Patient-Reported Quality of Life as a Predictor of Mortality and Ventricular Tachyarrhythmia's During 7 Years' Follow-Up in Patients With an Implantable Cardioverter Defibrillator (from the MIDAS Study)

Barbara van Veen, MSc[a], Christina Maar Andersen, PhD[a], Jens Brock Johansen, MD, PhD[b], Dominic AMJ Theuns, PhD[c], and Susanne S. Pedersen, PhD[a,b,*]

Preliminary evidence suggests that poor patient-reported quality of life (QoL) predicts mortality on the short term in patients with an implantable cardioverter defibrillator (ICD). It is unclear if this association persists on the long term. We evaluated whether patient-reported QoL at the time of implantation predicts mortality and ventricular tachyarrhythmias (VTa's) during 7 years' follow-up in patients with an ICD. A consecutive cohort of patients (80% men; mean [SD] age = 58 [12]) implanted with an ICD completed the Short Form Health Survey (SF-36). The 8 SF-36 subscales and the 2 component summary scores were used as predictors of VTa's and mortality at 7 years' follow-up. At 7 years' follow-up, 34% (132/392) of patients had died. Baseline physical functioning (hazard ratio [HR]: 1.59; 95% confidence interval [CI]: 1.11 to 2.29), role physical functioning (HR: 1.59; 95% CI: 1.09 to 2.31), vitality (HR: 1.53; 95% CI: 1.05 to 2.22), and general health (HR: 1.57; 95% CI: 1.09 to 2.27) were associated with 7-year mortality in adjusted analyses. There was a trend for low mental health being associated with an increased risk of mortality (HR: 1.38; 95% CI: 0.98 to 1.96). The other SF-36 dimensions were not significantly associated with mortality. Only baseline social functioning was associated with risk of VTa's during follow-up. In conclusion, patients with lower levels of physical functioning, role physical functioning, vitality, or general health had a greater risk of mortality, whereas only poor social functioning was associated with VTa's during 7 years' follow-up. Patient-reported QoL at the time of implant could be used to identify patients at risk for long-term mortality. **(Am J Cardiol 2019;123:605−610)**

Sudden cardiac arrest is the leading cause of death worldwide[1] and is generally caused by ventricular tachyarrhythmia's (VTa's).[2] To prevent sudden cardiac arrest in patients at high risk, implantable cardioverter defibrillator (ICD) therapy is standard care both for primary and secondary prevention.[3,4] Patients with an ICD have to live with risk of device-related complications,[5] appropriate and/or inappropriate shocks,[6] underlying heart disease,[7] and co-morbidities,[8] which may influence quality of life (QoL), morbidity, and mortality. Systematic reviews and meta-analyses show that QoL is a predictor of hospitalization and premature death independent of traditional risk factors in cardiac patients.[9,10] To our knowledge, only 4 studies have examined the value of patient-reported QoL as a predictor of health outcomes in patients with an ICD. Three of the studies used secondary data from the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial[11,12] and the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II),[13] and one study used a cross-sectional survey with follow-up register data.[14] Follow-up periods ranged from 1 to 3 years.[11−14] Hence, we have no prospective studies of "real world" unselected patient cohorts that have investigated the impact of patient-reported QoL at the time of implant on mortality and VT's in the ICD population on the long term. Hence, we examined whether patient-reported QoL predicts mortality and VTa's at 7 years postimplant in a consecutive cohort of patients from the "real world."

Methods

The study sample comprised a prospective cohort of 448 patients implanted with a first-time ICD or ICD with cardiac resynchronization therapy (CRT-D) between August 2003 and February 2010 at the Erasmus Medical Center (EMC), Rotterdam, The Netherlands enrolled in the MIDAS study (mood and personality as precipitants of arrhythmia in

[a]Department of Psychology, University of Southern Denmark, Odense, Denmark; [b]Department of Cardiology, Odense University Hospital, Odense, Denmark; and [c]Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands. Manuscript received September 19, 2018; revised manuscript received and accepted November 1, 2018.

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*Corresponding author: Tel: +45 65 50 79 92.

E-mail address: sspedersen@health.sdu.dk (S.S. Pedersen).

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patients with an implantable cardioverter defibrillator: a prospective study). Exclusion criteria were life expectancy less than 1 year, on the waiting list for heart transplantation or left ventricular assist device, previous psychiatric illness other than affective/anxiety disorders, or inadequate knowledge of the Dutch language. Patients completed a set of standardized and validated self-report questionnaires 1 day before implantation (i.e., baseline). The study protocol was approved by the medical ethics committee of the EMC [MEC 231.491/2003/148]. The Danish Data Protection Agency approved the study in 2017 (The University of Southern Denmark number 18/28527, cf. GDPR Article 30), as required by Danish law when transferring and using data from abroad. The study was conducted according to the ethical guidelines of the Helsinki Declaration. Oral and written information about the study was given to all patients, and all patients provided written informed consent.

Information on patients' demographic and clinical variables at baseline was collected from patients' electronic health records or from purpose-designed questions in the questionnaire sent out to patients.

Patients completed the 36-item Short Form Health Survey Questionnaire (SF-36) at baseline.[15] The SF-36 taps into 8 dimensions of QoL: 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 8 dimensions, it is possible to calculate 2 component summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS).[16] Using an algorithm, subscale and component summary scores are calculated that range from 0 to 100, with 0 representing the poorest QoL and 100 the best QoL.

The study end points were time to first appropriate ICD therapy and mortality. Information on ICD therapies were recorded prospectively in the institutional database of the EMC from the time of implant. Patients were seen in the outpatient clinic for interrogation of their device at 3-month intervals, and patients were asked to contact the outpatient clinic as soon as possible after a symptomatic event. The date, type, and mean cycle length of the VTa and the type and outcome of delivered ICD therapy were recorded every time. The arrhythmias were classified as (1) VTa *or* (2) atrial tachyarrhythmia (including atrial fibrillation, atrial flutter, atrial tachycardia, and sinus tachycardia) without a coexistent VTa. ICD therapy triggered by VTa's was considered appropriate, whereas therapy delivered due to atrial tachyarrhythmias *or* T wave oversensing and noise was considered inappropriate. Information on survival status was captured from patients' electronic health records and defined as all-cause mortality.

To examine between group differences, we used the chi-square test (Fisher's exact test if appropriate) for categorical data and Student's *t* test for independent samples for continuous data. Before conducting the Cox proportional hazard regression analyses, we divided QoL scores into 2 groups based on the median split for all dimensions; good QoL was used as the reference category. To examine the impact of different aspects of QoL on mortality and VTa's during the 7-year follow-up period, we used univariable and multivariable Cox proportional hazard regression analyses. In the multivariable models, we adjusted for age, sex, education, QRS >120 ms, coronary artery disease etiology, heart failure (mild [New York Heart Association {NYHA} class I to II]) versus severe (NYHA class III and IV), indication for ICD, amiodarone, and shocks during follow-up. These variables were chosen a priori based on the literature. The covariates were forced into the model using the enter method in order to reduce the risk of type 2 error (overfitting).[17] For all Cox regression analyses, the hazard ratio (HR) and the corresponding 95% confidence interval (CI) are reported. For all analyses, we used 2-tailed tests and a p value <0.05 was regarded as statistically significant. All statistical analyses were performed using SPSS 24 for Windows (SPSS Inc., Chicago, Illinois).

Results

Of 448 eligible patients, 32 patients did not complete the SF-36 at baseline and 25 patients had a heart transplantation. One patient both had a missing score on the SF-36 and undergone a heart transplantation. Hence, 392 patients were included in the final analyses. Excluded patients (n = 57) were more likely to use psychopharmaca (33% vs 15%, p = 0.006) and digoxin (28% vs 13%, p = 0.003) and have atrial fibrillation (45% vs 20%, p < 0.001) but less likely to have a QRS >120 ms (34% vs 50%, p = 0.028), a partner (34% vs 50%, p < 0.001) and low education (34% vs 58%, p < 0.001), as compared with participants. The 2 groups did not differ significantly on any of the other baseline characteristics, as presented in Table 1 (data not shown). The follow-up periods for the included patients were: Interquartile range = 7.0 to 3.5, median = 7.0, and mean ± SD = 5.4 ± 2.3. Baseline characteristics for the total sample and stratified by survival status are presented in Table 1. Of the 392 participants, 132 (34%) patients died during follow-up. Survivors were more likely to be women, to be younger and to be working, and less likely to have a CRT-D device, previous coronary artery bypass surgery, shocks during follow-up, severe heart failure (NYHA class III and IV), QRS >120 ms, previous myocardial infarction (MI), coronary artery disease, or atrial fibrillation. In addition, co-morbid diseases, such as diabetes, chronic obstructive pulmonary disease, and peripheral vascular disease were less common in survivors, who were also less likely to use medication (e.g., amiodarone, angiotensin converting enzyme inhibitors, diuretics, statins, and digoxin). Overall, survivors had a more favorable health profile.

Table 2 presents baseline QoL for the 8 subscales of the SF-36 and the 2 component summary scores stratified by survival status and VTa's. Patients who died during the 7-year follow-up period had lower scores on PF (mean 50.3 ± 26.0 vs 60.5 ± 26.2, p = 0.0001) and GH (mean 45.9 ± 20.5 vs 54.7 ± 20.4, p = 0.0001) but did not differ significantly on the other 6 SF-36 subscales, as compared with patients who survived (Table 2). Patients who died during follow-up also had a lower PCS score as compared with patients who survived (mean 37.5 ± 9.9 vs mean 41.1 ± 10.3, p = 0.0010), whereas there was no significant difference between groups on the MCS score. Patients experiencing VTa's versus no VTa's did not differ significantly on any of the SF-36

Table 1
Baseline characteristics for the total sample and stratified by mortality 7 years post implant*

Characteristics	Total (n = 392)	Dead (n = 132)	Alive (n = 260)	p Value
Women	82 (21%)	11 (8%)	71 (27%)	<0.0001
Age − mean (SD)	58 (12)	64 (9)	55 (12)	<0.0001
Single/no partner#	27 (7%)	8 (6%)	19 (7%)	0.618
Lower education‡,#	227 (58%)	84 (64%)	143 (55%)	0.151
Work#	303 (77%)	25 (19%)	134 (52%)	<0.0001
Primary prevention	254 (65%)	82 (62%)	172 (66%)	0.430
Cardiac resynchronization therapy	112 (29%)	51 (39%)	61 (24%)	0.002
Previous coronary bypass	82 (21%)	43 (33%)	39 (15%)	<0.0001
Shocks during follow-up†	92 (24%)	45 (34%)	47 (18%)	<0.0001
Severe heart failure (NYHA class III-IV)#	116 (30%)	57 (43%)	59 (23%)	<0.0001
Previous percutaneous coronary intervention	103 (26%)	39 (30%)	64 (25%)	0.295
QRS >120 ms#	194 (50%)	84 (64%)	110 (42%)	<0.0001
Previous myocardial infarction	202 (52%)	89 (68%)	113 (44%)	<0.0001
Coronary artery disease	235 (60%)	101 (77%)	134 (52%)	<0.0001
Left ventricular ejection fraction ≤ 35%#	287 (73%)	104 (79%)	183 (70%)	0.137
Atrial fibrillation	79 (30%)	38 (29%)	41 (16%)	0.002
Diabetes#	54 (14%)	29 (22%)	25 (10%)	0.001
Chronic obstructive pulmonary disease#	31 (8%)	17 (13%)	14 (5%)	0.010
Peripheral vascular disease#	28 (7%)	15 (11%)	13 (5%)	0.021
Cancer#	31 (8%)	12 (9%)	19 (7%)	0.544
Smoking	45 (12%)	19 (14%)	26 (10%)	0.207
Amiodarone	68 (17%)	43 (33%)	25 (10%)	<0.0001
Beta-blockers	315 (80%)	109 (83%)	206 (79%)	0.431
Diuretics	216 (55.1%)	94 (71%)	122 (47%)	<0.0001
Angiotensin converting enzyme Inhibitors	280 (71.4%)	103 (78%)	177 (68%)	0.039
Statins	233 (59.4%)	98 (74%)	135 (52%)	<0.0001
Digoxin	52 (13.3%)	27 (21%)	25 (10%)	0.003
Psychotropic medication#	57 (14.7%)	21 (16%)	36 (15%)	0.264
Psychological treatment#	20 (5.1%)	4 (3%)	16 (6%)	0.596
Cardiac rehabilitation#	25 (6.5%)	11 (9%)	14 (7%)	0.178

* Results are presented as n (%) unless otherwise indicated.

† Appropriate or inappropriate shocks during follow-up.

‡ ≤13 years.

There were missings on: Single/no partner (n = 4); lower education (n = 8); work (n = 2); severe heart failure (NYHA class III-IV) (n = 2); QRS >120 ms (n = 1); left ventricular ejection fraction £ 35% (n = 54); diabetes (n = 1); chronic obstructive pulmonary disease (n = 4); peripheral vascular disease (n = 4); cancer (n = 4); smoking (n = 2); psychotropic medication (n = 4); psychological treatment (n = 3); cardiac rehabilitation (n = 7).

subscales nor the component summary scores at baseline (Table 2).

Poorer baseline physical functioning (HR: 1.59; 95% CI: 1.11 to 2.29, p = 0.012), role physical functioning (HR: 1.59; 95% CI: 1.09 to 2.31, p = 0.015), vitality (HR: 1.53; 95% CI: 1.05 to 2.22, p = 0.27), and general health (HR: 1.57; 95% CI: 1.09 to 2.27, p = 0.016) were all associated with a higher mortality risk during the 7-year

Table 2
Baseline quality of life stratified by survival status and ventricular tachyarrhythmia's

	Total (n = 392)		Dead (n = 132)		Alive (n = 260)		p	VT	(n = 92)	No-VT	(n = 300)	p
	Mean	SD	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Physical functioning	57.1	26.5	50.3	26.0	60.5	26.2	0.0001	52.2	50.2	45.3	49.9	0.251
Role physical functioning	35.4	40.2	30.1	38.3	38.1	40.9	0.0635	37.7	49.5	37.7	48.5	0.532
Bodily pain	66.0	27.7	63.3	27.3	1.7	27.9	0.1646	56.5	49.8	47.7	50.0	0.138
Social functioning	65.2	28.7	65.8	28.8	65.0	28.6	0.7782	40.2	49.3	31.3	46.5	0.128
Mental health	70.9	19.2	69.3	20.7	71.8	18.4	0.2250	44.6	50.0	41.7	49.4	0.624
Role emotional functioning	58.7	42.2	53.0	43.00	61.5	41.6	0.0593	53.3	50.2	42.0	49.4	0.580
Vitality	56.0	21.9	53.4	23.7	57.4	20.0	0.0905	47.8	50.2	39.0	48.9	0.133
General health	51.7	20.8	45.9	20.5	54.7	20.4	0.0001	47.8	50.2	45.0	49.8	0.635
PCS	39.9	10.3	37.5	9.9	41.1	10.3	0.0010	51.3	50.3	49.7	50.1	0.812
MCS	45.5	11.3	45.2	12.1	45.7	10.8	0.6652	55.4	50.0	48.3	50.1	0.234

MCS = Mental Component Summary Score; PCS = Physical Component Summary Score; QoL = Quality of life; VT = ventricular tachyarrhythmia.

Table 3
Associations between baseline quality of life* and mortality during 7-years' follow-up (unadjusted and adjusted analyses†)

	Unadjusted HR [95% CI]	p	Adjusted† HR [95% CI]	p
Physical functioning	1.53 [1.08−2.17]	0.017	1.59 [1.11−2.29]	0.012
Role physical functioning	1.57 [1.09−2.26]	0.016	1.59 [1.09−2.31]	0.015
Bodily pain	1.10 [0.78−1.55]	0.586	1.04 [0.74−1.48]	0.816
Social functioning	0.89 [0.62−1.27]	0.513	1.19 [0.82−1.73]	0.374
Mental health	1.18 [0.83−1.67]	0.362	1.38 [0.96−1.98]	0.079
Role emotional functioning	1.34 [0.94−1.90]	0.104	1.25 [0.87−1.79]	0.226
Vitality	1.35 [0.94−1.92]	0.102	1.53 [1.05−2.22]	0.027
General health	1.69 [1.18−2.41]	0.004	1.57 [1.09−2.27]	0.016
PCS	1.37 [0.97−1.93]	0.073	1.27 [0.88−1.83]	0.199
MCS	1.28 [0.91−1.81]	0.152	1.38 [0.98−1.96]	0.068

MCS = mental component summary score; PCS = physical component summary score.
* QoL scores were divided into two groups based on the median split for all dimensions; good QoL was used as the reference category.
† Analyses were adjusted for age, sex, education, QRS >120, coronary artery disease (etiology), mild (NYHA class I-II) versus severe (NYHA class III-IV) heart failure, indication for ICD, amiodrone, and shocks during follow-up.

Table 4
Associations between baseline quality of life* and ventricular tachyarrhythmias during 7-years' follow-up (unadjusted and adjusted analyses†)

	Unadjusted HR [95% CI]	p	Adjusted HR [95% CI]	p
Physical functioning	0.98 [0.71−1.36]	0.919	0.98 [0.69−1.38]	0.892
Role physical functioning	1.11 [0.80−1.54]	0.539	1.15 [0.82−1.61]	0.433
Bodily pain	0.85 [0.61−1.17]	0.317	0.78 [0.56−1.09]	0.148
Social functioning	0.70 [0.50−0.97]	0.034	0.68 [0.48−0.96]	0.028
Mental health	1.08 [0.78−1.50]	0.636	1.15 [0.82−1.61]	0.429
Role emotional functioning	0.93 [0.68−1.29]	0.672	0.91 [0.65−1.27]	0.585
Vitality	0.79 [0.57−1.08]	0.142	0.84 [0.59−1.19]	0.319
General health	1.09 [0.79−1.51]	0.605	1.01 [0.72−1.42]	0.952
PCS	1.00 [0.73−1.39]	0.981	0.96 [0.68−1.36]	0.835
MCS	0.88 [0.63−1.22]	0.431	0.91 [0.65−1.28]	0.583

MCS = mental component summary score; PCS = physical component summary score.
* QoL scores were divided into two groups based on the median split for all dimensions; good QoL was used as the reference category.
† Analyses were adjusted for age, sex, education, QRS >120, coronary artery disease (etiology), mild (NYHA class I-II) versus severe (NYHA class III-IV) heart failure, indication for ICD, amiodrone, and shocks during follow-up.

follow-up period in adjusted analyses, with increase in risk ranging from 53% to 59% (Table 3). Better social functioning was associated with a 32% (adjusted HR: 0.68; 95% CI: 0.48 to 0.96, p = 0.028) reduced risk of VTa's during follow-up (Table 4). None of the other QoL dimensions was significantly associated with VTa's during follow-up.

Discussion

To the best of our knowledge, this is the first study to examine the role of patient-reported QoL at the time of implant as a predictor of long-term mortality in a "real world" consecutive and prospective cohort of patients implanted with a first-time ICD. Patients with poorer physical functioning, role physical functioning, general health, and vitality at the time of implant had 53% to 59% higher mortality risk 7 years later, after statistical adjustment for relevant confounders. Only social functioning, y but none of the other QoL dimensions, was associated with risk for VTa's during the follow-up period, with better social functioning associated with a 32% reduced risk.

Our findings are in line with results of earlier studies that used secondary data from the MADIT II[13] and AVID trials[11,12] that had shorter follow-up periods (range 1 to 3 years). In the MADIT II trial based on data from 1,058 patients,[13] lower scores on the MCS and PCS of the SF-36 were associated with a 39% and 89% higher mortality risk at 12 months' follow-up, respectively. The study did not report on the individual 8 domains of the SF-36. In the AVID trial, QoL data were collected both with the SF-36 and the Quality of Life Index-cardiac version, however, the data published in 2008 included 740 patients, whereas in 2010 results were based on 507 patients.[11,12] Overall, the results showed that survivors reported better QoL and that poorer QoL for some domains (e.g., physical functioning, physical role functioning, general health, vitality, and social functioning of the SF-36) were associated with all-cause mortality adjusting for potential confounders.[11,12]

In our study, we found little evidence that QoL is associated with VTa's, with only better social functioning being associated with a decreased and substantial risk reduction of 39%. The MADIT II[13] and DenHeart studies[14] also

found no link between QoL and VTa's. The evidence for a link between depression and anxiety and VTa's is also mixed, with some studies finding an association[18–20] and others not.[21–23] It is difficult to discern why some studies find a link with VTa's and others do not, which may be attributed to sample size, study design, follow-up duration, and so on.

With respect to underlying mechanisms that may explain the associations between poor patient-reported QoL and risk of mortality, Idler et al[24] have proposed 4 possibilities. First, patient self-rated health may represent a more inclusive and complex judgement call as compared with information captured from medical records or rating scales used by physicians, such as the NYHA functional status classification. Second, the patient is better able to reflect on his or her entire health trajectory and not only on the current state. Third, self-rated health might reflect behaviors that are likely to promote health, with poor perceptions of health leading to less health-promoting behaviors. Fourth, self-rated health may also reflect the number of resources that patients have available—both within-patient factors and factors from the patient's environment, including the health care system—which in turn might contribute to maintaining good health. Inflammation may provide another mechanism, as markers such as high-sensitivity C-reactive protein and interleukin-6 have been associated with poorer QoL.[25]

In clinical practice, screening and monitoring patients with an ICD for QoL both at baseline and postimplant is worth considering given that it is an independent risk indicator for mortality above and beyond traditional risk factors. In terms of mitigation of this risk indicator, cardiac rehabilitation has been shown to increase the QoL of patients with acute coronary syndrome.[26,27] Introduction of such programs seems reasonable as a supplement to the integrated care for patients with an ICD and should be tailored to the individual patient's needs and preferences to have the largest effect.[28]

The results of this study should be interpreted with the following limitations in mind. We had no information about changes in cardiac and psychotropic medication nor whether heart failure progressed during the follow-up period, which could have influenced our results. The study was single-center, which limits the generalizability to other centers, and the majority of our patients were men. We did not have information about cause of death and therefore, were only able to examine the impact of QoL on all-cause mortality. We also used baseline QoL as a predictor of outcomes rather than changes in QoL over time. However, if a one-time assessment of QoL at the time of implant is a strong predictor of mortality 7 years later, as shown in the present study, this has a strong clinical applicability.[12] If these high-risk patients are identified in clinical practice already at the time of implant, there is a window of opportunity to ensure that they receive not only the most appropriate device treatment and medication but also psychological treatment if warranted, which impact not only on QoL, treatment adherence and risk factor management, but also risk of mortality.[29] In addition, these patients should be monitored closely over time in order to ensure that they receive optimal treatment. Other strengths of the study include the use of a "real world" consecutively implanted cohort, as strict inclusion criteria used in randomized trials like MADIT II (primary prevention trial) and AVID (secondary prevention trial) increase risk of selection bias and that results may not generalize to the entire ICD population.[30] Additional strengths are the prospective study design, the high response rate, the relatively large sample size, the use of a well-validated measurement of QoL (the SF-36),[15] and the long-term follow-up of 7 years.

In conclusion, the results of the present study showed that patients with poorer physical functioning, role physical functioning, vitality, and general health at the time of implant are at higher risk for mortality 7 years postimplant, even when adjusting for traditional risk factors. We found little evidence that QoL is associated with VTa's, with only social functioning being associated with a reduced risk. Further research is warranted to evaluate if access to cardiac rehabilitation—which is not standard for patients with an ICD in all countries—can lead to an improvement in QoL and whether improvement versus deterioration will influence mortality risk.

Disclosures

None of the authors have any conflicts of interests to report related to this manuscript.

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