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

Madelein T. Hoogwegt[1], Nina Kupper[1], Dominic A.M.J. Theuns[2], Luc Jordaens[2], and Susanne S. Pedersen[1,2]*

[1]CoRPS—Center of Research on Psychology in Somatic diseases, Tilburg University, Tilburg, The Netherlands; and [2]Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands

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

Methods and results Between 2003 and 2010, 448 consecutively implanted ICD patients were enrolled in the prospective **M**ood and personality as precipitants of arrhythmia in patients with an **I**mplantable cardioverter **D**efibrillator: **A** prospective **S**tudy (MIDAS), of which 429 completed the Hospital Anxiety and Depression Scale (HADS) and the ICD Patient Concerns questionnaire (ICDC) at baseline. Eighty per cent of all patients received beta-blocker therapy. In univariate analysis, beta-blocker therapy was not significantly associated with symptoms of anxiety, depression, and ICD concerns ($\beta = -0.030$, $\beta = 0.007$, and $\beta = -0.045$, respectively; all P's > 0.36). Type of beta-blocker showed a trend towards significance for mean levels of ICD concerns ($P = 0.09$). No association was found between dosage and emotional distress (all P's > 0.21). After adjustment for relevant clinical and demographic variables, the association of beta-blocker therapy and symptoms of anxiety, depression, and ICD concerns remained non-significant ($\beta = 0.009$, $\beta = 0.037$, and $\beta = 0.019$, respectively; all P's > 0.47).

Conclusion In patients receiving an ICD, beta-blocker therapy was not associated with symptoms of anxiety, depression, and ICD concerns. Research is warranted that further elucidates the link between beta-blocker therapy and emotional distress in this vulnerable patient group.

Keywords Implantable cardioverter–defibrillator • Beta-blockers • Anxiety • Depression

Introduction

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

In addition to the ICD implant, ICD patients are often prescribed beta-blockers, lipid-lowering drugs, calcium antagonists and angiotensin-converting enzyme (ACE)-inhibitors to treat their

* Corresponding author. Tilburg University, Room P506, PO Box 90153, 5000 LE Tilburg, The Netherlands. Tel: +31 13 466 2503; fax: +31 13 466 2067, Email: s.s.pedersen@uvt.nl

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

Methods

Patients and study design

Between August 2003 and February 2010, a consecutive series of 448 patients implanted with an ICD at the Erasmus Medical Center, Rotterdam, The Netherlands, were enrolled in the prospective **M**ood and personality as precipitants of arrhythmia in patients with an **I**mplantable cardioverter **D**efibrillator: **A** prospective **S**tudy (MIDAS). Exclusion criteria included a life-expectancy of <1 year, being on the waiting list for heart transplantation, having a history of psychiatric illness other than affective/anxiety disorders, or insufficient knowledge of the Dutch language. The Medical Ethics Committee of the Erasmus Medical Center approved the study. An ICD nurse approached patients while being admitted to hospital, provided information regarding the study, and asked them to complete a set of standardized and validated psychological questionnaires at baseline (i.e., 1 day before ICD implantation). All patients provided written informed consent before enrollment in the study.

Measures

Demographic and clinical variables

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

Anxiety and depression

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

Implantable cardioverter–defibrillator concerns

Patient concerns related to ICD treatment were assessed with the Dutch version of the Patient ICD Concerns questionnaire consisting of eight items (e.g. 'I am worried about my ICD firing' and 'I am worried about symptoms/pain associated with my ICD firing'; ICDC).[33] Items are rated on a 5-point Likert scale from 0 (not at all) to 4 (very much so), with a score range from 0 to 32, and with a higher score indicating more ICD-related concerns. The ICDC is a disease-specific measure that assesses a different construct than general measures of anxiety and depression. The measure has also been shown to predict mortality in ICD patients.[34] Both the original and the Dutch translation of the ICDC have good psychometric properties, with a Cronbach's alpha of 0.94 and 0.91, respectively.[33,35] For the current study, scores on the ICDC were divided into equal tertiles and dichotomized into a high score of ≥7 and a low score of ≤6.

Statistical analyses

Baseline demographic and clinical variables for patients on beta-blocker vs. no beta-blocker therapy were compared with the χ^2 test (Fisher's exact test when appropriate) for nominal variables

and with Student's *t*-test for continuous variables, respectively. The association between beta-blocker therapy and symptoms of depression and anxiety and ICD concerns was assessed in the main analysis using univariate and multivariate linear regression. In multivariate analyses using an enter approach, we adjusted for variables that have been associated with emotional distress in the arrhythmia literature, which include atrial fibrillation and symptomatic heart failure,[36,37] indication for ICD therapy,[38] diabetes mellitus,[39] and the use of amiodarone and psychotropic medication,[37] and variables that were expected to be related to emotional distress, including CAD and age. The rationale for a priori selection of variables is recommended by others.[40] We checked for multicollinearity between the independent variables using Spearman's ρ, with a threshold of >0.70 indicating multicollinearity. Results of the linear regression analyses are presented as β's with accompanying *P* values. In a secondary analysis, the association between beta-blocker type and dosage and emotional distress, and possible interaction effects were examined with univariate analysis of variance (ANOVA), with a *post hoc* Bonferroni test when the ANOVA showed a significant main effect to investigate between group differences. For all tests, a *P* value <0.05 (two sided) was considered significant. All statistical analyses were performed using SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results

Participants vs. non-participants

A total of 448 patients were enrolled in the MIDAS study. Of these, 19 refused to participate. All remaining 429 patients (response rate = 95.8%) filled in sufficient items to obtain summary scores on the psychological measures and thus were eligible for analysis. Patients who refused to participate were more likely to have ischaemic heart disease, atrial fibrillation, and diabetes (all *P*'s < 0.05). No systematic differences in medication use between responders and non-responders were demonstrated (all *P*'s > 0.05).

Baseline characteristics

Baseline characteristics for the total patient sample and stratified by beta-blocker use are listed in *Table 1*. Of all patients, 342 (80%) were on beta-blocker therapy compared with 87 (20%) without beta-blocker therapy. The mean age was 58.4 $\pm$ 12.1 years, 78.6% of the patients were male. Mean scores of anxiety, depression, and ICD concerns were 5.53 ($\pm$4.00), 4.99 ($\pm$3.97) and 9.97 ($\pm$7.71), respectively. Beta-blocker users were more likely to have had a previous MI ($P = 0.02$), and were more often treated with ACE-inhibitors ($P < 0.001$) and statins ($P < 0.001$). In contrast, beta-blocker users were less likely to be treated with amiodarone compared with patients not on beta-blocker therapy ($P < 0.001$). No differences on symptoms of depression, anxiety, and ICD concerns between beta-blocker users and non-beta-blocker users were found (all *P*'s > 0.36).

Univariate analyses

Baseline scores on the HADS-A, HADS-D, and ICDC of beta-blocker users were compared with those of non beta-blocker users. In univariate analysis, there was no significant association between beta-blocker therapy and symptoms of anxiety ($\beta = -0.030$, $P = 0.54$), depression ($\beta = 0.007$, $P = 0.89$), and ICD concerns ($\beta = -0.045$, $P = 0.36$). In order to investigate the relationship between beta-blocker type and dosage and possible interaction effects with emotional distress, we performed univariate ANOVA analyses. The association between beta-blocker type and emotional distress is presented in *Figure 1*, whereas descriptive data on beta-blocker dosage stratified by type are displayed in *Table 2*. Overall, type of beta-blocker was significantly associated with higher scores on the ICDC only ($F = 2.681$, $P = 0.03$). After performing a *post hoc* Bonferroni test, sotalol and bisoprolol were the only types of beta-blockers showing a trend towards significant differences in mean levels of ICD concerns. However, the difference fell short of significance ($P = 0.09$). No association between beta-blocker dosage and emotional distress was found (all *P*'s > 0.21), nor an interaction effect between type of beta-blocker and percentage of the maximum recommended therapeutic dosage in relation to distress (all *P*'s > 0.06). As there was no association between beta-blocker type and dosage and emotional distress, respectively, these variables were not included in multivariate analysis.

Multivariate analyses

Prior to multivariate analysis, we checked for multicollinearity between the independent variables using Spearman's ρ. There were no problems with multicollinearity as all Spearman's ρ's were <0.36. Adjusting for the a priori selected covariates, we composed a four-step model. In Step 1, variables significantly associated with beta-blocker therapy and variables showing a trend towards an association with beta-blocker therapy were included (CAD, atrial fibrillation, and amiodarone). In step 2, ICD indication, NYHA functional class, diabetes mellitus, psychotropic medication and age were added. Because we had no information on LVEF for 13.5% of patients, LVEF was added in Step 3. In order to assess the unique association between beta-blocker therapy and emotional distress, beta-blocker use was added in the final model (Step 4, *Table 3*). The association between beta-blocker therapy and symptoms of anxiety, depression, and ICD concerns remained non-significant ($\beta = 0.009$, $\beta = 0.037$, and $\beta = 0.019$, respectively; all *P*'s > 0.47) when controlling for the appropriate covariates.

Discussion

In the present study, we examined the association between beta-blocker therapy and emotional distress in a consecutive cohort of patients receiving an ICD. Our results neither support a relationship between beta-blocker use and symptoms of anxiety, depression, and ICD concerns, respectively, nor a type- or dose-dependent relationship. The relationship between beta-blocker use and symptoms of depression has been previously studied, specifically in post-MI patients.[14,21,22] However, little is known about the relationship between beta-blocker therapy and anxiety in the general cardiovascular literature. In addition, to our knowledge this study is one of the first to investigate this relationship in patients implanted with an ICD.

Table 1 Baseline characteristics for the total study population and stratified by use of beta-blocking agents[a]

	Total	Beta-blocker users	Non-beta-blocker users	*P* value
n	429 (100)	342 (79.7)	87 (20.3)	
Demographics				
Mean age (±SD)	58.43 (12.1)	58.84 (11.5)	56.83 (14.5)	0.17
Men	337 (78.6)	268 (78.4)	69 (79.3)	0.85
Single/no partner[b]	28 (6.6)	20 (5.9)	8 (9.2)	0.27
Lower education[c]	245 (58.2)	194 (57.7)	51 (60.0)	0.71
Clinical risk factors				
Primary prevention indication	282 (65.7)	231 (67.5)	51 (58.6)	0.12
CRT	122 (28.4)	103 (30.1)	19 (21.8)	0.13
LVEF ≤35%[d]	318 (85.7)	263 (86.8)	55 (80.9)	0.21
Mean QRS (±SD)[e]	129.89 (36.4)	130.65 (36.2)	126.92 (37.1)	0.39
CAD	247 (57.6)	204 (59.6)	43 (49.4)	0.09
Previous MI	210 (49.0)	177 (51.8)	33 (37.9)	0.02
Previous PCI	111 (25.9)	91 (26.6)	20 (23.0)	0.49
Previous CABG	87 (20.3)	71 (20.8)	16 (18.4)	0.62
Symptomatic heart failure[f]	137 (31.9)	113 (33.0)	24 (27.6)	0.33
Atrial fibrillation	95 (22.1)	69 (20.2)	26 (29.9)	0.05
Diabetes	62 (14.5)	54 (15.8)	8 (9.2)	0.12
Smoking[g]	46 (10.8)	37 (10.9)	9 (10.3)	0.89
Medication use				
Amiodarone	80 (18.6)	51 (14.9)	29 (33.3)	<0.001
Diuretics	244 (56.9)	201 (58.8)	43 (49.4)	0.12
ACE inhibitors	307 (71.6)	264 (77.2)	43 (49.4)	<0.001
Statins	253 (59.0)	225 (65.8)	28 (32.2)	<0.001
Digoxin	65 (15.2)	52 (15.2)	13 (14.9)	0.95
Psychotropic medication[h]	70 (16.5)	55 (16.2)	15 (17.4)	0.79
Antidepressants[i]	14 (3.3)	2 (2.3)	12 (3.5)	0.57
Benzodiazepines	29 (6.8)	8 (9.2)	21 (6.1)	0.31
Hypnotics	5 (1.2)	0 (0.0)	5 (1.5)	0.26
>1 type	4 (0.9)	1 (1.1)	3 (0.9)	0.81
Psychological functioning				
Mean depression (±SD)	4.99 (3.97)	5.00 (4.00)	4.93 (3.88)	0.89
Depression score ≥ 8[j]	108 (25.2)	84 (24.6)	24 (27.6)	0.56
Mean anxiety (±SD)	5.53 (4.00)	5.47 (3.95)	5.76 (4.19)	0.54
Anxiety score ≥ 8[j]	119 (27.7)	95 (27.8)	24 (27.6)	0.97
Mean ICD concerns (±SD)	9.97 (7.71)	9.79 (7.53)	10.65 (8.41)	0.36
ICD concerns ≥ 12[j,k]	161 (37.5)	124 (36.3)	37 (42.5)	0.53

[a]Results are presented as *n* (%), unless otherwise indicated.
[b]3 of 429 (0.7%) missing.
[c]Education less than or equal to 13 years, 8 of 429 (1.9%) missing.
[d]58 of 429 (13.5%) missing. [e]1 of 429 (0.2%) missing.
[f]Defined as NYHA class III and IV.
[g]2 of 429 missing (0.5%).
[h]4 of 429 missing in general (0.9%), in 18of 70 (25.7%) type of psychotropic medication was missing.
[i]SSRI ($n = 11$), TCA ($n = 1$), lithium ($n = 1$), serotonergic/noradrenergic antidepressant ($n = 1$).
[j]Based on common used cut-off scores.
[k]4 of 429 missing (0.9%).

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

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

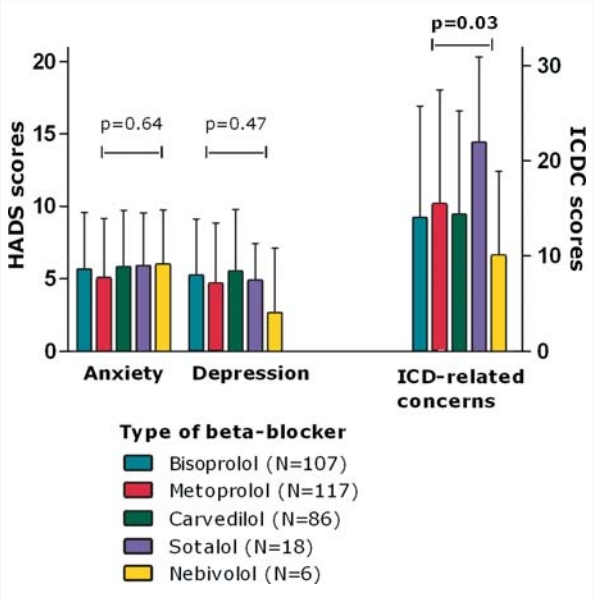

Figure 1 Association between beta-blocker type and emotional distress (unadjusted analysis).

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

The absence of an association between beta-blocker therapy and symptoms of depression is concurrent with the results of multiple recent studies.[14,19–22] In contrast to early findings in this field, when the hypothesis of the depression-inducing effect of beta-blockers was developed, more recent results find no support for this hypothesis. Rabiner *et al.*[45] reported that there are certain beta-blockers, including pindolol and penbutolol, that bind to serotonin receptors in the brain, thereby increasing the amount of free serotonin, which could explain the absence of a negative effect of beta-blockers on mood.[45] In addition, arguments have been made that physical symptoms, including fatigue, are sometimes being misinterpreted as depression.[46] This could lead to an overestimation of the prevalence of depressive symptoms. Besides, instead of examining the presence of depressive symptoms, a number of studies have investigated the relationship between beta-blocker therapy and the use of antidepressants, with antidepressant use serving as a proxy measure for depression.[15,17] Although symptoms of depression and the use of antidepressants are likely to be correlated, as was the case in our study, recent research suggests that ICD patients with clinical significant levels of depressive symptoms are undertreated.[47] It is unclear as to whether these studies[15,17] have used standardized and psychometrically sound instruments to measure depressive symptoms, or whether they did not assess these symptoms at all. In a recent comprehensive review on studies mainly investigating patients with hypertension, MI or heart failure, Verbeek *et al.*[48] concluded that the risk of a beta-blocker-induced

Table 2 Descriptives beta-blockers[a]

Type[b]	Bisoprolol	Metoprolol	Carvedilol	Sotalol	Nebivolol	*P* value
n	107	117	86	18	6	–
Daily dosage (mg)	3.89 (3.61)	86.44 (63.67)	27.99 (22.07)	144.44 (74.06)	4.79 (3.00)	–
% maximum therapeutic dosage[c]	19.45 (18.06)	21.69 (15.96)	37.32 (29.43)	45.14 (23.14)	47.92 (30.02)	<0.001

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

Table 3 Multivariate associations between beta-blocker therapy and emotional distress

	Anxiety		Depression		ICD concerns	
	β	*P*	*β*	*P*	*β*	*P*
Step 1						
CAD	−0.001	0.98	0.028	0.59	0.030	0.57
Atrial fibrillation	−0.091	0.09	0.069	0.20	−0.064	0.23
Amiodarone	0.043	0.42	0.013	0.82	0.056	0.29
Step 2						
ICD indication	0.038	0.49	0.056	0.32	−0.018	0.76
NYHA	0.023	0.66	0.117	0.03	−0.087	0.11
DM	0.068	0.18	0.022	0.67	0.032	0.54
Psychotropic medication	0.285	<0.001	0.281	<0.001	0.219	<0.001
Age	−0.146	0.01	−0.036	0.53	−0.138	0.02
Step 3						
LVEF≤35%	−0.108	0.047	−0.059	0.28	−0.021	0.71
Step 4						
Beta-blocker	0.009	0.86	0.037	0.47	0.019	0.72

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

depression is small and that only in vulnerable subpopulations, including patients with a positive personal or family history of depression, one should stay vigilant with prescribing certain types of beta-blockers, in particular propranolol.[48]

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

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

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