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Research paper

Patients with an implantable cardioverter defibrillator at risk of poorer psychological health during 24 months of follow-up (results from the Danish national DEFIB-WOMEN study)

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ABSTRACT

Objective: Identify implantable cardioverter defibrillator (ICD) patients at risk of distress (i.e., depression, anxiety, and ICD concerns) and associated risk factors.
Method: First-time ICD patients (n = 1503) from the Danish national DEFIB-WOMEN study completed questionnaires at baseline, 3, 6, 12 and 24 months.
Results: Of patients with low scores on distress, only 4%–7.2% experienced an increase in distress during 24 months of follow-up (FU), while 30.5%–52.5% with increased levels were likely to maintain increased levels at FU. Higher education, higher age, female sex, and good physical functioning at baseline were associated with less depression, anxiety and ICD concerns at FU. Previous psychological problems, smoking, Type D personality, NYHA class III-IV – all assessed at baseline – and shocks during FU were associated with depression, anxiety and ICD concerns.
Conclusions: Generally, patients' psychological health improved, but patients with increased baseline scores were more likely to have increased scores at FU. We need to be vigilant if patients report elevated distress, particularly if they have depression at baseline, as depression seems more persistent. Given the impact of depression on health-related quality of life and prognosis, they should be screened and monitored closely.

1. Introduction

Most patients with an implantable cardioverter defibrillator (ICD) manage to live a full life with their device and balance the pros and cons associated with ICD therapy. Some patients refer to this as a 'love-hate' relationship [1]. On the one hand, the ICD will save their life in the event of a life-threatening ventricular tachyarrhythmia, as the ICD monitors the heart rhythm and will provide appropriate treatment, such as anti-tachycardia pacing or/and one or more shocks to restore the heart to a normal rhythm. On the other hand, the life-saving high-voltage shock therapy is painful if the patient is conscious and may instill fear [2]. In turn, this may lead to anxiety. An estimated 20% of patients with an ICD suffer from symptoms of anxiety [3]. A recent study shows that of those patients who have elevated symptoms of anxiety, as many as 84% of these patients also have one or more anxiety diagnoses [4]. Due to the concern for further ICD shocks, patients can develop symptoms of hypervigilance, which may deter them from engaging in activities that they used to enjoy. This behavior increases the risk of depression, which carries a prevalence between 11%-28% in ICD patients [3], and leads to impaired health-related quality of life (HRQoL) in subsets of patients

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[5]. Hence, it is not surprising that the impact of shocks has received considerable attention in the ICD literature [6] and that guidelines provide advice how to manage patients with shocks in the clinic [7].

However, it is important to understand that fear of shocks may in some cases have a larger impact on patients' lives than actual shocks. In a prospective cohort study of Dutch patients with an ICD, patients with a high score on ICD concerns prior to implant had a 2-fold higher risk of mortality than patients scoring low on ICD concerns [2]. In patients scoring high on ICD concerns and who also had a distressed (Type D) personality, their risk for mortality increased to >3-fold [2]. All items in the ICD Concerns Questionnaire (ICDC) tap into patients' concerns about shocks (e.g., I am worried about *"My ICD firing"*; *"Having no warning that my ICD will fire"*; "*Doing activities/hobbies that may cause my ICD to fire"*) [8].

Given evidence that anxiety and depression are associated with impaired HRQoL and greater risk of premature death despite state-of-the-art treatment with ICD therapy, and independent of traditional risk factors in this population [2,9,10] and poorer HRQoL [5], it is paramount to identify and treat the subset of patients with psychological distress early on. Hence, based on data from the national Danish DEFIB-WOMEN cohort [11], the objective of the current study is to identify *(1)* patients at risk of poorer psychological health (i.e., depression, anxiety, and ICD concerns) between the time of implantation and 24 months of FU, and *(2)* risk factors associated with poorer psychological health between implantation and follow-up.

2. Method

2.1. Study design

The DEFIB-WOMEN study (Utilization of implantable cardioverter DEFIBrillator therapy in the treatment of heart disease: Clinical and psychological outcomes in WOMEN) was initiated in 2010 and is a Danish national, multi-center observational study. The study was designed – among other things – to examine potential sex differences in patient-reported and clinical outcomes [11]. Patients who received a first-time ICD were consecutively recruited between June 2010 to April 2013 from the five university hospitals (Odense University Hospital, Aalborg University Hospital, Aarhus University Hospital, Copenhagen University Hospital, and Gentofte University Hospital) implanting ICDs in Denmark at that time.

2.1.1. Eligibility and recruitment

Patients with a first time ICD or ICD with resynchronization therapy (CRT-D—) and 18 years or older were eligible for inclusion into the study provided that they were not on the waiting list for heart transplantation, had a left ventricular assist device, a history of severe psychiatric illness, or insufficient knowledge of the Danish language to complete questionnaires [11].

Out of 2914 patients who received an ICD at one of the five participating centers, 1598 were screened and 1503 were eligible for participation in the current study, gave initial consent and did not withdraw consent during the study period. We had to exclude six patients who had no data and 89 patients who had missing scores on the ICDC [8,12,13], the Hospital Anxiety and Depression Scale (HADS-A or HADS-D) at baseline or who had no other measurement than the ICDC, HADS-A or HADS-D than at baseline.

Patients for the DEFIB-WOMEN study were recruited between June 10 to April 2013 [11]. A study nurse at each of the participating hospitals approached patients for participation one day after implantation and prior to discharge from the hospital. All patients received oral and written information about the study and patients provided written informed consent. Patients who were included into the study received a questionnaire with a self-addressed stamped envelope with the instruction to return the questionnaire within 7 days post discharge to the hospital. A reminder with a new questionnaire was sent to patients if the questionnaire was not received within 7 days. Follow-up questionnaires were sent out to patients with the same instruction to return the questionnaire within 7 days and with a reminder sent to patients if they did not adhere to the deadline.

2.1.2. Ethics

We submitted the study protocol to the Regional Committee on Health Research Ethics in the Region of Southern Denmark. According to Danish law, the protocol does not require their approval. The study protocol was also submitted to and approved by the Danish Data Protection Agency via the Umbrella Scheme of the Region of Southern Denmark (Odense University Hospital # 16/30926). The Danish Data Protection Agency supervises the compliance with the rules on protection of personal data and is an independent authority. The study was conducted in accordance with the Helsinki Declaration and all patients received information about the study and provided written informed consent.

2.1.3. Measures and data collected

Information on demographic and clinical variables are captured from patients' medical records, the Danish Pacemaker and ICD Register (e.g., shocks, device-related complications), the Danish National Patient Register, and purpose-designed questions that were added to the questionnaires that patients complete at baseline and FU. For full details, see the design article [11]. In addition, patients completed the Hospital Anxiety and Depression Scale (HADS) [13], the ICD Concerns Questionnaire (ICDC) [8], the Short Form Health Survey (SF-36) [14], and the Type D Scale (DS14) [15] at baseline, and at 3-, 6-, 12- and 24 months of follow-up. The HADS consists of 14 items, with 7 items measuring anxiety (HADS-A) and 7 items depressive symptoms (HADS-D). The score range for the HADS-A and HADS-D is 0–21, with a higher score indicating a higher symptom level [13]. Generally, a cut-off of ≥8 is used to indicate clinically relevant levels of distress that warrant treatment [16]. The ICDC is an 8-item questionnaire that measures patients' concerns about the ICD giving a shock. The score range is from 0 –32, with a higher score indicating more concerns [8]. The SF-36 taps into physical and mental functioning [14]. In the current study, we only used the physical functioning scale, as the focus of the paper was on changes in psychological health that were measured with other questionnaires, including the ICDC, which is a disease-specific measure. The DS14 measures the presence of the distressed (Type D) personality. The scale consists of 14 items that contribute to two subscales (i.e., Negative Affectivity and Social Inhibition) with 7 items contributing to each. Patients with a score of 10 on both subscales are classified as having a Type D personality [15].

2.1.4. Statistical analyses

We compared baseline demographic and clinical characteristics between the study population and excluded patients, using the Chi-square test for categorical variables and Student's *t*-test for continuous variables, where missing categories were excluded.

To ensure comparability of scores on HADS-A, HADS-D and the ICDC, we first transferred all scores to a scale from 0-100. To determine the number of patients who experience a worsening in depression, anxiety, and ICD concerns during follow-up, we used patients' scores on the HADS-A, HADS-D and ICDC at baseline and compared them to their scores at 6, 12, and 24 months, respectively. We decided to use the baseline assessment as the reference category for all follow-ups, as it enables the immediate identification of patients at risk of increased psychological distress. To assess changes from baseline, we examined both means and standard deviations of the scores as well as (binary) categorisation into normal and increased levels. Increased levels were scores ≥8 for both HADS-A and HADS-D and ≥ 13 for ICDC.

For each of the three outcomes, i.e., changes from baseline for HADS-A, HADS-D and ICDC based on the transferred scores, we estimated a separate multivariable linear mixed model, including a random

intercept for each individual patient. We considered the following a-priori defined covariates: FU times (categorical: 3 months as reference, 6, 12 and 24 months), continuous baseline score (transferred), female sex (yes), age (in categories, 60+ vs. 20–59), smoking (yes), married / partner (yes), working (yes), education ≥10 years (yes), NYHA III-IV (yes), secondary prevention indication (yes), Type D personality at baseline (yes), physical functioning (SF-36 PCS) (categorized in tertiles at baseline: low [7.7-], middle [37.7-], upper tertile [46.9–70.7]), IHD diagnosis (yes), device type: Single/Dual vs. CRT-D as reference category, left ventricular ejection fraction (LVEF >35%) (yes), Beta-blockers (yes), psychotropic medication (yes), previous psychological problems (defined as self-reported psychological treatment and/or a psychiatric diagnosis (yes)), and shocks but only in the period before (yes) related to the FU times. All covariates except for shocks in the previous period were measured at baseline. Potential missing covariates were analyzed together with the majority category for all covariates except for physical functioning, where missing values were grouped together with the middle tertile. Corresponding univariable regression models were also estimated. All statistical analyses were performed using StataCorp 2019. Stata Statistical Software: Release 17. College Station,TX: StataCorp LLC. For all tests, a *p*-value of <0.05 was considered statistically significant.

3. Results

Baseline demographic and clinical characteristics of the study population versus excluded patients are shown in Table 1. Patients excluded from the study population were less likely to be on statins, more likely to have a secondary prevention ICD indication, a higher categorical (≥8) HADS-A score, a higher mean HADS-A (SD) score, a higher categorial (≥8) HADS-D, and a higher mean HADS-D (SD) score. We found no other systematic differences on the demographic and clinical characteristics between the study population and excluded patients.

During the follow-up period, the cumulative number of patients who dropped out of the study or who did not complete all follow-up assessments on the ICDC, HADS-A and HADS-D was 300, leaving still a total of 7051 observations: 1208 patients were observed at all FU times, 176 patients at four times and 119 patients three or two times. Table S1 (*supplementary material*) provides details on the number of patients with missing data on ICDC, HADS-A and HADS-D at baseline, 3, 6, 12, and 24 months of FU.

As shown in Table S2. (*supplementary material*), when looking at changes in psychological health between time of implant and 3-, 6-, 12-, and 24 months, stratified by whether patients had a normal level versus an increased level of distress (i.e., either on ICD concerns (ICDC), anxiety (HADS-A) or depressive symptoms (HADS-D)), we found that of patients starting out with a normal level, few patients (i.e., 5.6%, 4.2%, 4.0%, and 4.0% at 3-, 6,- 12- and 24 months, respectively) experienced an increase in ICD concerns. By contrast, of patients starting out with increased levels of ICD concerns at baseline, 44.4%, 35.1%, 35.1% and 30.5% still had increased levels of ICD concerns at 3-, 6,- 12- and 24 months, respectively, implying that patients with an increased baseline score had a 50% or larger chance of reducing their scores. We found the same pattern for anxiety (HADS-A), with only few patients with a normal level of anxiety at baseline experiencing increased levels of anxiety at follow-up (i.e., 5.9%, 6,8%, 4.0% and 6.4%) at 3-, 6,- 12- and 24 months, respectively. By contrast, patients starting out with increased levels at baseline had increased anxiety levels (i.e., 50%, 44.6%, 46.3%, and 37%) at 3-, 6,- 12- and 24 months, respectively. Also here, patients with an increased baseline score had a 50% or larger chance of reducing their scores. With respect to depression (HADS-D), we found similar results. Of all patients with normal depression levels at baseline only few experienced an increase in symptoms during follow-up (i.e., 5.8%, 6,5%, 6,5% and 7.2% at 3-, 6,- 12- and 24 months, respectively). Similarly, as seen with ICD concerns and anxiety, of patients with increased depression levels at baseline, 51.1%, 49.6%, 48.3% and

Table 1
Baseline demographic and clinical characteristics of the study population and excluded patients where data were available ($N = 89$). Data were analyzed with the Chi-square test for categorical variables and Student's *t*-test for continuous variables, where missing categories were excluded. Data are presented as n (%) unless otherwise specified.

Covariate	Categories	N Missing	Study population	Excluded patients	p-value
All			1503 (100.0)	89 (100.0)	
Demographics					
Sex	Female	0	277 (18.4)	13 (14.6)	0.3639
	Male	0	1226 (81.6)	76 (85.4)	
Age	20-	0	165 (11.0)	11 (12.4)	0.9639
	50-	0	303 (20.2)	17 (19.1)	
	60-	0	546 (36.3)	31 (34.8)	
	70-	0	489 (32.5)	30 (33.7)	
Mean Age (SD)		0	63.5 (10.9)	63.5 (11.4)	0.9850
Married / partner	Yes	18	1161 (77.2)	55 (61.8)	0.2110
Working	Yes	33	304 (20.2)	11 (12.4)	0.2411
Education ≥10 years	Yes	40	461 (30.7)	18 (20.2)	0.2397
Clinical					
Smoking	Yes	35	212 (14.1)	11 (12.4)	0.8914
Device type	CRT-D	10	433 (28.8)	27 (30.3)	0.9427
	Single chamber ICD	0	704 (46.8)	42 (47.2)	
	Dual chamber ICD	0	356 (23.7)	20 (22.5)	
QRS duration >120 msec	Yes	9	504 (33.5)	29 (32.6)	0.8234
NYHA Class	NYHA I	168	355 (23.6)	17 (19.1)	0.7222
	NYHA II	0	663 (44.1)	38 (42.7)	
	NYHA III	0	325 (21.6)	22 (24.7)	
	NYHA IV	0	4 (0.3)		
NYHA III-IV	Yes	168	329 (21.9)	22 (24.7)	0.4115
Ischemic heart disease as cardiac diagnosis at implant	Yes	9	997 (66.3)	64 (71.9)	0.3129
Secondary prevention ICD indication	Yes	16	645 (42.9)	50 (56.2)	**0.0181**
PCI prior to ICD implantation	Yes	25	592 (39.4)	40 (44.9)	0.3133
CABG prior to ICD implantation	Yes	17	381 (25.3)	26 (29.2)	0.4140
LVEF >35%	Yes	11	465 (30.9)	27 (30.3)	0.8696
Physical functioning (SF-36 PCS) [in tertiles] at baseline	7.7-	153	457 (30.4)	22 (24.7)	0.6910
	37.7-		459 (30.5)	21 (23.6)	
	46.9–70.7		463 (30.8)	17 (19.1)	
Medication and treatment					
Beta-blockers	Yes	100	1229 (81.8)	53 (59.6)	0.5840
Amiodarone	Yes	100	149 (9.9)	9 (10.1)	0.2571
Digoxin	Yes	100	103 (6.9)	3 (3.4)	0.5172
ACE-Inhibitors	Yes	100	1148 (76.4)	49 (55.1)	0.7752
Dieuretics	Yes	100	874 (58.2)	34 (38.2)	0.4972
Statins	Yes	100	1048 (69.7)	51 (57.3)	**0.0418**
Psychotropic medication	Yes		167 (11.1)	4 (4.5)	0.2340

(*continued on next page*)

Table 1 (*continued*)

Covariate	Categories	N Missing	Study population	Excluded patients	p-value
Psychological health at baseline					
Previous psychological problems	Yes		108 (7.2)	5 (5.6)	0.8354
Type D personality	Yes	33	230 (15.3)	13 (14.6)	0.2086
HADS-A, categorical (≥8)	Yes	30	259 (17.2)	21 (23.6)	**<0.001**
Mean HADS-A (SD)		30	4.0 (3.7)	5.0 (4.7)	**0.0430**
HADS-D, categorical (≥8)	Yes	30	137 (9.1)	11 (12.4)	**0.0142**
Mean HADS-D (SD)		30	3.0 (3.1)	3.9 (4.0)	**0.0235**
ICDC, categorical (≥13)	Yes	27	318 (21.2)	19 (21.3)	0.0749
Mean ICDC SCORE		27	7.7 (7.2)	8.7 (8.2)	0.2647
Shocks during follow-up					
0–3 months	Yes	18	34 (2.3)	4 (4.5)	0.0806
3–6 months	Yes	34	16 (1.1)	2 (2.2)	0.1728
6–12 months	Yes	68	38 (2.5)	1 (1.1)	0.5502
12–24 months	Yes	150	49 (3.3)		0.1311

ACE-inhibitors: Angiotensin-converting enzyme inhibitors; ARVC: Arrhythmogenic right ventricular cardiomyopathy; CABG: Coronary artery bypass surgery; CRT-D: ICD with cardiac resynchronization therapy; ICD: Implantable cardioverter defibrillator; ICDC: ICD Concerns; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association functional class; PCI: Percutaneous coronary intervention; PCS: Physical Component Summary Score (SF-36).

52.5% had increased levels at at 3-, 6,- 12- and 24 months, respectively, implying that the chance of reducing their symptoms over time stayed constant for about 50% (i.e., did not increase over time as with ICDC or HADS-A). For all outcomes, increased baseline levels were associated with a larger chance to experience an improvement in psychological health. Generally, patients experienced improvement in symptoms of anxiety, depression and ICD concerns during the FU period, although the extent of improvement varied. Fig. 1A shows changes in HADS-A, HADS-D and ICDC for patients who went to increased levels from normal baseline levels.

Fig. 1 A shows patients who changed to increased levels from normal baseline levels, while Fig. 1B shows patients who changed to normal levels from increased baseline levels.

For both Fig. 1A and B, bar style changes (in %) are represented. To the right, estimates are listed with 95% confidence intervals.

Fig. 2A-C provides an overview of mean changes in psychological health from baseline for the overall population, and for female and male patients separately. ICD concerns and symptoms of anxiety show greater improvement as compared to depressive symptoms, suggesting that depressive symptoms may be more persistent. In addition, women seem to experience more improvement in symptoms as compared to men.

As shown in Table 2 that presents the multivariable analyses, baseline ICD concerns ($p < 0.001$) and ICD concerns at all timepoints (i.e., 6-, 12, and 24 months [all p-values <0.001]), education ≥10 years ($p < 0.0271$), and better physical functioning (upper tertile; $p = 0.0236$) were associated with better psychological health, while use of psychotropic medication ($p = 0.0122$) was associated with poorer psychological health.

We found similar results with respect to anxiety (HADS-A), with baseline anxiety ($p < 0.001$) and 24 months ($p = 0.0085$), higher age ($p < 0.001$), and higher education (≥10 years; $p = 0.0462$), and better physical functioning (upper tertile; $p < 0.001$) being associated with better psychological health, while previous psychological problems ($p > 0.001$), use of psychotropic medication (0.0178), and Type D personality ($p > 0.01$) were associated with poorer psychological health.

With respect to depression (HADS-D), baseline depression (<0.001), 12 months ($p = 0.0021$) and 24 months ($p = 0.058$) depression scores, smoking ($p < 0.001$), NYHA class III-IV ($p = 0.134$), Type D personality (<0.001), previous psychological problems ($p = 0.0011$) and shocks during follow-up (0.0011) were associated with poorer psychological health. By contrast, the baseline HADS-D score ($p < 0.001$), female sex ($p < 0.001$), older age ($p = 0.0173$), higher education (≥10 years; $p = 0.0477$)), and good physical functioning (upper tertile; $p = 0.0051$) were associated with better psychological health.

Table S3 ***(Supplementary material)*** provides an overview of the univariable analyses.

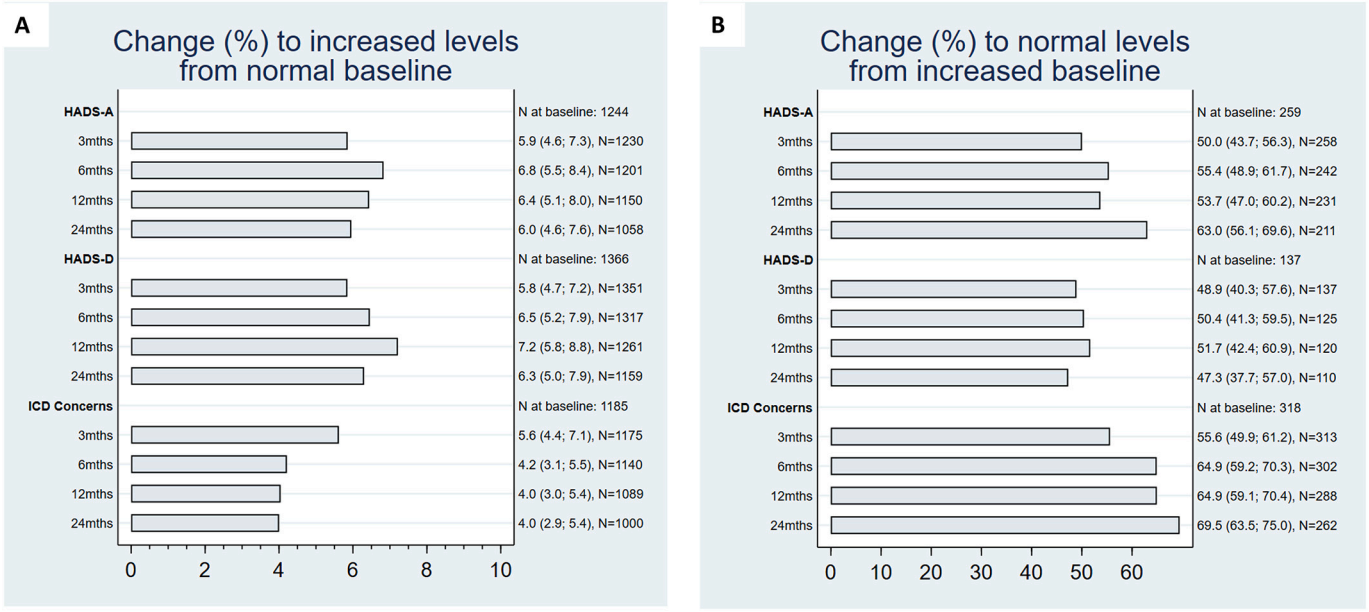

Fig. 1. A. Change to increased levels from normal baseline. B Change to normal levels from increased baseline.

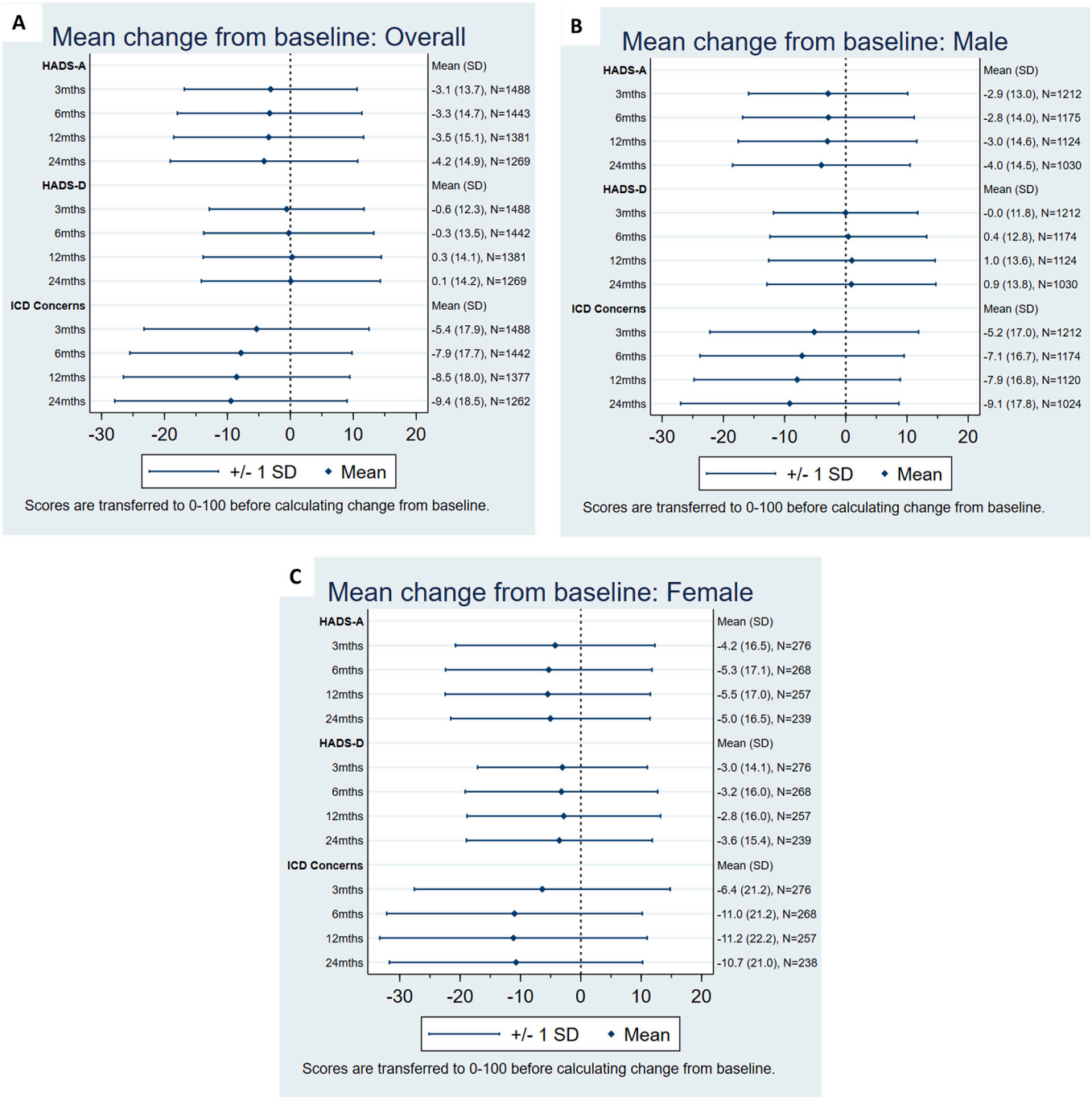

Fig. 2. A. Mean change from baseline: Overall. B. Mean change from baseline: Male. C. Mean change from baseline: Female.

4. Discussion

In the current study, 21% of patients had a high score on ICD Concerns, 17% a high score on anxiety, and 9% a high score on depression at baseline. Patients with low scores on distress (i.e., ICD concerns, anxiety, and depression) – equivalent to good psychological health at the time of implant – were unlikely to experience an increase in distress over time, with only between 4%-7.2% of these patients experiencing an increase over the 24 months of FU. In addition, over 50% of patients dropped to normal levels.

However, patients with increased scores (i.e., ICD concerns, anxiety, and depression) at the time of implant were more likely also to have increased levels at all follow-up times, with as many as 30.5%-52.7% of patients having an increased score during the 24 months of FU. Studies on ICD patients show that patients need some time to adjust to living with their device. Generally, around 3 months, the majority of patients experience stability and a kind of normalization in terms of their HRQoL and move on with their lives [17]. However, if patients start out with high levels, it is not necessarily a given that their levels will decrease to a very low level. This may be related to their personality (e.g., Type D Personality) that was also assessed in this study and was associated with poorer psychological health and which in previous studies also has been shown to impact patients' HRQoL [5]. However, previous adverse life events, lack of support etc. – although not assessed in the current study – might also play a role. Also, as seen in the current study, particularly depression seems to be more persistent as compared to anxiety and ICD

Table 2
Variables associated with psychological health (multivariable analyses).*

	ICDC		HADS-A		HADS-D	
	beta [95%CI]	p	beta [95%CI]	p	beta [95%CI]	p
N	5548		5548		5548	
Time: 3 months	Ref		Ref		Ref	
6 months (vs. 3-months as Ref)	−2.468 (−3.180; −1.756)	**<0.001**	−0.077 (−0.695; 0.541)	0.8063	0.438 (−0.161; 1.037)	0.1522
12 months (vs. 3-months as Ref)	−3.102 (−3.824; −2.380)	**<0.001**	−0.151 (−0.778; 0.476)	0.6373	0.953 (0.345; 1.561)	**0.0021**
24 months (vs. 3-months as Ref)	−4.156 (−4.899; −3.412)	**<0.001**	−0.866 (−1.512; −0.220)	**0.0086**	0.771 (0.145; 1.396)	**0.0158**
Baseline score (100)	−0.488 (−0.517; −0.458)	**<0.001**	−0.478 (−0.512; −0.444)	**<0.001**	−0.497 (−0.536; −0.458)	**<0.001**
Female sex	1.360 (−0.344; 3.063)	0.1177	0.712 (−0.731; 2.155)	0.3333	−2.389 (−3.737; −1.042)	**<0.001**
Age 60+ vs. 20–59 as Ref	−1.063 (−2.596; 0.470)	0.1740	−2.613 (−3.915; −1.310)	**<0.001**	−1.475 (−2.690; −0.260)	**0.0173**
Smoking (yes)	1.417 (−0.416; 3.251)	0.1297	1.470 (−0.079; 3.020)	0.0629	2.704 (1.251; 4.157)	**<0.001**
Married / partner (yes)	−0.873 (−2.404; 0.658)	0.2636	−0.221 (−1.516; 1.074)	0.7382	−0.316 (−1.534; 0.902)	0.6112
Working (yes)	0.637 (−1.106; 2.380)	0.4737	−0.581 (−2.054; 0.892)	0.4395	−1.144 (−2.530; 0.242)	0.1056
Education ≥10 years (yes)	−1.557 (−2.938; −0.177)	**0.0271**	−1.189 (−2.357; −0.020)	**0.0462**	−1.109 (−2.207; −0.011)	**0.0477**
NYHA III-IV (yes)	−0.504 (−2.216; 1.209)	0.5644	0.846 (−0.600; 2.292)	0.2514	1.718 (0.357; 3.079)	**0.0134**
Secondary prevention indication (yes)	0.105 (−1.354; 1.563)	0.8882	0.155 (−1.080; 1.391)	0.8057	0.394 (−0.769; 1.557)	0.5064
Type D personality at baseline (yes)	1.758 (−0.028; 3.543)	0.0536	4.281 (2.686; 5.877)	**<0.001**	5.095 (3.582; 6.609)	**<0.001**
Physical functioning (SF-36 PCS) [in tertiles] at baseline [7.7-]	0.463 (−1.067; 1.993)	0.5533	0.874 (−0.425; 2.174)	0.1873	1.758 (0.527; 2.990)	**0.0051**
Middle [37.7-]	Ref		Ref		Ref	
Upper tertile [46.9–70.7]	−1.776 (−3.313; −0.238)	**0.0236**	−2.764 (−4.061; −1.467)	**<0.001**	−2.235 (−3.466; −1.005)	**<0.001**
IHD diagnosis (yes)	−1.232 (−2.709; 0.246)	0.1022	−0.348 (−1.597; 0.901)	0.5850	−0.262 (−1.436; 0.913)	0.6623
Device type: Single/Dual vs. CRT-D as ref	0.804 (−0.797; 2.405)	0.3248	1.081 (−0.273; 2.435)	0.1175	1.149 (−0.125; 2.423)	0.0772
LVEF >35% (yes)	0.043 (−1.708; 1.794)	0.9617	−0.801 (−2.281; 0.679)	0.2889	−1.039 (−2.431; 0.353)	0.1434
Beta-blockers (yes)	−0.426 (−2.275; 1.423)	0.6517	0.001 (−1.561; 1.563)	0.9992	0.864 (−0.604; 2.333)	0.2487
Psychotropic medication (yes)	2.786 (0.608; 4.964)	**0.0122**	2.228 (0.386; 4.069)	**0.0178**	1.593 (−0.141; 3.326)	0.0717
Self-reported psychological treatment and/or psychiatric diagnosis (yes)	1.804 (−0.877; 4.485)	0.1872	4.810 (2.543; 7.078)	**<0.001**	3.551 (1.417; 5.686)	**0.0011**
Shocks in period before (yes)	0.003 (−0.009; 0.016)	0.5792	0.006 (−0.005; 0.016)	0.3052	0.017 (0.007; 0.027)	**0.0011**
Constant	7.939 (4.672; 11.206)		6.931 (4.185; 9.677)		5.675 (3.099; 8.250)	
	2.401 (2.357; 2.446)		2.227 (2.183; 2.273)		2.159 (2.113; 2.205)	
	2.276 (2.254; 2.298)		2.135 (2.113; 2.157)		2.104 (2.082; 2.126)	
Intraclass correlation coefficient (ICC)	56.2%		54.6%		52.7%	

P-values in bold-face in the the table indicates statistical significance [please add this to table 2 so that Table 1 and 2 are identifical with respect to this information].

* Separate mixed linear models for each outcome with a random intercept for patients (scores are expanded to 100 to ensure comparability).

concerns.

Taken together, these results indicate that we need to be particularly vigilant with respect to patients who start out with elevated distress scores, as we know that this subset of patients is at greater risk of poor HRQoL [5], morbidity, and mortality [2,9,10]. Another implication is that it may not be sufficient to screen patients for distress only at baseline, which a recent study corroborates, as 14.5% of patients developed new onset anxiety during follow-up and 11.3% new depression onset [18]. In the latter study, also minimal scores on the HADS-A and HADS-D – that usually would not be a cause of concern nor be considered clinically relevant – were associated with new onset anxiety and depression.

A Dutch study of 328 consecutive patients with a first-time ICD implant from the "Mood and personality as precipitants of arrhythmia in patients with an implantable cardioverter defibrillator: a prospective study" (MIDAS) examined psychological health 12 months post implant with respect to patients who preserved, improved or deteriorated [19]. Only few patients with normal levels of ICD concerns (i.e., 5.8%), anxiety symptoms (i.e., 5.7%) and depressive symptoms (i.e., 8.1%) experienced an increase in symptoms at 12 months follow-up. By contrast patients with increased levels of ICD concerns, anxiety symptoms and depressive symptoms at baseline had a higher risk of experiencing a deterioration in symptoms (i.e., ICD concerns: 9.1%; anxiety: 9.9%; depression: 12.7%) [19].

Thus, the results of the current study on data from the DEFIB-WOMEN support the results of the MIDAS study that compared baseline psychological health to psychological health at 12 months follow-up, while also extending the results of the MIDAS study. Our sample size was larger, the FU period longer (i.e., up to 24 months of follow-up), and included more FU assessments, which enabled us to examine changes in psychological health between baseline assessment and four FU times (i.e., 3, 6, 12, and 24 months).

However, although the correlates of poorer psychological health in the two studies had some overlap, with shocks associated with all domains in the MIDAS study, we only found an association with shocks and depressive symptoms in the current study and not ICD concerns and anxiety. Type D personality was a correlate of poor psychological health of all domains in the MIDAS study, while we only found a relationship with anxiety and depression. Generally, baseline psychological health in both studies were associated with improvement in psychological health [19]. Contrary to the MIDAS study, we found no association between primary prevention indication and anxiety, depression, and ICD concerns. However, both studies found that older age was associated with better psychological health. With respect to shocks, the MIDAS study found an association between shocks and poorer psychological health for all domains [19], while we only found a relationship with depression in the current study. These differences in results may partly be attributable to differences in the variables that were included in the multivariable analyses but likely also differences in the sample size of the two studies. In addition, over the years there has been a change in how the ICD is programmed related to the detection rate before the ICD provides a shock, leading to a reduction in appropriate shocks [20]. It is important also to emphasize that many patients consider potential shocks part of the package and see the ICD as a life saver and a friend, and that many other factors than shocks may have an impact on patients' HRQoL, including heart failure, anxiety, depression and Type D personality [6].

With respect to ICD concerns, we found that ICD concerns at baseline and at all FU times, education ≥10 years, and physical functioning (upper tertile) were associated with better psychological health (i.e., less ICD concerns), while previous psychological problems were associated with poorer psychological health. Likewise, with respect to anxiety, baseline anxiety and 24 months, higher age, education ≥10 years, and physical functioning (upper tertile) were associated with better psychological health (i.e., less symptoms of anxiety), while Type D personality and previous psychological problems were associated with poorer psychological health. With respect to depression, 12- and 24-months were associated with poorer psychological health (more symptoms of depression), while the baseline score, female sex, higher age, education ≥10 years, and physical functioning (upper tertile) were associated with better psychological health. By contrast, smoking, shocks, Type D personality, and NYHA class III-IV were associated with worse psychological health (i.e., more symptoms of depression). It is notable that none of the latter "more negative" variables were associated with ICD concerns, and of these variables that only Type D personality was associated with symptoms of anxiety but not ICD concerns nor depressive symptoms.

4.1. Limitations and strengths

The current study has some limitations. Patients excluded from the study population differed systematically from patients included in the study, and were less likely to be on statins, more likely to have a secondary prevention ICD indication, a higher categorical (≥8) HADS-A score, a higher mean HADS-A (SD) score, a higher categorial (≥8) HADS-D, and a higher mean HADS-D (SD) score. Hence, the results of the study can only be generalized to patients who participated in the study and the analyses, and not to the entire DEFIB-WOMEN ICD cohort. We used questionnaires and not diagnostic interviews to assess anxiety and depression. However, even minimal symptoms of anxiety and depression on the HADS-A and HADS-D have been shown to be associated with considerable risk of new onset anxiety in ICD patients free of anxiety and new onset depression in patients free of anxiety or depression at study entry – respectively a hazard ratio (HR) of 2.85 for a HADS-A score of 3–4 and a HR of 5.97 for a HADS-A score of 5–7. Similar results have been found for new onset depression – respectively a HR of 2.91 for a score of 3–4 and a HR of 6.24 for a score of 5–7 on HADS-D [18]. In the analyses, we did not distinguish between patients who experienced a shock versus patients where we had no information. Thus, we cannot rule out that patients with no information may not have received a shock. Hence, these results can be considered conservative, as the differences between groups may be underestimated.

Strengths of the study include that it is a multi-center, national cohort study with all Danish ICD centers at the time of setting up the study participating. Another strength is that only a relatively small number of patients did not complete all follow-up assessments on the ICDC, HADS-A and HADS-D. In addition, we had a "rich" data set, including both patient reported outcomes and questionnaire data, and data from the Danish Pacemaker and ICD Register. Except a smaller Dutch single center study with a smaller sample size and less follow-up times [19], to our knowledge the current study is unique in the ICD literature with its focus on changes in psychological health and risk factors associated with poor psychological health, and the large sample size, several assessment times, and a follow-up duration of 24 months.

5. Conclusions

Generally, patients experienced an improvement in psychological health over the 24 months of FU with respect to symptoms of depression, anxiety, and ICD concerns. However, a subset of patients (30.5%-52.7%) with increased scores already at the time of implant were more likely to have increased scores at FU. Hence, we need to be vigilant with respect to patients who start out with elevated distress scores and in particular those patients with elevated depression scores, as these symptoms seem to be more persistent than ICD concerns and symptoms of anxiety, which is of concern. We also know that full-blown depression is more difficult to treat than sub-clinical symptoms. In addition, patients with long-term and severe depression may be more difficult to treat, with some patients developing treatment-resistant depression [21]. Moreover, depression is associated with poorer HRQoL [5] and increased risk of mortality in patients with an ICD [9]. Another implication of this study is that it may not be sufficient to screen patients for distress only at baseline, which a recent study corroborates, as 14.5% of patients developed new onset

anxiety during follow-up and 11.3% new depression onset [18].

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Author contribution statement

Susanne S Pedersen: Conceived and designed the analysis; collected the data; wrote the paper; revision of the paper.
Sonja Wehberg: Conceived and designed the analysis; performed the analysis; provided feedback on the paper; revision of the paper.
Jens Cosedis Nielsen: Provided feedback on the paper.
Sam Riahi: Provided feedback on the paper.
Charlotte Larroudé: Provided feedback on the paper.
Berit T. Philbert: Provided feedback on the paper.
Jens Brock Johansen: collected the data; provided feedback on the paper

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Appendix A. Supplementary data

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