at the Van Maerlant Lyceum in Eindhoven in 2004, and subsequently studied Medicine at Leiden University Medical Center for one year. After finding out that the field of psychology better suited her interests and qualities, she started studying Psychology in 2005 and obtained her bachelor's degree in Clinical Psychology at Leiden University in 2008. Next, she obtained her master's degree in Medical Psychology at Tilburg University in 2010. In September 2010, she started her PhD-project at Tilburg University. From April 2014, Madelein Hoogwegt is working as a psychologist at Ikazia Hospital, Rotterdam.