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New onset anxiety and depression in patients with an implantable cardioverter defibrillator during 24 months of follow-up (data from the national DEFIB-WOMEN study)

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ABSTRACT

Objective: To examine the cumulative incidence of and covariates' association with new onset anxiety and depression in implantable cardioverter defibrillator (ICD) patients during 24 months of follow-up in patients without depression and anxiety at implant.

Methods: Patients ($n = 1040$; 155 (14.9%) women; mean age: 64.2 ± 10.6) with a first-time ICD enrolled in the national, multi-center prospective observational DEFIB-WOMEN study comprised the study cohort. We obtained information on demographic and clinical data from the Danish Pacemaker and ICD Register.

Results: During 24 months of follow-up, 138 (14.5%) patients developed new onset anxiety and 109 (11.3%) new onset depression. Age ≥ 60 [HR:0.60;95%CI:0.40–0.90] and an anxiety score between 3 and 4 [HR:2.85; 95% CI:1.71–4.75] and 5–7 [HR:5.97; 95%CI:3.77–9.45] on the Hospital Anxiety and Depression Scale (HADS) were associated with different hazards of new onset anxiety during follow-up. Age ≥ 60 [HR:0.62;95%CI:0.42–0.93] and a HADS depression score between 3 and 4 [HR:2.99;95%CI:1.80–4.95] and 5–7 [HR:6.45; 95% CI:4.12–10.10] were associated with different hazards of new onset depression.

Conclusion: During 24 months of follow-up, respectively 14.5% and 11.3% of patients developed new onset anxiety and depression, suggesting that screening patients at several timepoints, and in particular those with even minimally elevated HADS scores at baseline, may be warranted to identify patients at risk for poor health outcomes.

1. Introduction

The implantable cardioverter defibrillator (ICD) is the treatment of choice for primary and secondary prevention of sudden cardiac death in patients at risk of life-threatening arrhythmias due to significant risk reductions in arrhythmic death and all-cause mortality compared to anti-arrhythmic drugs [1]. Overall, patients adjust well to living with an implantable cardioverter defibrillator (ICD) but 10%–20% report clinically relevant levels of anxiety and depression [2–4] that may compromise their quality of life (QoL) and increase risk of ventricular tachyarrhythmias and mortality [5,6].

Research in the ICD population has primarily focused on the prevalence of anxiety and depression at the time of implant or changes in symptoms over time. The literature shows that distress in patients tend to abate over time up to 3 months of follow-up post implant, after which symptom levels tend to stabilize. Although this is good news for patients,

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this approach may have led us to overlook patients at risk. A study of patients undergoing a percutaneous coronary intervention showed that of patients free of depressive symptoms at 6 months (baseline in the study) 8% developed depression up to 12 months [7]. New onset depression could not be attributed to a new cardiac event during follow-up. However, both diabetes and the distressed personality type (Type D) were associated with new onset depression, with the incidence of depression more than doubling per risk factor [7].

To our knowledge, no study has examined the incidence of new onset anxiety and depression in ICD patients and the association of covariates with the hazard of new onset. Identification of patients at risk of new onset distress after implantation is important due to potential impairments to their QoL [4,8], and risk of non-adherence, ventricular tachyarrhythmias and mortality [5,6]. Hence, the aims of the current study were to examine *(i)* the cumulative incidence of new onset anxiety and depression during 24 months of follow-up, defined by an increased symptom level (cut-off ≥8 on the Hospital Anxiety and Depression Scale (HADS)), as also used by others [9], referred to as anxiety and depression in the remainder of the article, and *(ii)* the association of covariates with the hazard of new onset anxiety and depression in a national cohort of ICD patients with a first-time ICD implant without clinical levels of anxiety and depression at the time of implant. We hypothesized that some patients, free of symptoms of anxiety and depression at the time of implant, would develop new-onset symptoms during the follow-up period, as shown in other cardiac populations [7,9].

2. Methods

2.1. Study design, eligibility criteria and recruitment

DEFIB-WOMEN (Utilization of implantable cardioverter DEFIBrillator therapy in the treatment of heart disease: Clinical and psychological outcomes in WOMEN) is a national, multi-center, prospective, observational study of patients with a first-time ICD, designed a priori to examine potential sex differences in patient-reported outcomes (PROs) [10]. A consecutive cohort of patients who received a first-time ICD between June 2010 to April 2013 at one of the five implanting hospitals (Odense University Hospital, Aarhus University Hospital, Aalborg University Hospital, Copenhagen University Hospital and Gentofte University Hospital) comprised the patient cohort [2]. Patients were approached one day post implantation and prior to discharge from hospital for study participation if they fulfilled all the inclusion criteria and none of the exclusion criteria. All patients received written and oral information about the study. Patients willing to participate were asked to sign an informed consent form and complete a set of standardized and validated questionnaires, which they were asked to return within one week in a self-addressed, stamped envelope. Patients would receive a reminder by mail including another questionnaire, if the first one was not returned within one week. The same procedure was used for the follow-up questionnaires. Information on demographic and clinical characteristics was obtained from the Danish Pacemaker and ICD Register or purpose-designed questions in the questionnaires.

Patients were eligible for inclusion, if they had a first-time single- or dual-chamber ICD or ICD with cardiac resynchronization therapy (CRT-D) and were >18 years of age. Patients were excluded, if they had a history of severe psychiatric illness, were on the waiting list for heart transplantation, had a left ventricular assist device, or insufficient knowledge of the Danish language to complete the questionnaires. In addition to the inclusion and exclusion criteria for the overall DEFIB-WOMEN study, due to the objective of the current sub-study focusing on new onset depression and anxiety, we chose for a conservative strategy to ensure we had a "clean" cohort with no indication of psychological issues. Hence, we also excluded patients with an indication of a psychological condition (i.e., baseline symptoms of anxiety or depression (cut-off ≥8 on the HADS), prescribed psychotropic medication, in treatment for a psychological condition), and patients with a missing HADS-A or HADS-D score at baseline, patients with no other measurement of HADS-A and HADS-D than at baseline, with missing HADS-A and HADS-D measurements during follow-up. We do not know if patients excluded due to these criteria had been diagnosed with prior depression or anxiety, but that might be the case for some of the excluded patients.

The study was conducted according to the principles of the Helsinki Declaration. Permission was granted by the Danish Data Protection Agency to conduct the study and we obtained permission to use data from the Danish Pacemaker and ICD Register. The study protocol was submitted to the Regional Committees on Health Research Ethics for Southern Denmark. According to Danish law, official ethics approval related to health research (§ 14, 1), such as the DEFIB-WOMEN study, is not required [decision on 25 February 2010].

2.2. Demographic and clinical variables

We obtained information on patients' demographic and clinical variables from the Danish Pacemaker and ICD Register, patients' electronic health records, and via purpose-designed questions in the questionnaire that also included standardized and validated questionnaires, as described in the following section. Information included age, sex, marital status, working status, smoking, educational level, device type, New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), indication for the ICD (secondary prophylactic indication *[*e.g., *patients with a history of dangerous sustained ventricular arrythmia]* versus primary prophylactic indication *[*e.g., *patients with a medical condition that places them at increased risk for such arrhythmias and sudden cardiac arrest]* [1], QRS duration, cardiac diagnosis at implant, procedures prior to implant (e.g., percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG)), medication, and device therapies (e.g., shocks) during follow-up.

2.3. Description of questionnaires

2.3.1. The hospital anxiety and depression scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a self-report measure of symptoms of anxiety and depression that has been validated and frequently used in patients with heart disease [11]. The HADS consists of 14 items, with 7 items contributing to the anxiety subscale and 7 items contributing to the depression subscale. Items are rated on a 4-point Likert scale from 0 to 3, with the anxiety and depression subscale scores ranging from 0 to 21. A high score indicates increased symptom levels. In the current study, we used a cut-off ≥8 to classify patients with anxiety and depression, as this cut-off reflects a clinically relevant symptom level and has been associated with increased risk of mortality in ICD patients [6]. Patients completed the HADS at baseline, 3-, 6-, 12-, and 24 months post implant.

2.3.2. The type D scale

The Type D Scale (DS14) is a 14-item scale that typifies individuals into a Type D versus a non-Type D personality, based on scores on the two sub-scales Negative Affectivity (NA) and Social Inhibition (SI). The 14 items are answered on a five-point Likert scale (0 = false, 4 = true), with NA and SI sum scores ranging from 0 to 28 [12]. Item Response Theory has shown that a cut-off of ≥10 on both sub-scales is the most optimal for determining Type D [12]. Individuals with a Type D personality are prone to experience increased negative emotions and unease (e.g., *"I often feel unhappy"*) worries and irritation (e.g., *"I often find myself worrying about something"*), feel discomfort '(e.g., *'I am a closed kind of person"*) and lack of social confidence (e.g., *"I often feel inhibited in social interactions"*). We assessed Type D, as patients with this personality type have been shown to report poorer PROs, including QoL, anxiety and depression, and to have a worse prognosis, although more recent studies show mixed results with respect to prognosis [13]. Patients completed the Type D Scale at baseline.

2.3.3. Short form health survey 36

We assessed physical QoL with the Short Form Health Survey 36 (SF-36) [14] at baseline and at 3-, 6-, 12-, and 24 months post implantation. The SF-36 consists of 36 questions that contribute to 8 subscales: Physical Functioning (PF), Role-Physical Functioning (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional Functioning (RE), and Mental Health (MH). Based on the 36-items, it is also possible to generate a Physical Component Summary (PCS) and Mental Component Summary (MCS). All 8 subscales contribute to both the PCS and MCS, based on a weighting system. Using an algorithm, responses to the individual items are transferred to scale scores that range from 0 to 100, with 100 representing the best QoL, except for Bodily Pain, where 100 reflects the total absence of pain. In the current study, we adjusted for PCS at baseline, as poor physical functioning has been associated with risk of anxiety and depression [15].

2.4. Statistical analyses

Differences on baseline demographic and clinical characteristics between patients stratified by sex were compared with the Chi-square test for categorical variables and student's *t*-test for independent samples for continuous variables. Cox regression survival models and discrete survival models were used to estimate the association of covariates (i.e., sex, age, marital status, smoking, working, education, NYHA class, indication for ICD, Type D personality, ICD type, shocks during follow-up, physical functioning, cardiac diagnosis at implant, and baseline HADS scores) with the hazard of time to new onset anxiety and depression separately, treating deaths as censored. These covariates were selected a priori based on the literature (e.g., [5,8,13,16]). Both univariable and multivariable models were fitted. We intended to include the variable *shocks* as time-dependent variable during the 24-months follow-up period. However, shocks predicted non-failures perfectly for time to onset of depression. Therefore, only baseline covariates were included in the analysis of depression. We performed sensitivity analyses, using discrete *cloglog* survival models. We used Nelson-Aalen graphs to illustrate the cumulative hazard estimates for new onset anxiety and new onset depression for the total sample and stratified by sex. All statistical analyses were performed using StataCorp 2019. *Stata Statistical Software: Release 16.* College Station, TX: StataCorp LLC. For all tests, a *p*-value of less than 0.05 was considered statistically significant.

3. Results

Of 2914 patients who received an ICD between June 2010 and April 2013 at one of the five implanting hospitals in Denmark, 1592 consented to participate in the study and did not withdraw their consent during the study period. Of these patients, 1040 were included in the statistical analyses (see flowchart in Fig. 1). Of the 1040 patients, 155 (14.9%) were women; mean age: 64.2 ± 10.6) and 885 were men; mean age: 65.0 ± 9.8). The number of women and men included in the current study reflects the ratio of women versus men implanted with an ICD in Denmark, as shown in the latest Annual Report from the Danish Pacemaker and ICD Register from 2017 to 2018, with 214 women (18.8%) and 927 (81.2%) implanted with an ICD [17].

We found some differences between patients included versus excluded in the analyses on sex, age, marital status, smoking, cardiac diagnosis at implant, indication for ICD implant, percutaneous coronary intervention (PCI) prior to implant, Type D personality, physical functioning, and shocks between 0 and 3 months, which was to be expected as the study objective warranted that we exclude patients who had

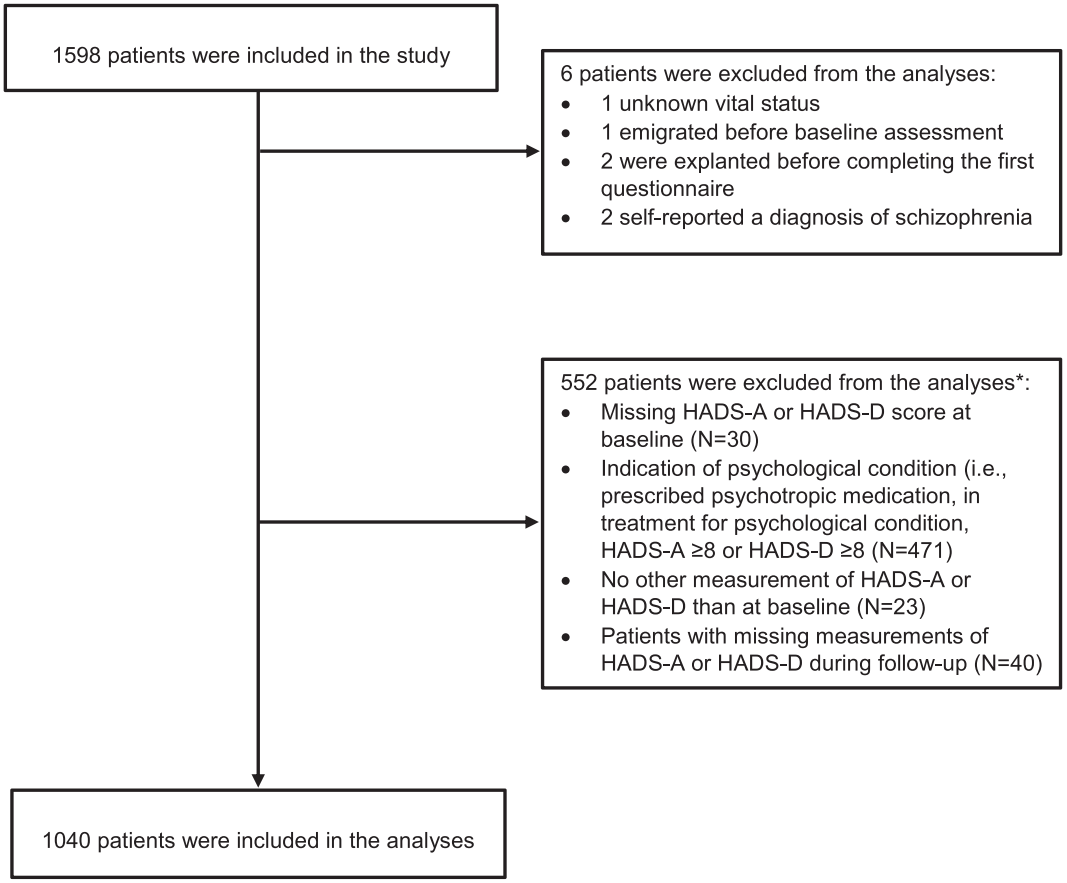

Fig. 1. Flowchart of included patients in the study and analyses.

anxiety or depression at baseline or received psychopharmaca (i.e, being treated for anxiety and depression), in order to have a cohort of patients who were free of anxiety and depression at baseline.

Baseline demographic and clinical characteristics of the study population stratified by sex are shown in Table 1 (*supplementary material*). Men were more likely to be married, to have ischemic heart disease as cardiac diagnosis at implant, to have had a PCI or coronary artery bypass graft surgery (CABG), but less likely to have a LVEF) >35% as compared to women. Men were more likely to be in the middle and upper tertile of physical functioning, while women were more likely to be in the lower tertile. Men were also more likely to be prescribed beta-blockers, angiotension-converting enzyme (ACE) inhibitors, and statins as compared to women. We also found differences between men and women on age, with more women being in the age groups 20–49 and 50–59, while men were more likely to be in the age groups 60–69 and ≥70.

Fig. 2 (*supplementary material*) shows the cumulative hazard estimates for new onset anxiety and new onset depression for the total sample. Fig. 3 (*supplementary material*) shows the cumulative hazard estimates for new onset anxiety and new onset of depression stratified by sex. These results represent raw percentages, with the number of patients at risk changing per assessment time, not considering patients who died during follow-up or were lost to follow-up. For this reason, we have added Table 1 that takes into account the change in number of patients at risk for new onset anxiety and depression per assessment time (i.e., at 3, 6, 12, and 24 months). As shown in Table 1, during 24 months of follow-up, 138 (14.5%) patients developed new onset anxiety and 109 (11.3%) new onset depression. The covariates age ≥ 60 years [HR:0.60; 95%CI: 0.40–0.90] and a HADS baseline anxiety score between 3 and 4 [HR:2.85; 95%CI: 1.71–4.75] and 5–7 [HR:5.97; 95%CI: 3.77–9.45] were associated with different hazards of new onset anxiety during follow-up in adjusted cox regression models (Table 2). Higher age was associated with a 40% reduced risk of new onset anxiety, and a HADS score from 3 to 4 or from 5 to 7 with a higher risk. These results were confirmed in sensitivity analyses using discrete survival models. As shown in Table 3, age ≥ 60 years [HR:0.62; 95%CI: 0.42–0.93] and a HADS depression score between 3 and 4 [HR:2.99; 95%CI: 1.80–4.95] and between 5 and 7 [HR:6.45; 95%CI:4.12–10.10] were associated with different hazards of new onset depression. Higher age was associated with a 38% reduced risk of new onset depression, and a HADS score from 3 to 4 or from 5 to 7 with a higher risk. Sensitivity analyses using discrete survival models confirmed these results.

4. Discussion

In the current study, we examined the cumulative incidence of new onset anxiety and new onset depression during 24 months of follow-up in patients with a first-time ICD enrolled in the national DEFIB-WOMEN study without clinical levels of anxiety and depression at the time of implant and the association of covariates with the hazard of new onset anxiety and depression. During 24 months of follow-up, 138 (cumulative incidence: 14.5%) patients developed new onset anxiety and 109 (cumulative incidence: 11.3%) new onset depression. This compares to an average incidence of depression in Denmark in 2010–2012 of 4000 in women and 6500 in men in a population of 5,560,628 [18], equal to 0.7% in women and 0.1% in men. In the same period, the average incidence of anxiety was 10,000 in women and 6500 in men, equal to 1.8% in women and 1% in men [18].

The incidence of depression found in the current study is similar to that found in patients undergoing PCI with drug-eluting stents [7]. In the latter study, the risk associated with Type D personality was 3-fold, while in the current study Type D was not significantly associated with new onset anxiety and depression, likely due to the adjustment of baseline anxiety and depression scores in the current study and the overlap between Type D and HADS. The association of covariates with the hazard of new onset anxiety and depression were similar. Age ≥ 60 years was protective for both new onset anxiety and depression, while baseline HADS scores between 3 and 4 and 5–7 as compared to a score between 0 and 2 were associated with greater risk of both new onset anxiety and depression. Screening for anxiety and depression with HADS at the time of implant would be useful to identify patients at risk for new onset anxiety and depression, in particular given the finding that a HADS score that is considered mild (3–4 and 5–7) in the current study shows that these patients are at increased risk. A recent study using routine practice data from the British Heart Foundation National Audit of Cardiac Rehabilitation (NACR) found that 20% of patients without initial depression developed new onset depression [19]. Factors associated with risk of onset depression included increased anxiety, physical inactivity, male sex, deprivation, and comorbidities, such as diabetes, stroke, and chronic back pain [19]. The incidence of new onset anxiety and depression found in this study was slightly lower, with 138 (cumulative incidence: 14.5%) and 109 (cumulative incidence: 11.3%), respectively in the first 24 months post implant. In addition, the latter study did not adjust for baseline HADS scores, as was done in the current study, which likely has an influence on the few number of covariate associations found in the current study. Taken together, the identified patients with new onset anxiety and depression and the 459 excluded patients who had anxiety or depression already at baseline or received psychopharmaca in the current study indicate that a considerable number of patients has clinically relevant symptoms of psychological distress that may go unnoticed and untreated [20], unless we screen patients not only at baseline but also several times during follow-up.

4.1. Clinical and research implications

Since we identified the majority of patients with new onset anxiety and depression in the first year post implant and few in the second year, one might argue that it is not worthwhile to screen ICD patients beyond one year post implant. However, given that anxiety and depression are associated with poor QoL and risk of morbidity and mortality in ICD patients [5,6], it is paramount that we identify the subset of patients at risk and offer them treatment for their psychological symptoms as also

Table 1
Patients at risk for new onset anxiety or depression per assessment time.

New onset anxiety						New onset depression					
Months FU	N at risk	No	Yes	Total	Incidence[a]	Months FU	N at risk	No	Yes	Total	Incidence[a]
3	1040	23	50	73	4.8%	3	1040	24	42	66	4.0%
6	967	28	36	64	3.7%	6	974	29	28	57	2.9%
12	903	74	32	106	3.5%	12	917	78	23	101	2.4%
24	797	777	20	797	2.5%	24	816	800	16	816	2.0%
Total		902	138	1040	14.5%	Total		931	109	1040	11.3%

FU = Follow-up.

[a] As the number of patients at risk declines per follow-up assessment, the incidence (%) is calculated per follow-up assessment with cases of new onset anxiety and depression in the numerator and the total number of patients at risk in the denominator [e.g., for anxiety, the denominator at 3 months is 1040–73 = 967 and at 6 months 1040-73-64 = 903, respectively].

Table 2
Covariate associations with new onset anxiety, univariable and multivariable models (Cox regression model and discrete survival model).

Cox regression model				
	Unadjusted HR [95% CI]	*p-value*	Adjusted HR [95% CI]	*p-value*
Female sex	1.39 [0.92–2.12]	0.1216	1.04 (0.66–1.63)	0.8739
Age ≥ 60	0.52 [0.37–0.73]	**<0.001**	0.60 (0.40–0.90)	**0.0136**
Married/partner	1.64 [1.01–2.66]	**0.0451**	1.58 (0.96–2.60)	0.0723
Smoking	1.12 [0.68–1.84]	0.6483	1.13 (0.68–1.87)	0.6473
Working	1.35 [0.93–1.98]	0.1174	1.14 (0.73–1.77)	0.5750
Education ≥10 years	0.88 [0.61–1.28]	0.5052	0.77 (0.52–1.14)	0.1891
ICD (single- and dual chamber)[1]	1.22 [0.83–1.78]	0.3047	1.09 (0.71–1.67)	0.7055
NYHA III-IV	1.16 [0.78–1.71]	0.4611	1.43 (0.91–2.25)	0.1176
Ischemic heart disease as cardiac diagnosis at implant	0.80 [0.56–1.13]	0.2075	1.09 (0.74–1.61)	0.6571
Secondary prophylactic indication	1.37 [0.98–1.91]	0.0663	1.35 (0.95–1.94)	0.0966
Type D personality	2.63 [1.72–4.03]	**<0.001**	1.46 (0.94–2.29)	0.0954
Physical functioning (PCS) [tertiles][2]				
Lower	1.56 [1.07–2.28]	**0.0215**	1.33 (0.90–1.95)	0.1508
Upper	0.76 [0.48–1.19]	0.2316	0.80 (0.50–1.28)	0.3515
Shocks during follow-up	0.87 [0.12–6.25]	0.8892	0.88 (0.12–6.37)	0.8956
HADS-A baseline: 0–2	1 (Ref)		1 (Ref)	
3–4	3.21 (1.95–5.28)	**<0.001**	2.85 (1.71–4.75)	**<0.001**
5–7	7.31 (4.71–11.35)	**<0.001**	5.97 (3.77–9.45)	**<0.001**
Discrete survival model				
	Unadjusted HR [95% CI]	*p-value*	Adjusted HR [95% CI]	*p-value*
Female sex	1.40 [0.92–2.14]	0.1136	1.03 (0.65–1.61)	0.9055
Age ≥ 60	0.51 [0.36–0.72]	**<0.001**	0.59 (0.39–0.88)	**0.0098**
Married/partner	1.65 [1.02–2.69]	**0.0415**	1.62 (0.98–2.66)	0.0598
Smoking	1.13 [0.69–1.85]	0.6369	1.14 (0.68–1.90)	0.6116
Working	1.36 [0.93–2.00]	0.1087	1.14 (0.73–1.77)	0.5748
Education ≥10 years	0.88 [0.60–1.28]	0.4969	0.76 (0.52–1.12)	0.1671
ICD (single- and dual chamber)[1]	1.23 [0.84–1.79]	0.2925	1.09 (0.71–1.67)	0.7088
NYHA III-IV	1.16 [0.79–1.72]	0.4522	1.44 (0.92–2.26)	0.1145
Ischemic heart disease as cardiac diagnosis at implant	0.79 [0.56–1.13]	0.1967	1.10 (0.74–1.62)	0.6392
Secondary prophylactic indication	1.38 [0.99–1.92]	0.0605	1.36 (0.95–1.94)	0.0939
Type D personality	2.71 [1.77–4.15]	**<0.001**	1.48 (0.94–2.31)	0.0890
Physical functioning (PCS) [tertiles][2]				
Lower	1.58 [1.08–2.30]	**0.0184**	1.34 (0.91–1.97)	0.1373
Upper	0.75 [0.48–1.19]	0.2228	0.79 (0.50–1.27)	0.3327
Shocks during follow-up	0.87 [0.12–6.26]	0.8893	0.86 (0.12–6.23)	0.8780
HADS-A baseline: 0–2	REF		REF	
3–4	3.26 (1.98–5.37)	**<0.001**	2.91 (1.75–4.84)	**<0.001**
5–7	7.65 (4.92–11.87)	**<0.001**	6.24 (3.94–9.89)	**<0.001**

For analyses purposes, missings are placed in the largest category.
ICD: Implantable cardioverter defibrillator; NYHA: New York Heart Association functional class; PCS: Physical Component Summary Score (SF-36).
[1] CRT-D [ICD with cardiac resynchronization therapy] = reference category.
[2] Middle = reference category.

recommended in the guidelines for the management of patients with ventricular arrhythmias [1]. These symptoms are often unrecognized and undertreated [20] partly because systematic screening has not yet been implemented in clinical cardiology practice [21]. In addition, it is important to emphasize that we also had more follow-up and measurement points in the first year (i.e., at 3, 6 and 12 months), while in the second year we only had one measurement point (i.e., at 24 months of follow-up). Potentially, some patients may have developed new onset distress between 12 months and 24 months that we were not able to detect. From a clinical practice perspective, it may be relevant for health care professionals and patients to know that a subset of patients may develop anxiety and depression even up to 24 months post implant. This can be seen as part of patient education and empowerment, so that patients can seek help from their general practitioner in time.

Future studies in ICD patients are warranted to investigate if the results of the current study are replicable in other ICD cohorts and in other countries. We would recommend including more follow-ups than we did in the second year of the DEFIB-WOMEN study to ascertain whether more patients would develop new onset of anxiety and depression symptoms beyond the first year after implant than demonstrated in our study. It will also be important to explore whether screening ICD patients for anxiety and depression combined with psychological treatment lead to better health outcomes. Several societies in Europe and the US have published advisories recommending screening patients with heart disease for anxiety and depression (e.g., [22–24]). This has led to discussions and criticism, as there is no evidence to support this recommendation due to lack of randomized controlled trials combining screening with treatment [25,26]. The CODIACS-QoL study (Comparison of Depression Interventions After Acute Coronary Syndrome: Quality of Life) in patients with ischemic heart disease is the study that the field has been waiting for, as it examined the impact of systematic screening and treatment, however, showing no substantial improvement in QoL, depression free days, mortality, o patient-reported harms [27]. To our knowledge no such study has been conducted in ICD patients, although results will soon be available from the ACQUIRE-ICD study that offered a comprehensive intervention to ICD patients, including systematic screening for anxiety and depression followed by treatment (cognitive behavioral therapy) for the subset of patients who screened positive for anxiety and/or depression [28]. In the future, it would be important to explore whether systematic screening and treatment combined with cardiac rehabilitation would improve outcomes of ICD patients, as some patients post implant feel insecure about engaging in physical activity, increasing the risk of a sedentary lifestyle, anxiety, and depression. Unfortunately, in Denmark, currently ICD patients are not systematically referred to cardiac rehabilitation, as such a program is not yet available.

Table 3
Covariate associations with new onset depression, univariable and multivariable models (Cox regression model and discrete survival model)[a]

Cox regression model				
	Unadjusted HR [95% CI]	*p-value*	Adjusted HR [95% CI]	*p-value*
Female sex	1.21 [0.73–1.98]	0.4594	1.05 (0.62–1.76)	0.8628
Age ≥ 60	0.62 [0.42–0.92]	**0.0180**	0.55 (0.35–0.86)	**0.0091**
Married/partner	0.97 [0.61–1.54]	0.9015	1.15 (0.70–1.88)	0.5801
Smoking	2.28 [1.46–3.57]	**<0.001**	1.90 (1.18–3.07)	**0.0082**
Working	0.89 [0.55–1.43]	0.6207	0.97 (0.56–1.68)	0.9075
Education ≥10 years	0.80 [0.52–1.23]	0.3036	0.77 (0.50–1.20)	0.2545
ICD (single- and dual chamber)[1]	0.93 [0.62–1.40]	0.7388	1.07 (0.68–1.70)	0.7687
NYHA III-IV	1.71 [1.14–2.57]	**0.0093**	1.46 (0.91–2.34)	0.1151
Ischemic heart disease as cardiac diagnosis at implant	1.03 [0.69–1.56]	0.8740	1.08 (0.70–1.68)	0.7215
Secondary prophylactic indication	0.91 [0.62–1.34]	0.6420	1.00 (0.66–1.51)	0.9815
Type D personality	2.83 [1.78–4.53]	**<0.001**	1.54 (0.93–2.52)	0.0904
Physical functioning (PCS) [tertiles][2]				
Lower	1.79 [1.20–2.69]	**0.0048**	1.33 (0.88–2.03)	0.1781
Upper	0.43 [0.23–0.79]	**0.0062**	0.57 (0.30–1.06)	0.0739
HADS-D baseline: 0–2	1 (Ref)		1 (Ref)	
3–4	3.47 (2.18–5.54)	**<0.001**	3.02 (1.87–4.87)	**<0.001**
5–7	7.22 (4.60–11.33)	**<0.001**	5.04 (3.08–8.24)	**<0.001**
Discrete survival model				
	Unadjusted HR [95% CI]	*p-value*	Adjusted HR [95% CI]	*p-value*
Female sex	1.21 [0.74–1.98]	0.4506	1.05 (0.63–1.76)	0.8568
Age ≥ 60	0.62 [0.42–0.91]	**0.0160**	0.54 (0.34–0.85)	**0.0078**
Married/partner	0.97 [0.61–1.54]	0.9061	1.18 (0.72–1.94)	0.5041
Smoking	2.33 [1.49–3.64]	**<0.001**	1.96 (1.21–3.17)	**0.0062**
Working	0.89 [0.55–1.42]	0.6154	0.97 (0.56–1.69)	0.9158
Education ≥10 years	0.79 [0.52–1.22]	0.2951	0.76 (0.49–1.18)	0.2191
ICD (single- and dual chamber)[1]	0.93 [0.62–1.40]	0.7346	1.08 (0.68–1.73)	0.7312
NYHA III-IV	1.73 [1.15–2.59]	**0.0080**	1.46 (0.91–2.35)	0.1146
Ischemic heart disease as cardiac diagnosis at implant	1.03 [0.69–1.56]	0.8733	1.08 (0.69–1.67)	0.7449
Secondary prophylactic indication	0.91 [0.62–1.34]	0.6343	0.98 (0.65–1.49)	0.9230
Type D personality	2.90 [1.82–4.63]	**<0.001**	1.54 (0.94–2.54)	0.0891
Physical functioning (PCS)				
Lower	1.82 [1.21–2.73]	**0.0039**	1.35 (0.89–2.05)	0.1643
Upper	0.43 [0.23–0.78]	**0.0058**	0.56 (0.30–1.05)	0.0712
HADS-D baseline: 0–2	1 (Ref)		1 (Ref)	
3–4	3.54 (2.22–5.64)	**<0.001**	3.08 (1.91–4.97)	**<0.001**
5–7	7.62 (4.86–11.95)	**<0.001**	5.34 (3.26–8.74)	**<0.001**

For analyses purposes, missings are placed in the largest category.
ICD: Implantable cardioverter defibrillator; NYHA: New York Heart Association functional class; PCS: Physical Component Summary Score (SF-36).
[a] As none of the patients with new onset depression received a shock, this cannot be estimated and was not included in the model.
[1] CRT-D [ICD with cardiac resynchronization therapy] = reference category.
[2] Middle = reference category.

4.2. Strengths and limitations

The results of the current study should be interpreted with the following limitations in mind. Given the observational study design, we cannot be certain that we included all relevant variables, with the risk that the results might have been influenced by variables that we did not access during follow-up (e.g., acute myocardial infarction and procedures such as PCI and CABG). Another limitation of the study is that the results cannot necessarily be generalized to the entire ICD population, since 54% of patients declined to participate in the study. We did not include other time-dependent variables in the multivariable analyses than shocks during follow-up in order to prevent overfitting of the regression models [29]. We did consider patients who died during follow-up, but it was not possible to make a formal competing risk analysis due to incomplete information on the cause of loss to follow-up, which might influence risk estimates. In addition, we used a self-report measure – the HADS – and a cut-off ≥8 to classify patients with anxiety and depression and not a diagnostic interview. However, this cut-off reflects a clinically relevant symptom level and not only a diagnosis but also increased symptom levels have been associated with increased risk of mortality in ICD patients [6]. We used a conservative approach to determine patients at risk for new onset depression and anxiety in order to ensure a "clean" and homogenous group without indication of psychological challenges. Thus, it is only possible to generalize the results to this subset of patients.

Other limitations include that we did not have a control group and therefore cannot say if the new onset rates are normal in the background population. However, when comparing with Danish data from the general population published by the National Board of Health [18], the incidence of new onset depression and anxiety is much higher in the current ICD population. In addition, we decided to analyze onset of anxiety and depression separately, even though some patients develop both. However, we wanted to explicitly investigate differences between these two outcomes with respect to their separate hazard ratios. Given some systematic differences between patients included versus excluded in the analyses, the results cannot be generalized to the entire ICD population. However, these differences were expected given that we excluded patients with a previous psychological condition, those prescribed psychotropic medication or in treatment for a psychological condition, and patients with missing anxiety and depression data.

Despite these limitations, the results of the current study contribute to the existing literature, as to our knowledge this is the first study to examine the incidence of new onset anxiety and depression in patients with an ICD.

5. Conclusion

Taken together, our results show that in clinical practice screening ICD patients at one timepoint (e.g., at the time of implant) will not be sufficient, as 14.5% experienced new onset anxiety and 11.3% new onset

depression the first 24 months post implant. Moreover, adding those who were excluded, we reach a substantial number of patients with psychological challenges that may warrant treatment. Our findings also show that patients with even minimally elevated HADS scores at baseline are at greater risk of new onset anxiety and depression, indicating that re-screening this subset off patients may be particularly warranted, as they may be at risk of poor health outcomes. Thus, we may have to consider screening patients at multiple timepoints, which can be done with a brief measure, such as the 4-item Patient Health Questionnaire (PHQ-4) that assesses both symptoms of anxiety and depression [30], when the patient is seen in the outpatient clinic [21,31]. If the patient screens positive, further evaluation may be needed by a mental health professional either as part of the multi-disciplinary team or through a referral, ensuring the correct management and treatment of the patient's symptoms.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2021.07.003.

References

[1] 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;36:2793–867.

[2] Frydensberg VS, Johansen JB, Moller S, Riahi S, Wehberg S, Haarbo J, et al. Anxiety and depression symptoms in Danish patients with an implantable cardioverter-defibrillator: prevalence and association with indication and sex up to 2 years of follow-up (data from the national DEFIB-WOMEN study). Europace 2020;22:1830–40.

[3] Magyar-Russell G, Thombs BD, Cai JX, Baveja T, Kuhl EA, Singh PP, et al. The prevalence of anxiety and depression in adults with implantable cardioverter defibrillators: a systematic review. J Psychosom Res 2011;71:223–31.

[4] 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;166:215–20.

[5] Pedersen SS, van den Broek KC, Erdman RA, Jordaens L, Theuns DA. Pre-implantation implantable cardioverter defibrillator concerns and type D personality increase the risk of mortality in patients with an implantable cardioverter defibrillator. Europace 2010;12:1446–52.

[6] 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.

[7] Pedersen SS, Ong K, Sonnenschein P, Serruys PW, Erdman RA, van Domburg RT. Type D personality and diabetes predict the onset of depressive symptoms in patients after percutaneous coronary intervention. Am Heart J 2006;151:367.e1–6.

[8] 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. Circ Cardiovasc Qual Outcomes 2012;5:373–80.

[9] Sever S, Doherty P, Golder S, Harrison AS. Is improvement in depression in patients attending cardiac rehabilitation with new-onset depressive symptoms determined by patient characteristics? Open Heart 2020;7.

[10] Pedersen SS, Nielsen JC, Riahi S, Haarbo J, Videb AR, Larsen ML, et al. Study design and cohort description of DEFIB-WOMEN: a National Danish Study in patients with an ICD. Pacing Clin Electrophysiol 2016;39:1261–8.

[11] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.

[12] 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.

[13] Kupper N, Denollet J. Type D personality as a risk factor in coronary heart disease: a review of current evidence. Curr Cardiol Rep 2018;20:104.

[14] Ware JE, Sherbourne CD. The MOS 36-item short-form health survey. Med Care 1993;30:473–83.

[15] Thylen I, Dekker RL, Jaarsma T, Stromberg A, Moser DK. Characteristics associated with anxiety, depressive symptoms, and quality-of-life in a large cohort of implantable cardioverter defibrillator recipients. J Psychosom Res 2014;77:122–7.

[16] Pedersen SS, Hoogwegt MT, Jordaens L, Theuns DA. Relation of symptomatic heart failure and psychological status to persistent depression in patients with implantable cardioverter-defibrillator. Am J Cardiol 2011;108:69–74.

[17] Johansen JB. Danish Pacemaker and ICD register - annual report. Denmark: Odense University Hospital; 2017-2018.

[18] Authority DH. Disease-burden in Denmark [Disease Burden in Denmark]. 2015.

[19] Sever S, Golder S, Doherty P. Factors associated with acute depressive symptoms in patients with comorbid depression attending cardiac rehabilitation. BMC Cardiovasc Disord 2018;18:230.

[20] Lang S, Becker R, Wilke S, Hartmann M, Herzog W, Lowe B. Anxiety disorders in patients with implantable cardioverter defibrillators: frequency, course, predictors, and patients' requests for treatment. Pacing Clin Electrophysiol 2014;37:35–47.

[21] Jha MK, Qamar A, Vaduganathan M, Charney DS, Murrough JW. Screening and management of depression in patients with cardiovascular disease: JACC state-of-the-art review. J Am Coll Cardiol 2019;73:1827–45.

[22] Albus C, Jordan J, Herrmann-Lingen C. Screening for psychosocial risk factors in patients with coronary heart disease-recommendations for clinical practice. Eur J Cardiovasc Prev Rehabil 2004;11:75–9.

[23] Lichtman JH, Bigger Jr JT, Blumenthal JA, Frasure-Smith N, Kaufmann PG, Lesperance F, et al. 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;118:1768–75.

[24] Whooley MA. Screening for depression–a tale of two questions. JAMA Intern Med 2016;176:436–8.

[25] Thombs BD, Roseman M, Coyne JC, de Jonge P, Delisle VC, Arthurs E, et al. Does evidence support the American Heart Association's recommendation to screen patients for depression in cardiovascular care? An updated systematic review. PLoS One 2013;8:e52654.

[26] Thombs BD, de Jonge P, Coyne JC, Whooley MA, Frasure-Smith N, Mitchell AJ, et al. Depression screening and patient outcomes in cardiovascular care: a systematic review. JAMA 2008;300:2161–71.

[27] Kronish IM, Moise N, Cheung YK, Clarke GN, Dolor RJ, Duer-Hefele J, et al. Effect of depression screening after acute coronary syndromes on quality of life: the CODIACS-QoL randomized clinical trial. JAMA Intern Med 2020;180:45–53.

[28] Pedersen SS, Skovbakke SJ, Wiil UK, Schmidt T, dePont Christensen R, Brandt CJ, et al. Effectiveness of a comprehensive interactive eHealth intervention on patient-reported and clinical outcomes in patients with an implantable cardioverter defibrillator [ACQUIRE-ICD trial]: study protocol of a national Danish randomised controlled trial. BMC Cardiovasc Disord 2018;18:136.

[29] Babyak MA. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. Psychosom Med 2004;66:411–21.

[30] Kroenke K, Spitzer RL, Williams JB, Lowe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. Psychosomatics 2009;50:613–21.

[31] Colquhoun DM, Bunker SJ, Clarke DM, Glozier N, Hare DL, Hickie IB, et al. Screening, referral and treatment for depression in patients with coronary heart disease. Med J Aust 2013;198:483–4.