Depression, anxiety and quality of life the first 12 months post implant: A matched cohort study of patients with a subcutaneous implantable defibrillator versus patients with a transvenous system

(From the EFFORTLESS S-ICD Quality of Life Substudy)

Susanne S Pedersen[1,2], Nathan Carter[3], Craig Barr[4], Petr Neuzil[5], Marcoen Scholten[6], Pier D Lambiase[7,] Lucas Boersma[8], Jens Brock Johansen[,2], Dominic AMJ Theuns[9] on behalf of the EFFORTLESS Investigators

[1]Department of Psychology, University of Southern Denmark, Odense, Denmark
[2]Department of Cardiology, Odense University Hospital, Odense, Denmark
[3]Boston Scientific Corporation, St Paul MN, USA
[4]Department of Cardiology, Russels Hall Hospital, Dudley, UK
[5]Department of Cardiology, Homolka Hospital, Prague, Czech Republic
[6]Department of Cardiology, Thorax Center Twente, Medisch Spectrum Twente, Enschede, the Netherlands
[7]Institute of Cardiovascular Science, University College London & Barts Heart Centre, London, UK
[8]St Antonius Ziekenhuis, Nieuwegein, the Netherlands
[9]Department of Cardiology, Erasmus Medical Center, Rotterdam, the Netherlands

Total number of tables and figures: 5

***Corresponding author:** Susanne S Pedersen (PhD), Department of Psychology, University of Southern Denmark, Campusvej 55, DK-5230 Odense M, Denmark.

Phone: +45 65 50 79 92; *Fax (none); E-mail:* sspedersen@health.sdu.dk

ABSTRACT

Aims: The subcutaneous implantable defibrillator (S-ICD) is a safe and effective alternative to the transvenous (TV)-ICD system, but little is known about the impact of type of device on patient-reported outcomes. We compared S-ICD patients with TV-ICD patients and the influence of device type, personality, heart failure severity, and shocks on QoL, depression, and anxiety up to 12 months' follow-up.

Methods: A matched cohort of S-ICD (N=167) and TV-ICD patients (N=167) completed measures on QoL, depression, anxiety and personality at baseline, 3-, 6- and 12 months post implant. Data were analysed using multivariate modelling with repeated measures.

Results: In adjusted analyses, we found no statistically significant differences between cohorts on physical and mental QoL and depression up to 12 months post implant (all *p*s>0.05), while S-ICD patients reported lower anxiety (*p*=0.0007). Both cohorts experienced improvements in physical and mental QoL and a decrease in depression and anxiety over time (all *p*s<0.001). Both cohorts experienced similar improvements in physical and mental QoL and anxiety scores over time (*p*s>0.05), while S-ICD patients experienced greater reductions in depressive symptoms (*p*=0.0317).

Conclusions: The QoL of S-ICD and TV-ICD patients and improvements in QoL over time were similar for both cohorts. S-ICD patients reported lower anxiety but similar depression levels to TV-ICD patients. During follow-up S-ICD patients experienced a greater reduction in depression over time as compared to TV-ICD patients.

Keywords: Anxiety; depression; implantable cardioverter defibrillator; quality of life; subcutaneous.

Abstract word count: 225

CONDENSED ABSTRACT

S-ICD and TV-ICD patients experienced similar levels of quality of life and depression up to 12 months' post implant. S-ICD patients reported lower anxiety levels and experienced greater improvements in depression during follow-up as compared to TV-ICD patients.

WHAT'S NEW

- To our knowledge this is the first study to report on prospective data on quality of life and anxiety and depression up to 12 months' follow-up in patients with a subcutaneous implantable cardioverter defibrillator S-(ICD) as compared to patients with a transvenous (TV)-ICD system
- S-ICD and TV-ICD patients experienced similar levels of quality of life and depression
- Both cohorts experienced improvements in quality of life and depression and anxiety levels during the 12 months' follow-up period
- Patients with an S-ICD reported lower anxiety levels and experienced greater improvements in depression during follow-up as compared to TV-ICD patients

INTRODUCTION

The entirely subcutaneous implantable defibrillator (S-ICD) has gained recognition as a safe and effective alternative to the transvenous (TV)-ICD system [1, 2]. Initially, the S-ICD was a device for the selected few, including young patients, patients with a high risk of infection, or patients with inadequate vascular access [2]. Since the S-ICD received approval from the US Food and Drug Administration in 2012, there has been a general increase in use of the device, with the number of implants increasing from 985 in the international Evaluation of Factors Impacting Clinical Outcome and Cost Effectiveness of the S-ICD (EFFORTLESS S-ICD) Registry to 1637 devices S-ICD Post Approval Study and with current US S-ICD trends showing an implant rate of 3717 devices [2]. This suggests a paradigm shift towards the S-ICD being considered in present-day ICD candidates.

The S-ICD is included in the European Society of Cardiology and in the American Heart Association (AHA), the American College of Cardiology (ACC) and the Heart Rhythm Society (HRS) guidelines as an indication in patients with inadequate vascular access, high risk of infection, and in patients not dependent on pacing therapy for bradycardia or antitachycardia, or resynchronization therapy [3, 4]. However, data on quality of life (QoL) and depression and anxiety in patients with an S-ICD as compared to patients with a TV-ICD system are scarce, albeit the recommendation from both the American Heart Association and the European Society of Cardiology that the assessment of QoL and patient reported outcomes (PROs) is important in clinical studies [5, 6].

We have previously published the results of a comparison of patients with an S-ICD from the EFFORTLESS S-ICD Registry and patients with a TV-ICD system from the MIDAS cohort (**M**ood and personality as precipitants of arrhythmia in patients with an **I**mplantable cardioverter **D**efibrillator: **A** prospective **S**tudy) on QoL up to 6 months of follow-up [7]. EFFORTLESS was designed to evaluate the clinical and system performance of the S-ICD and the impact of the device on PROs in the “real world” [1, 8]. In the EFFORTLESS QoL substudy, we found no statistically significant differences between patients with an S-ICD versus a TV-ICD system on QoL at baseline, 3- and 6 months follow-up in adjusted analyses

[7]. In addition, the QoL of both cohorts improved significantly between time of implant and 3 months and 6 months, respectively, but not between 3 and 6 months. To our knowledge, Köbe and colleagues from Germany are the only other investigators that have compared the QoL of patients with the S-ICD to a matched cohort with a TV-ICD system, using a cross-sectional study design that also examined potential differences between the two cohorts on psychological disorders [9]. Hence, to our knowledge we have no data on QoL beyond 6 months of follow-up and no prospective data on psychological disorders in patients with an S-ICD.

Hence in the current study, we compared patients with an S-ICD from the EFFORTLESS QoL substudy to patients with a TV-ICD system from the MIDAS study on QoL and symptoms of depression and anxiety up to 12 months post implant and examined the predictors of these study endpoints at 12 months follow-up.

METHODS

Participants and design

We used a matched case-control cohort design. Details of the two cohorts have been published elsewhere [7, 8]. In brief, the S-ICD patients (N=167; mean age=54.0 ± 15.7; 73.1% men) were recruited between March 2011 and July 2014 from 29 sites in Europe and New Zealand for the international EFFORTLESS S-ICD registry and were eligible for inclusion if they also participated in the QoL substudy. The EFFORTLESS S-ICD Registry QoL was designed to use the MIDAS cohort as a comparison group [8]. The TV-ICD patients (N=167; mean age=53.8 ± 13.2; 71.9% men) were also first-time implant patients and recruited as part of the MIDAS study between August 2003 and February 2010 from the Erasmus Medical Center, Rotterdam, the Netherlands [10, 11]. Both cohorts were matched on a priori selected baseline characteristics including baseline physical and mental QoL scores, using propensity score matching. Prior to matching, MIDAS patients with an indication for bradycardia or resynchronization therapy were excluded, as these patients would not be eligible for an S-ICD system [3].

Measures

Demographic and clinical variables

Information on demographic and clinical variables were captured either from patients' electronic health records or purpose-designed questions that patients were asked to complete as part of a questionnaire package that also contained standardized and validated measures.

Quality of life

We assessed QoL with the Short Form Health Survey 12 (SF-12) [12]. The SF-12 is a generic measure that consists of 12 items. Based on an algorithm, the 12 items are converted to a scale from 0-100 that contribute to the Physical Component Summary (PCS) score and the Mental Component Summary (MSC) score, respectively. For both QoL dimensions, 100 represents the best QoL. The validity and reliability of the SF-12 has previously been established in patients with heart disease [13]. Patients completed the SF-12 at 4 timepoints (i.e., at baseline, 3-, 6- and 12 months post implant).

Depression and anxiety

We measured symptoms of depression and anxiety with the Hospital Anxiety and Depression Scale (HADS) [14]. The HADS is comprised of 14 items that are answered on a four-point Likert scale from 0-3, with 7 items contributing to the depression score and 7 items contributing to the anxiety score (score range for both is 0-21). A higher symptom score indicates more depression and anxiety symptom severity. The HADS has frequently been used to assess anxiety and depression in the general population, patients with somatic disease, including heart disease, and primary care and psychiatric patients [15, 16]. It has been shown to perform well in assessing both caseness of anxiety and depression disorders and symptom severity in these populations [15, 16] and to predict mortality in patients with acute coronary syndrome [17, 18] and in patients with ICD [19]. More recent studies and reviews have been somewhat critical of the HADS, due to difficulties with confirming the scale's two-factor

structure of anxiety and depression, [20, 21]. Patients completed the HADS at 4 timepoints (i.e., at baseline, 3-, 6- and 12 months post implant). A cut-off of 8 or higher for both the depression and anxiety subscale is most commonly used, reflecting a mild level of symptomatology and also the best balance between sensitivity and specificity [16].

Type D personality

Type D personality – also called the *distressed personality type* – was assessed with the 14-item Type D Scale (DS14) [22], which with 7 items contribute to the negative affectivity (e.g. *'I often feel unhappy'*) and social inhibition (e.g. *'I am a closed kind of person'*) subscales, respectively. Items are rated on a 5-point Likert scale from 0-4, with the score range for each of the traits being 0-28. A score of ≥10 on both traits typify those who have a Type D personality, with Item Response Theory showing this cut-off to be the most optimal [22, 23]. The validity and internal consistency of the DS14 have been demonstrated previously, with Cronbach's alpha of 0.80 for negative affectivity and 0.86 for social inhibition [22]. As Type D personality has been associated with poor compliance, increased risk of depression and anxiety, poor quality of life and premature death in patients with heart disease and patients with an ICD [11, 24], it was included in both the MIDAS study and the EFFORTLESS S-ICD registry due to its potential impact on PROs and clinical outcomes. Patients only completed the DS14 at baseline.

Ethics

Medical ethics committees in each participating country of the EFFORTLESS S-ICD Registry study approved the study protocol. The medical ethics committee of the Erasmus Medical Center, Rotterdam, the Netherlands, approved the MIDAS study protocol (MEC # 231.491/2003/148 - September 9, 2003). The EFFORTLESS S-ICD Registry was also registered on http://www.ClinicalTrials.gov (NCT01085435). Both the EFFORTLESS S-ICD Registry and the MIDAS study were conducted according to the Helsinki Declaration. All

participating patients received oral and written information about the study and provided written informed consent.

Statistical analysis

As patients with an indication for cardiac resynchronization therapy, bradycardia, or a secondary prevention indication due to monomorphic VTs are not eligible for an S-ICD system, these patients were excluded from the MIDAS cohort prior to propensity score matching. Subsequently, EFFORTLESS and MIDAS patients 1:1 were matched on a priori selected variables that included age, gender, indication for ICD (primary versus secondary), ischemic versus non-ischemic etiology, and baseline mental and physical QoL. We used the greedy matching algorithm with the recommended caliper width by Austin when performing the propensity score matching [25]. Data on QoL, depression and anxiety across baseline, 3-, 6-, and 12 months were analyzed using multivariable modeling with repeated measures. In the multivariable modeling, we also considered the time *by* ICD system (S-ICD versus TV-ICD) interaction, provided that it was statistically significant ($p<0.05$). For all study endpoints (i.e., mental QoL, physical QoL, depression, and anxiety), two models were run.

In model 1, we adjusted for Type D personality, shocks (any) during 12 months' follow-up, New York Heart Association (NYHA) functional class III-IV, low educational level, amiodarone, treatment for psychological problems, and cardiac rehabilitation attendance. These variables were selected a priori based on the literature.

In model 2, we added all baseline variables that were systematically different between the EFFORTLESS and MIDAS cohorts despite matching to the variables in model 1. All data were analyzed using SAS version 9.4

RESULTS

Baseline characteristics

As indicated in Table 1, patients with an S-ICD system did not differ systematically from patients with a TV-ICD system on the majority of baseline characteristics. However, S-ICD

patients were less likely to have ventricular fibrillation as index arrhythmia (20% vs. 30%, *p*=0.0480) and to be on statins (30% vs. 45%, *p*=0.0047) but more likely to have ventricular tachycardia as index arrhythmia (5% vs. 1%, *p*=0.0426), diabetes (19% vs. 10%, *p*=0.0183), heart failure (41% vs. 17%, *p*<0.0001) and to be on diuretics (48% vs. 34%, *p*=0.0105) as compared to TV-ICD patients. S-ICD patients had a shorter QRS duration (105 ± 21 vs. 112 ± 27, *p*=0.0071) and a lower score on anxiety as compared to TV-ICD patients (mean ±SD 5.3±3.8 vs. 6.5±3.7, *p*=0.0047).

Comparison of patients with an S-ICD versus a TV-ICD system on QoL

When comparing patients with an S-ICD versus a TV-ICD system on QoL during the course of 12-months' follow-up, differences were found on physical QoL despite adjustment for a priori selected covariates but not on mental QoL (Table 2, model 1). S-ICD patients experienced somewhat lower physical QoL than the TV-ICD patients. When adjusting for both a priori selected covariates and baseline differences between the two cohorts, there were no statistically significant differences between S-ICD and TV-ICD patients on physical and mental QoL at baseline, 3-, 6-, and 12 months post implant (Table 2, model 2). There was a main effect for time for both physical (*p*<0.0001) and mental (*p*<0.0001) QoL, with QoL in both cohorts improving over time. For physical QoL, there was a significant improvement between baseline and 3 months (*p*<0.0001), baseline and 6 months (*p*<0.0001), baseline and 12 months (*p*<0.0001), but not between 3 and 6 months, 3 and 12 months, and 6 and 12 months (all *p*s>0.05). Similar results were found for mental QoL, except that there was a significant improvement between 6 and 12 months (*p*=0.0141). The evolution in mean scores over time was similar for both cohorts, as the interaction effects for time by both physical and mental QoL were non-significant (both *p*s>0.05).

Figure 1. shows the absolute mean differences in unadjusted physical and mental QoL during the course of 12 months' follow-up, stratified by ICD system (S-ICD versus TV-ICD), heart failure (NYHA class I-II versus III-IV), personality (Type D versus non-Type D), and shocks during follow-up (shocks versus no shocks). For physical QoL, the differentiation in

mean scores between the two ICD systems (range: 0.1-2.7), heart failure class (range: 7.9-10.1), personality type (range: 3.8-6.6), and shocks (range: 1.2-4.2) across follow-up shows that the greatest difference in physical QoL is found between NYHA class I-II and III-IV and the least difference between the two ICD systems. For mental QoL, the differentiation in mean scores between the two ICD systems (range: 0.3-2.4), heart failure class (range: 4.0-6.1), personality (range: 8.9-10.2), and shocks (range: 0.9-2.9) across follow-up shows that the greatest difference in mental QoL was found between Type D versus non-Type D and the least difference between the two ICD systems.

Type D (distressed) personality, severe heart failure (NYHA III-IV), use of diuretics, and diabetes were independent predictors of poor physical QoL (all *p*s<0.05). Type D personality, severe heart failure (NYHA III-IV), low educational level, being treated for depression / anxiety were independent predictors of poor mental QoL, while use of statins and increased QRS duration were associated with better mental QoL.

Comparison of patients with an S-ICD versus a TV-ICD on depression and anxiety

We found no statistically significant differences between S-ICD and TV-ICD patients on depression at baseline, 3-, 6-, and 12 months post implant when adjusting for the interaction effect for time *by* study, and a priori selected variables (*p*=0.3354) (Table 3, model 1), while a difference was found on anxiety *p*<.0001), with S-ICD patients scoring lower on anxiety. With additional adjustment for differences on baseline characteristics between the two cohorts, there were still no statistically significant differences on depression between S-ICD and TV-ICD patients (*p*=0.3354), while a difference was found for anxiety, with S-ICD patients experiencing lower scores at all time points (*p*=0.0007) (Table 3, model 2). There was a main effect for time for both depression (*p*=0.0074) and anxiety (*p*<0.0001), with symptoms decreasing in both cohorts over time. The improvements were found between baseline and 3 months, baseline and 6 months, baseline and 12 months (all *ps*<0.01), but not between 3 and 6 months, 3 and 12 months, and 6 and 12 months (all *p*s>0.05). The evolution in mean anxiety scores over time was similar for both cohorts (*p*=0.0539). For depression scores, the

interaction between study cohort and time was significant (p=0.0317), with S-ICD patients experiencing greater reductions in depressive symptoms over time.

Figure 2. shows the absolute mean differences in unadjusted symptoms of depression and anxiety during the course of 12 months' follow-up, stratified by ICD system (S-ICD versus TV-ICD), heart failure class (NYHA class I-II versus III-IV), personality (Type D versus non-Type D), and shocks during follow-up (shocks versus no shocks). For depression, the differentiation in mean scores between the two ICD systems (range: 0-0.5), heart failure class (range: 1.5-1.19), personality type (range: 3.4-4.2), and shocks (range: 0.7-1.2) across follow-up shows that the greatest difference in depression was found between Type D versus non-Type D and the least difference between the two ICD systems. For anxiety, the differentiation in mean scores between the two ICD systems (range: 1.2-2.1), heart failure class (range: 0.2-0.6), personality type (range: 3.2-4.5), and shocks (range: 0.1-1.2) across follow-up shows that the greatest difference in anxiety was found between Type D versus non-Type D, followed by device type, while the least difference was found between heart failure I-II versus III-IV.

Type D (distressed) personality, dilated cardiomyopathy, and psychological treatment were independent predictors of depression (all ps<0.05). Type D and psychological treatment were associated with increased depression scores while dilated cardiomyopathy was associated with decreased depression scores. Type D personality was the only independent predictor of anxiety (p<0.0001), with risk being increased in patients with this personality profile. Neither severe heart failure (NYHA III-IV) nor shocks during follow-up were significantly associated with depression and anxiety (ps >0.05).

DISCUSSION

The objectives of the current study were to examine potential differences in QoL, depression and anxiety in patients with an S-ICD versus TV-ICD system and the influence of device type, personality, heart failure severity, and shocks on QoL, depression, and anxiety up to 12 months' follow-up, using data from the international EFFORTLESS registry and the MIDAS

study. We found no statistically significant differences in physical and mental QoL and depression between S-ICD and TV-ICD patients between time of implant and up to 12 months' follow-up, adjusting for potential confounders. However, we did find a difference in anxiety, with S-ICD patients scoring lower on anxiety at all time points. S-ICD patients also experienced greater reductions in depressive symptoms over time.

Previously, we examined the physical and mental QoL of S-ICD versus TV-ICD patients and found no differences up to 6 months' follow-up [7]. The results of the current study confirm and extend these results, as S-ICD and TV-ICD patients reported similar physical and mental QoL up to 12 months and experienced similar QoL improvements between implant and follow-up. A recent cross-sectional case-control study comparing 60 S-ICD patients to 60 TV-ICD patients on QoL and psychological disorders, including posttraumatic disorder, found no differences between groups on psychological disorders and mental QoL, while physical QoL was more impaired in TV-ICD patients [9]. To our knowledge, our previous study, the current study and that of Kobe and colleagues[9] represent the only studies that have compared the QoL and the prevalence of psychological disorders in patients with an S-ICD versus a TV-ICD. While we await the results of the ongoing large-scale, randomized, controlled, multicenter, prospective PRAETORIAN trial that also include QoL as a secondary endpoint [26], available studies point towards slightly more favourable outcomes in S-ICD patients. When the S-ICD was initially launched, there was great concern in the arrhythmia community that the size and the weight of the device would lead to poorer QoL in these patients [27]. So far there is no evidence to support this notion. In addition, the size and weight of the S-ICD has been reduced with the second generation EMBLEM™ S-ICD system.

In the current study, other factors, such as personality (Type D) and heart failure class, had a greater influence on the physical and mental QoL and symptoms of depression and anxiety than type of device (S-ICD versus TV-ICD) and shocks during follow-up. This result is consistent with that of other studies in TV-ICD patients, showing that severity of heart failure [28], lower perceived control [29, 30], anxiety [29], depression [29], and Type D personality[30] had a greater impact on QoL than e.g. shocks. One study comparing patients with an ICD without

heart failure, patients with heart failure but no ICD, and patients with heart failure and ICD, in order to examine the relative influence on QoL of heart failure versus device placement showed that disease severity had a greater impact than device placement itself [28]. Nevertheless, patients with an S-ICD system reported a lower anxiety score and experienced a greater reduction in their depression score than TV-ICD patients. We can only speculate why S-ICD patients experienced less anxiety than TV-ICD patients in the current study, but the absence of leads in and on the vasculature of the heart may play a role, although this needs to be replicated in future studies.

The current study has some limitations. The S-ICD patients were recruited internationally across multiple centers, but the TV-ICD patients from the MIDAS cohort were recruited from a single center and during the course of 7 years as compared to 3 years for the EFFORTLESS S-ICD patients. However, the mean QoL scores of the MIDAS cohort were similar to those found in other cohorts with a TV-ICD system [31, 32]. As the indication for an S-ICD differs from that of a TV-ICD system, patients from the MIDAS cohort with an indication for cardiac resynchronization therapy, bradycardia, or a secondary prevention indication due to monomorphic VTs were excluded prior to propensity score matching, as they are not eligible for an S-ICD system. Despite matching on a priori selected characteristics, the two cohorts differed on some characteristics, warranting that we adjusted for these in the statistical analyses. The current study also has several strengths. To our knowledge, it is the first prospective study that compares S-ICD versus TV-ICD patients on physical and mental QoL and depression and anxiety with data up to 12 months' follow-up. The two cohorts are also well described both with respect to their demographic, clinical and psychological profile, and medication use.

In conclusion, these first results on prospective data up to 12 months of follow-up of S-ICD versus a TV-ICD system on QoL, depression, and anxiety show that patients with an S-ICD experience similar QoL and are not at greater risk of experiencing depression as compared to patients with an TV-ICD system. With respect to anxiety and reductions in depressive symptoms during the course of follow-up, S-ICD patients seem to have a more

favorable course with less anxiety and greater reduction in depressive symptoms during follow-up.

Table 1. Baseline characteristics for the EFFORTLESS (S-ICD) and MIDAS (TV-ICD) cohorts

Characteristics	EFFORTLESS (S-ICD system) (n = 167)	MIDAS (TV-ICD system) (n = 167)	*p*
Demographics			
Men	122 (73%)	120 (72%)	0.8065
Age, mean ±SD (years)	54 ± 16	55 ± 13	0.8831
Low education (<13 years)	73 (45%)	90 (55%)	0.0597
Clinical, comorbidities and previous events			
Primary prevention indication	123 (74%)	115 (69%)	0.3334
Ventricular fibrillation as index arrhythmia	32 (20%)	50 (30%)	**0.0480**
Ventricular tachycardia as index arrhythmia	8 (5%)	2 (1%)	**0.0426**
QRS duration	105 ± 21	112 ± 27	**0.0071**
Severe heart failure (NYHA III-IV)	20 (12%)	24 (15%)	0.5313
Heart failure	69 (41%)	28 (17%)	**<0.0001**
Atrial fibrillation	36 (22%)	30 (18%)	0.4097
Diabetes mellitus	31 (19%)	16 (10%)	**0.0183**
Renal failure (60 ml/kg/1.73m^2)	13 (8%)	23 (14%)	0.0841
Transient ischemic attack *or* stroke	13 (8%)	8 (5%)	0.2781
Dilated cardiomyopathy	25 (15%)	39 (23%)	0.0516
Ischemic cardiomyopathy	12 (7%)	12 (7%)	1.0000
Hypertrophic cardiomyopathy	22 (13%)	18 (11%)	0.5002

Previous myocardial infarction	66 (40%)	68 (40%)	0.8223
Previous percutaneous coronary intervention	32 (19%)	42 (25%)	0.1877
Previous coronary bypass	17 (10%)	17 (10%)	1.0000
Medication			
Angiotension converting enzyme inhibitors	92 (55%)	106 (64%)	0.1190
Beta-blockers	125 (75%)	133 (80%)	0.2964
Statins	50 (30%)	75 (45%)	**0.0047**
Diuretics	80 (48%)	57 (34%)	**0.0105**
Amiodarone	15 (9%)	12 (7%)	0.5470
Digoxin	10 (6%)	17 (10%)	0.1600
Other treatment			
Cardiac rehabilitation	7 (4%)	11 (7%)	0.3593
Treatment for psychological problems [1]	9 (5%)	14 (8%)	0.2798
Psychological and QoL			
Type D personality	44 (27%)	35 (21%)	0.2461
Physical QoL, mean ±SD	41 ± 12	41 ± 11	0.9787
Mental QoL, mean ±SD	42 ± 12	43 ± 12	0.8697
Depression[2] mean ±SD	4.6±3.9	4.2±3.6	0.3504
% depression (cut-off ≥8)	38 (23%)	28 (17%)	0.1691
Anxiety[2], mean ±SD	5.3±3.8	6.5±3.7	**0.0047**
% anxiety (cut-off ≥8)	41 (25%)	56 (34%)	0.0703

[1] Currently seeing a social worker, psychologist or psychiatrist for psychological problems

[2] Assessed with the Hospital Anxiety and Depression Scale (HADS)

Table 2. Physical and mental quality of life of patients with an S-ICD system versus a TV system up to 12 months post implant

	EFFORTLESS (S-ICD system) *Mean [95% CI]*	**MIDAS (TV-ICD system)** *Mean [95% CI]*	*p-value*
Model 1 [a]			
Physical QoL (PCS*)*			
Baseline	39.36 [37.75-40.96]	41.61 [40.02-43.21]	0.0329
3 months	42.40 [40.84-43.95]	44.65 [43.10-46.20]	
6 months	42.29 [40.69-43.90]	44.55 [42.95-46.14]	
12 months	42.95 [41.26-44.64]	45.21 [43.55-46.86]	
Mental QoL (MCS)			
Baseline	41.70 [40.11-43.29]	42.92 [41.33-44.51]	0.2353
3 months	45.11 [43.52-46.71]	46.33 [44.75-47.91]	
6 months	44.56 [42.88-46.23]	45.78 [44.11-47.45]	
12 months	45.87 [44.17-47.57]	47.09 [45.41-48.75]	
Model 2 [b]			
Physical QoL (PCS*)*			
Baseline	40.46 [38.66-42.27]	41.00 [39.35-42.67]	0.6665
3 months	43.48 [41.69-45.27]	44.02 [42.38-45.65]	

6 months	43.38 [41.55-45.21]	43.91 [42.24-45.59]	
12 months	43.94 [42.04-45.83]	44.47 [42.75-46.20]	
Mental QoL (MSC*)*			
Baseline	42.44 [40.63-44.25]	42.54 [40.87-44.20]	0.9388
3 months	45.75 [43.92-47.58]	45.85 [44.16-47.53]	
6 months	45.13 [43.22-47.04]	45.23 [43.46-47.00]	
12 months	46.32 [44.50-48.36]	45.52 [44.75-48.29]	

[a] *adjusted for a priori selected covariates*

[b] *adjusted for a priori selected covariates and baseline differences between the two cohorts*

Table 3. Depression and anxiety of patients with an S-ICD system versus a TV-ICD system up to 12 months post implant

	EFFORTLESS (S-ICD system) *Mean [95% CI]*	**MIDAS (TV-ICD system)** *Mean [95% CI]*	*p-value*
Model 1 [a]			
Depression			
Baseline	4.60 [0.26-4.08]	4.19 [0.27-3.67]	0.7264
3 months	3.73 [0.27-3.19]	4.19 [0.28-3.63]	
6 months	4.16 [0.28-3.60]	4.08 [0.30-3.50]	
12 months	3.69 [0.27-3.16]	4.19 [0.31-3.59]	
Anxiety			
Baseline	5.31 [0.26-4.80]	6.46 [0.26-5.94]	<.0001
3 months	3.76 [0.28-3.22]	5.62 [0.28-5.06]	
6 months	4.32 [0.30-3.74]	5.46 [0,31-4.85]	
12 months	3.81 [0.28-3.26]	5.60 [0,31-4.98]	
Model 2 [b]			
Depression			
Baseline	4.83 [0.28-4.29]	4.02 [0.31-3.42]	0.3354
3 months	3.96 [0.29-3.39]	3.91 [0.32-3.27]	

6 months	4.40 [0.30-3.81]	3.78 [0.34-3.11]	
12 months	3.92 [0.28-3.37]	3.83 [0.35-3.15]	
Anxiety			
Baseline	5.43 [0.28-4.89]	6.55 [0.31-5.94]	0.0007
3 months	3.87 [0.29-3.30]	5.69 [0.33-5.04]	
6 months	4.44 [0.32-3.82]	5.50 [0.36-4.80]	
12 months	3.92 [0.29-3.34]	5.63 [0.35-4.94]	

[a] *adjusted for the interaction effect for time by study and a priori selected covariates*

[b] *adjusted for the interaction effect for time by study, a priori selected covariates and baseline differences between the two cohorts*

Figure 1. Mean (SD) scores on physical and mental quality of life (QoL) stratified by ICD system, NYHA class, Type D personality and shocks during 12 months' follow-up*

**** QoL score range is 0-100 (100=best QoL)***

Figure 2. Mean (SD) scores on depression and anxiety stratified by ICD system, NYHA class, Type D personality and shocks during 12 months' follow-up*

**** Depression and anxiety score range is 0-21 (21=worst symptom score)***

ACKNOWLEDGEMENTS

We would like to thank all of the Investigators in the EFFORTLESS S-ICD Registry who contributed with patients to the Quality of Life Substudy.

FUNDING

The EFFORTLESS S-ICD Registry is sponsored in its entirety by Boston Scientific Corporation, St. Paul, Minnesota, USA. The MIDAS study was supported with a VENI grant (451-05-001) from the Netherlands Organisation for Scientific Research (NWO) and a VIDI grant (91710393) from the Netherlands Organisation for Health Research and Development (ZonMw), the Hague, the Netherlands to Professor Susanne S Pedersen.

CONFLICTS OF INTEREST

SSP has served as a consultant for Boston Scientific and has received speaker's fee from Servier and Astra-Zeneca, and independent research grants from Medtronic and Boston Scientific.

NC is an employee of Boston Scientific.

CB has no disclosures to report.

PN has no disclosures to report.

MS has no disclosures to report.

PDL serves as a consultant for Boston Scientific and have educational grants from Boston Scientific, St. Jude Medical and Medtronic. He is supported by UCLH Biomedicine NIHR.

LB serves as a consultant for Boston Scientific.

JBJ has no disclosures to report.

DAMJT serves as a consultant for Boston Scientific and has received research grants from Boston Scientific, Biotronik, and St. Jude Medical.

REFERENCES

[1] Lambiase PD, Barr C, Theuns DA, Knops R, Neuzil P, Johansen JB, et al. Worldwide experience with a totally subcutaneous implantable defibrillator: early results from the EFFORTLESS S-ICD Registry. *Eur Heart J* 2014; **35**: 1657-1665.

[2] Adduci C, Palano F, Francia P. Safety, Efficacy and Evidence Base for Use of the Subcutaneous Implantable Cardioverter Defibrillator. *J Clin Med* 2018; **7**.

[3] Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015; **36**: 2793-2867.

[4] Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Executive summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm* 2018; **15**: e190-e252.

[5] Anker SD, Agewall S, Borggrefe M, Calvert M, Jaime Caro J, Cowie MR, et al. The importance of patient-reported outcomes: a call for their comprehensive integration in cardiovascular clinical trials. *Eur Heart J* 2014; **35**: 2001-2009.

[6] Rumsfeld JS, Alexander KP, Goff DCJ, Graham MM, Ho PM, Masoudi FA, et al. Cardiovascular health: the importance of measuring patient-reported health status: a scientific statement from the American Heart Association. *Circulation* 2013; **127**: 2233-2249.

[7] Pedersen SS, Mastenbroek MH, Carter N, Barr C, Neuzil P, Scholten M, et al. A Comparison of the Quality of Life of Patients With an Entirely Subcutaneous Implantable Defibrillator System Versus a Transvenous System (from the EFFORTLESS S-ICD Quality of Life Substudy). *Am J Cardiol* 2016; **118**: 520-526.

[8] Pedersen SS, Lambiase P, Boersma LV, Murgatroyd F, Johansen JB, Reeve H, et al. Evaluation oF FactORs ImpacTing CLinical Outcome and Cost EffectiveneSS of the S-ICD: design and rationale of the EFFORTLESS S-ICD Registry. *Pacing and clinical electrophysiology : PACE* 2012; **35**: 574-579.

[9] Kobe J, Hucklenbroich K, Geisendorfer N, Bettin M, Frommeyer G, Reinke F, et al. Posttraumatic stress and quality of life with the totally subcutaneous compared to conventional cardioverter-defibrillator systems. *Clin Res Cardiol* 2017; **106**: 317-321.

[10] 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**: 1119-1126.

[11] Pedersen SS, Tekle FB, Hoogwegt MT, Jordaens L, Theuns DA. Shock and patient preimplantation Type D personality are associated with poor health status in patients with implantable cardioverter-defibrillator. *Circulation Cardiovascular Quality and Outcomes* 2012; **5**: 373-380.

[12] Ware JJ, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; **34**: 220-233.

[13] De Smedt D, Clays E, Doyle F, Kotseva K, Prugger C, Pajak A, et al. Validity and reliability of three commonly used quality of life measures in a large European population of coronary heart disease patients. *Int J Cardiol* 2013; **167**: 2294-2299.

[14] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**: 361-370.

[15] Farquhar JM, Stonerock GL, Blumenthal JA. Treatment of Anxiety in Patients With Coronary Heart Disease: A Systematic Review. *Psychosomatics* 2018; **59**: 318-332.
[16] 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.
[17] Doyle F, McGee HM, De La Harpe D, Shelley E, Conroy R. The Hospital Anxiety and Depression Scale depression subscale, but not the Beck Depression Inventory-Fast Scale, identifies patients with acute coronary syndrome at elevated risk of 1-year mortality. *J Psychosom Res* 2006; **60**: 461-467.
[18] Damen NL, Versteeg H, Boersma E, Serruys PW, van Geuns RJ, Denollet J, et al. 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**: 2496-2501.
[19] Mastenbroek MH, Versteeg H, Jordaens L, Theuns DA, Pedersen SS. Ventricular tachyarrhythmias and mortality in patients with an implantable cardioverter defibrillator: impact of depression in the MIDAS cohort. *Psychosom Med* 2014; **76**: 58-65.
[20] Cosco TD, Doyle F, Ward M, McGee H. Latent structure of the Hospital Anxiety And Depression Scale: a 10-year systematic review. *J Psychosom Res* 2012; **72**: 180-184.
[21] Emons WH, Sijtsma K, Pedersen SS. Dimensionality of the hospital anxiety and depression scale (HADS) in cardiac patients: comparison of Mokken scale analysis and factor analysis. *Assessment* 2012; **19**: 337-353.
[22] Denollet J. DS14: standard assessment of negative affectivity, social inhibition, and Type D personality. *Psychosom Med* 2005; **67**: 89-97.
[23] Emons WH, 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**: 27-39.
[24] Versteeg H, Spek V, Pedersen SS, Denollet J. Type D personality and health status in cardiovascular disease populations: a meta-analysis of prospective studies. *Eur J Prev Cardiol* 2012; **19**: 1373-1380.
[25] Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011; **10**: 150-161.
[26] Olde Nordkamp LR, Knops RE, Bardy GH, Blaauw Y, Boersma LV, Bos JS, et al. Rationale and design of the PRAETORIAN trial: a Prospective, RAndomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy. *Am Heart J* 2012; **163**: 753-760 e752.
[27] Santini M, Cappato R, Andresen D, Brachmann J, Davies DW, Cleland J, et al. Current state of knowledge and experts' perspective on the subcutaneous implantable cardioverter-defibrillator. *J Interv Card Electrophysiol* 2009; **25**: 83-88.
[28] Habibovic M, Versteeg H, Pelle AJ, Theuns DA, Jordaens L, Pedersen SS. Poor health status and distress in cardiac patients: the role of device therapy vs. underlying heart disease. *Europace* 2013; **15**: 355-361.
[29] Hammash M, McEvedy SM, Wright J, Cameron J, Miller J, Ski CF, et al. Perceived control and quality of life among recipients of implantable cardioverter defibrillator. *Aust Crit Care* 2018.
[30] Israelsson J, Thylen I, Stromberg A, Bremer A, Arestedt K. Factors associated with health-related quality of life among cardiac arrest survivors treated with an implantable cardioverter-defibrillator. *Resuscitation* 2018; **132**: 78-84.
[31] Berg SK, Svendsen JH, Zwisler AD, Pedersen BD, Preisler P, Siersbaek-Hansen L, et al. COPE-ICD: a randomised clinical trial studying the effects and meaning of a

comprehensive rehabilitation programme for ICD recipients -design, intervention and population. *BMC Cardiovasc Disord* 2011; **11**: 33.

[32] Chair SY, Lee CK, Choi KC, Sears SF. Quality of life outcomes in chinese patients with implantable cardioverter defibrillators. *Pacing Clin Electrophysiol* 2011; **34**: 858-867.