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Prevalence of anxiety and risk associated with ventricular arrhythmia in patients with an implantable cardioverter defibrillator

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\textit{All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation}

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\textbf{Conflict of interest}

None declared
ABSTRACT

Background: Anxiety has been associated with adverse clinical outcomes in patients who have received an implantable cardioverter defibrillator (ICD). However, results are inconclusive likely due to different measures being used to assess anxiety. Hence, the current study aims to examine the prevalence and the association between anxiety, ventricular tachyarrhythmia’s (VTa’s) and all-cause mortality, respectively.

Methods: Patients who received an ICD for the first time were recruited from 6 Dutch referral hospitals as part of the WEBCARE trial. Patients filled in validated questionnaires (GAD-7, STAI-S, HADS-A, ANX4, ICDC, FSAS) to assess their baseline anxiety symptomatology. Logistic regression analysis and Cox Regression analysis were performed to examine the association between anxiety with 1) VTa’s and 2) mortality, respectively.

Results: A total of 214 Patients were included in the analysis with mean age 58.9 and 82.7% being male. The prevalence rates of anxiety varied depending on which questionnaire was used 12.4% (GAD-7), 17.5% (HADS-A), and 28.1% (STAI-S). (Cox) Regression analysis revealed that none of the anxiety measures was associated with VTa’s or all-cause mortality in the current sample. Stratifying the sample by gender, the analysis showed that GAD-7, STAI-S, and ANX4 scores were associated with increased risk of VTa’s but only in male patients.

Conclusions: Prevalence rates of anxiety varied depending on the measurement tool used. No significant association between anxiety and VTa’s and all-cause mortality was observed in the total sample. GAD-7, STAI-S, and ANX4 were associated with increased risk for VTa’s but only in male patients.

Key-words: implantable cardioverter defibrillator; anxiety; ventricular arrhythmia; mortality
INTRODUCTION

Implantable cardioverter defibrillator (ICD) therapy is the treatment of choice for the primary and secondary prevention of sudden cardiac death with a demonstrated survival benefit as compared to antiarrhythmic drugs[1, 2]. Sudden cardiac death is precipitated by ventricular tachyarrhythmia’s (VTa’s), which can be terminated by the ICD through cardiac pacing and/or high voltage shock to the heart muscle. The ICD is generally well accepted by the majority of the patients[3]. However, a subgroup tends to experience increased distress (e.g. anxiety, depression, posttraumatic stress) and impaired quality of life post ICD implantation[4-6].

Previous studies have shown that distress is associated with adverse clinical outcomes in ICD patients, such as VTa’s and mortality[5, 7, 8]. In particular, anxiety has shown to be highly prevalent within the ICD sample ranging between 8-63%[4] and has received attention as a possible correlate of VTa’s [9-12]. The autonomic nervous system (ANS) has been proposed as one of the mechanisms that underlie the link between anxiety and VTa’s, with anxiety leading to activation of the sympathetic nervous system and the initiation and maintenance of VTa’s[13].

However, findings on the relationship between anxiety and adverse outcomes have been mixed. These mixed findings could partly be attributed to the varying assessment tools that have been used to assess anxiety, making it difficult to compare the results of existing studies as they might reflect different levels[14] and types of anxiety (e.g. generic versus disease specific anxiety, state versus trait anxiety). For example, the use of disease specific measures has previously been advocated as these measures would be more sensitive in measuring anxiety in particular populations[3]. In addition, individual differences have rarely been taken into account in previous
studies. For example, there is evidence to support that sex differences might be of importance when focusing on (adverse) clinical outcomes in patients with an ICD[15, 16]. Studies showed evident sex differences with respect to prevalence and etiology of VTa’s and survival benefit in ICD patients[15, 16]. Despite these differences, currently male and female patients receive the same treatment neglecting the fact that female patients are underrepresented in ICD trials that inform the evidence base. Hence, more research is warranted on possible sex specific correlates of adverse clinical outcomes.

Using generic and diseases specific, validated assessment tools, the current study will examine (i) the prevalence of anxiety in patients with an ICD, (ii) the association between anxiety and VTa’s and all-cause mortality, and (iii) the association between anxiety and VTa’s and all-cause mortality stratified by sex.

METHODS

Participants and study design

The study sample was comprised of patients implanted with a first-time ICD between April 2010 and February 2013 in five Dutch referral hospitals (Amphia Hospital, Breda; Canisius-Wilhelmina Hospital, Nijmegen; Catharina Hospital, Eindhoven; Erasmus Medical Center, Rotterdam; Onze Lieve Vrouwe Gasthuis, Amsterdam). Inclusion criteria were: first-time ICD implant and age between 18-75 years. Exclusion criteria were: significant cognitive impairments (e.g. dementia), history of psychiatric illness other than affective/anxiety disorders, life-threatening co-morbidities (e.g. cancer), life expectancy <1 year, being on the waiting list for heart transplantation, and insufficient knowledge of the Dutch language. Patients were enrolled as part
of the WEBCARE trial and were therefore required to also have sufficient internet/computer skills. For a detailed description and results of the WEBCARE trial, we refer the reader to previous publications[17]. In brief, the WEBCARE study was a randomized controlled trial assessing the effectiveness of a 12-week fixed, online course, based on problem solving therapy to reduce anxiety and improve quality of life in patients with an ICD.

Procedure

An ICD nurse or ICD technician approached eligible patients prior to or briefly after ICD implantation. Patients were informed about the study both in writing and orally and were given an informed consent form. They were instructed to read the information carefully and if they decided to sign the informed consent form during their stay at the hospital, they were provided with the first set of (baseline) questionnaires (after implantation). Patients who could not decide on participation during hospitalization were given the set of questionnaires to take home with the instruction that they could return the questionnaires to Tilburg University (core-lab) in an enclosed, pre-stamped envelope within 2 weeks in case they decided to participate. If the questionnaires were not returned within 2 weeks, patients received up to 3 reminder phone calls from the researcher (MH). Information on demographic and clinical baseline characteristics were captured at the time of implantation from patients’ medical records.

The study was approved by the Medical Ethics Committee (METC number MEC-2009-211 / NL25617.078.09) of the participating hospitals and all patients provided written informed consent. The study was conducted in accordance with the Helsinki declaration and the trial was registered on www.clinicaltrials.gov (NCT:00895700).
Measures

Information on demographic (sex, age, marital status) and clinical data (ICD indication, diabetes, Charlson Comorbidity Index, left ventricular ejection fraction, psychotropic medication, beta-blockers and digoxin) were collected using purpose-designed questionnaires and patients’ health records. All questionnaire data were collected at baseline using established, validated questionnaires, administered after implantation (up to 10 days post implantation). Follow up data on ICD shocks were collected from ICD electrocardiograms by the electrophysiologists of the participating hospitals.

Endpoints

Study endpoints were VTa’s and mortality at 4-7 year follow-up. Information on VTa’s and mortality were collected from patients’ medical records. Information on VTa’s during the follow-up, were derived from ICD data and stored electrocardiograms by qualified electrophysiologists. If only the month and year of passing were reported in the record, the actual data was set as the 15th of the month. Since in the current sample, only a small proportion of deaths (N=5) could be attributed to cardiac cause, the study will focus on all-cause mortality as one of the outcome measures.

Generic anxiety measures

GAD-7

Generalized Anxiety Disorder scale (GAD-7)[18] was used to assess symptoms of anxiety. The GAD-7 consists of 7 items that are rated on a 4-point Likert scale from 0 to 3. The total score can
range between 0 to 21, with a higher score indicating higher probable clinical levels of anxiety. A cut-off of ≥10 is used to indicate the presence of probable clinical levels of anxiety. The GAD-7 has previously been used in the cardiac population. In the current sample, the scale has a good reliability with a Cronbach’s alpha of .91

**HADS-A**

The Hospital Anxiety and Depression Scale (HADS-A)[19] was administered to assess anxiety symptoms at baseline. The 7-item subscale was used for the assessment of anxiety. Items are rated on a 4-point Likert scale from 0 to 3, with a score range of 0-21. A higher score indicates more symptoms of anxiety. A cut-off score of ≥8 is used to indicate the presence of probable clinical levels of anxiety. The HADS-A is a reliable measure with a Cronbach’s alpha of .82 in the current sample.

**STAI-S**

The Dutch 20-item state version of Stait-Trait Anxiety Inventory (STAI-S)[20] was used to assess symptoms of general anxiety at baseline. Each item is rated on a 4-point Likert scale from 1 to 4 with the total score ranging between 20 to 80. A higher score indicates a higher levels of symptomatology. A cut-off of ≥40 indicates elevated levels of anxiety symptomatology. The STAI-S is a valid and reliable measure of anxiety with a Cronbach’s alpha of .93 within the current sample.
The newly developed brief anxiety questionnaire (ANX4) has been administered in the current sample to assess general anxiety. The questionnaire consists of 4 items that are rated on a 5-point Likert scale. Answers are provided on a 5-point Likert scale from 0 to 4, resulting in a total score ranging between 0 to 16. The scale has shown to reliable in the current sample with a Cronbach’s alpha of .88.

**Disease specific anxiety measures**

**ICDC**

Patients’ concerns about the ICD were assessed using the ICD Patients Concerns questionnaire (ICDC)[21]. The scale consists of 8 items that are rated on a 5-point Likert scale ranging from 0 to 4. The total score can range between 0 to 32, with a higher score indicating higher levels of concerns. The ICDC is a reliable measure with a Cronbach’s alpha of .93 (current sample).

**FSAS**

The Florida Shock anxiety Survey (FSAS)[22] was used to assess ICD shock anxiety. The survey consists of 10 items that are rated on a 5-point Likert scale from 1 (never) to 5 (always). The total score on the FSAS ranges between 10 to 50, with a higher score indicating higher levels of shock anxiety. The FSAS is a reliable measure with a Cronbach’s alpha of .87 (current sample).
Statistical Analysis

Patients’ baseline characteristics were analyzed using Student’s T-test (continuous variables) and Chi-square test (dichotomous variables) and are presented as means ± standard deviation (SD) or total(percentages), respectively.

Univariate and multivariate logistic regression analysis and Cox survival analysis were performed to examine the association between anxiety measures and 1) VTa’s and 2) all-cause mortality, respectively. Covariates that were included in the multivariate models were selected based on the literature and significant baseline differences within the sample (Table 1) and included sex, age, marital status, ICD indication, diabetes, Charlson Comorbidity Index left ventricular ejection fraction, psychotropic medication, beta-blockers and digoxin. In secondary analysis, logistic regression and Cox survival analysis were performed to examine whether the association between anxiety and outcomes differ depending on gender.

Missing data on questionnaires were imputed, only if <80% was missing, using the mean score of the patient on the available completed items.

All tests were 2-tailed, with an alpha of <.05 indicating statistical significance. The assumptions for the tests that were performed were checked and met. All data were analyzed using SPSS statistics 24.0 for Windows.
RESULTS

Patient characteristics

Consecutive ICD patients (N=1024) were approached for participation between April 2010 and February 2013 as part of the WEBCARE study (see Figure 1 for sample selection). A total of 340 patients consented to participate in the study. Of these patients, 51 patients did not fill in baseline measures and were excluded from the study. Overall, these patients more often had NYHA class III/IV (p=.045), peripheral artery disease (p=.022), and used more often psychotropic medication (p=<.001) as compared to remaining 289 patients who were randomized. Of the 289 who filled in the baseline measures, 9 patients did not fill in (one of the) anxiety questionnaires that are analyzed in the current study. Of the remaining sample, 26 patients had missings on mortality and/or VTa’s data and were therefore excluded from the analyses. Additionally, 40 patients were excluded due to missings on demographic and/or clinical variables. A total of 214 patients had complete data and were included in the current analyses. As compared to patients who were included in the analysis, excluded patients were less likely to use ACE-inhibitors (52% vs. 66%; p=.01) and statins (53% vs 66%; p=.02), but more likely to use psychotropic medication (15% vs 7%; p=.02). No other systematic baseline differences were observed. Baseline characteristics of the sample are presented in Table 1.

Descriptives

Mean follow-up was 5.8 years ranging between 4-7 years post inclusion with an interquartile range of 1. During follow-up, a total of 88 patients experienced VTa’s, while 33 died due to all cause mortality. The prevalence of generic anxiety, using traditional, validated cut-off scores
were 12.4% for GAD-7, 17.5% for HADS-A, and 28.1% for STAI-S. For the ANX-4 (M=1.86 SD=2.92) questionnaire and the disease-specific measures ICDC (M=6.18 SD=6.55) and FSAS (M=16.30 SD=5.75) no validated cut-off score has been determined.

**Ventricular tachyarrhythmia’s**

Univariate analysis revealed that there were no significant associations between, and GAD-7, HADS-A, STAI-S, ICDC, FSAS and VTa’s observed. Only a significant association between ANX4 and VTa’s was observed (see Table 2).

After adjusting for demographic and clinical covariates (as previously specified), the multivariate models revealed that there was no significant association between any of the anxiety measures and VTa’s (see Table 2).

Secondary (univariate) analyses were performed to examine the association between anxiety and VTa’s stratified by gender. The univariate analysis revealed that only the scores on the GAD-7 (OR=1.069; 95%CI .99-1.14; p=.05), STAI-S (OR=1.038; 95%CI 1.01-1.07; p=.02), and ANX-4 (OR=1.189; 95%CI 1.19-1.06; p=.004) scale, were significantly associated with VTa’s in male but not female patients.

**All-cause mortality**

In univariate Cox Regression models, we found no significant association between GAD-7 (HR=1.001; 95%CI .91-1.11; p=.99), HADS-A (HR=.962; 95%CI .83-1.11; p=.60), STAI-S (HR=.94; 95%CI .95-1.04; p=.77), ANX-4 (HR=.978; 95%CI .85-1.12; p=.75), ICDC (HR=.999; 95%CI .94-1.06; p=.97), FSAS (HR=.973; 95%CI .90-1.05; p=.49) and all-cause mortality.
Multivariate Cox Regression revealed the same results. No significant associations between any of the variables and all-cause mortality were observed (data not shown).

Secondary (univariable) subgroup analysis stratifying the sample by gender also revealed no significant association between anxiety measures and all-cause mortality in male and female patients separately (results not shown).

Discussion

To the best of our knowledge, this is the first study where multiple questionnaires (generic and disease-specific) have been evaluated to examine the prevalence and association of anxiety with VTa’s and mortality in patients with an ICD. Our results showed that the prevalence rate varied depending on which questionnaire was administered, with prevalence rates of 12.4% for GAD-7, 17.5% for HADS-A, and 28.1% for STAI-S. Other included questionnaires did not have a validated cut-off scores, hence, the prevalence rates could not be calculated. While the prevalence rates of anxiety seem to be within the range of what was previously reported[4], it is important to note that they vary significantly depending on which measure was used. This finding indicates that the levels and prevalence of anxiety cannot be compared between studies when using different assessment tools [14]. Hence, it is important to carefully consider which tool to use in your study and why.

Our findings further showed that anxiety (any measure) was not associated with VTa’s nor with all-cause mortality. Stratifying by gender, we found that higher scores on the GAD-7, STAI-S, and ANX4 questionnaires were associated with an increased risk of VTa’s, only in male patients. No other significant associations were observed.
The current results showed a significant association between the GAD-7, STAI-S, ANX4 and VTa’s, but only in male patients. This indicates that more generic anxiety (less related to having an ICD) could particularly be cardiotoxic. Generally, within the ICD population male and female patients tend to experience comparable distress levels[23]. However, studies have indicated that significant sex differences exist in heart rhythm disease[15]. These differences can partly be explained by anatomical differences (females have an average smaller heart size which contributes to shorter QRS complexes)[24] but also by the effects of sex hormones (estrogen, progesteron), which might have a protective effect on adverse outcomes in female patients[15]. Another explanation could be that the underlying heart disease varies between male and female patients, with male patients having more often ischemic pathology as compared to female patients[25]. Overall, studies indicate that female patients are less prone to VTa’s and that there might be gender specific correlates of adverse outcomes in cardiac patients[15]. Finally it is important to note that previous studies showed that type of anxiety may also be a gender related predictor with phobic anxiety in women being associated with increased risk of cardiac mortality and sudden cardiac death[26].

The findings with respect to the association between anxiety and adverse clinical outcomes are in line with some[12] but not all studies[7]. The discrepancy with previous studies could be attributed to the patient sample that was included in the current study. Patients who were enrolled in the WEBCARE trial were relatively healthy both physically and mentally[17]. Overall, patients reported relatively low anxiety scores at baseline, which might have contributed to the null findings. In previous studies, higher levels of anxiety were associated with VTa’s [7, 11]. In their study, van den Broek et al. (2009)[12] observed an association between anxiety and VTa’s
but only in patients with a Type D (distressed) personality. This indicates that there might be other (trait) factors which possibly modulate and reinforce the association between anxiety and VTa’s[16]. Another explanation could be that the current study focused on more generalized constructs of anxiety while other types of anxiety might be of more importance to examine. For example, an association between trait anxiety and ICD shock has also been observed in specific subgroups of patients[9] while anger has shown to be associated with VTa’s in ICD patients[10]. As a recent study showed that ICD patients experience different types of anxiety (e.g. panic, posttraumatic stress disorder)[27], future studies should examine which types of anxiety are related to VTa’s and what the underlying mechanisms are. In addition to this, future studies should also focus on the changing trajectories of anxiety over time and the impact on outcomes. Previous studies have established that anxiety changes over time in ICD patients, generally reaching general population level at 3 months post implantation [17, 28]. It would be worthwhile examining, for example, whether patients with persistent levels of anxiety have and increased risk for adverse outcomes.

The findings of the current study should be interpreted in light of some limitations. First, we did not have the date for the first VTa. Hence, it was not possible to perform Cox Regression analyses, which may have contributed to the null findings. Second, our sample mainly consisted of male patients. Despite that this is a reflection of clinical practice, it would have produced more reliable results on sex specific predictors, if more female patients were included. In line with this, due to low number of patients and events we were not able to perform multivariable analysis stratified by gender. Hence, these results should be considered as explorative and should be interpreted with caution. Third, due to the relatively low number of events, we were not able to use cardiac
mortality as a study outcome. This might have resulted in different findings as it can be expected that anxiety is particularly related to cardiac mortality as compared to all-cause mortality (due to the mentioned underlying mechanism). However, this is the first study to use multiple anxiety measures and evaluate their respective associations with long-term adverse clinical outcomes in ICD patients.

In clinical practice, it is important to understand that anxiety questionnaires are not necessarily interchangeable and that a careful assessment of the tool should be performed before using it in the clinical practice as a risk indicator of poor clinical outcomes. Healthcare professionals should consider for example whether false positives or false negatives should be avoided and based on that select the appropriate measure. In addition, it is important to pay attention to male patients who are experiencing anxiety post ICD implantation. This might be a group that is at increased risk of experiencing VTa’s in the future and who should be offered additional care. From previous studies, it is well documented that cognitive behavioral therapy is successful in reducing distress levels [29]. Whether this reduction will also lead to lower incidence of VTa’s should be examined in future studies. Future studies should also focus on examining, in sufficiently powered studies, what type of anxiety is cardiotoxic and which patients are at increased risk of experiencing adverse outcomes when reporting high baseline anxiety. This could further feed the patient tailored approach where individual differences are taken into account when providing healthcare.

In conclusion, current results show that anxiety is highly prevalent in ICD patients and that the prevalence rates tend to strongly vary depending on which measurement tool was used. Current results show that (generic) anxiety is only related to adverse outcomes (VTa’s) in male patients.
Hence, individual differences (e.g. sex), might explain why results to date have been inconsistent with respect to the association between anxiety and clinical outcomes in ICD patients.
Figure 1: Flowchart patient recruitment

Assessed for eligibility (n=1024)

Excluded (n=735)
- Not meeting inclusion criteria (n=492)
- Refused to participate (e.g. no time, not interested) (n=192)
- Did not return baseline questionnaire (n=51)

Randomized (n=289)

Excluded from current analysis (N=75)
- 9 no baseline anxiety
- 26 no outcome measure
- 40 no demographic and/or clinical data

Analyzed (n=214)
Table 1: Baseline sample characteristics

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<tr>
<th>Demographic</th>
<th>Total N=214</th>
<th>Ventricular tachyarrhythmia’s N=85</th>
<th>All-cause mortality N=181</th>
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<td>N=214</td>
<td>N=85</td>
<td>N=129</td>
</tr>
<tr>
<td></td>
<td>yes</td>
<td>no</td>
<td>p</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>177(82.7)</td>
<td>77(43.5)</td>
<td>100(56.5)</td>
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<tr>
<td>Age</td>
<td>58.9±9.9</td>
<td>58.4±9.6</td>
<td>59.3±10.1</td>
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<td>Marital status (partner)</td>
<td>183(85.5)</td>
<td>73(39.9)</td>
<td>110(60.1)</td>
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<td>Education (high)</td>
<td>155(72.4)</td>
<td>62(40.0)</td>
<td>93(60.0)</td>
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<th>All-cause mortality N=181</th>
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<td>N=85</td>
<td>N=129</td>
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<tr>
<td></td>
<td>yes</td>
<td>no</td>
<td>p</td>
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<tr>
<td>Indication</td>
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<td>36(58.1)</td>
<td>26(41.9)</td>
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<tr>
<td>IHD¹</td>
<td>132(61.7)</td>
<td>51(38.6)</td>
<td>81(61.4)</td>
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<tr>
<td>HF²</td>
<td>125(58.4)</td>
<td>48(38.4)</td>
<td>77(61.1)</td>
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<tr>
<td>Shocks (any)*</td>
<td>58(27.1)</td>
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<td>--</td>
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<td>Diabetes</td>
<td>31(14.5)</td>
<td>8(25.8)</td>
<td>23(74.2)</td>
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<td>CCI³</td>
<td>1.69±0.9</td>
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<td>1.7±1.1</td>
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<tr>
<td>LVEF_35⁴</td>
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<td>60(37.3)</td>
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<tr>
<td>NYHA II/III⁵ N=181</td>
<td>35(16.4)</td>
<td>11(31.4)</td>
<td>24(68.6)</td>
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<tr>
<td>Intervention⁶</td>
<td>103(48.1)</td>
<td>39(37.9)</td>
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<th>All-cause mortality N=181</th>
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<td>Psychotropics⁷</td>
<td>15(7.0)</td>
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<tr>
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<td>Statins</td>
<td>162(66.4)</td>
<td>56(39.4)</td>
<td>86(60.6)</td>
</tr>
</tbody>
</table>

¹Ischemic Heart Disease; ²Heart Failure; ³Charlson’s Comorbidity Index; ⁴Left Ventricular Ejection Fraction; ⁵New York Heart Association classification; ⁶WEBCare intervention group; ⁷Psychotropic Medication (any).

*Any shocks (appropriate and inappropriate) experienced between baseline and follow-up (mean 5.8 years)

Data are shown as Mean±Standard Deviation and Number(%)

18
Table 2: (Borderline) Significant correlates of ventricular tachyarrhythmia’s

<table>
<thead>
<tr>
<th>Variable</th>
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<th>95% CI</th>
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GAD-7: Generalized Anxiety Disorder scale; HADS-A: Hospital Anxiety and Depression Scale – Anxiety; STAI-S: State-Trait Anxiety Inventory - State; ANX4: Anxiety scale; ICDC: ICD-concerns scale; FSAS: Florida Shock Anxiety Scale
REFERENCES


