

**Original research article**

**A comparison of the quality of life of patients with an entirely subcutaneous implantable defibrillator system versus a transvenous system**

**(From the EFFORTLESS S-ICD Quality of Life Substudy)**

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**Running title:** QoL of patients with a subcutaneous ICD

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## **ABSTRACT**

The first clinical results from the EFFORTLESS S-ICD Registry on the entirely subcutaneous implantable defibrillator (S-ICD) system are promising, but the impact of the S-ICD system on patients' quality of life (QoL) is not known. We evaluated the QoL of patients with an S-ICD against an unrelated cohort with a transvenous (TV)-ICD system during 6 months of follow-up. Consecutively implanted patients with an S-ICD system were matched with patients with a TV-ICD system on a priori selected variables including baseline QoL. QoL was measured with the Short-Form Health Survey (SF-12) at baseline, 3- and 6 months post implant and compared using multivariable modelling with repeated measures. Patients with an S-ICD (n=167) versus a TV-ICD system (n=167) did not differ significantly on physical ( $p=0.8157$ ) and mental QoL scores ( $p=0.9080$ ) across baseline, 3- and 6 months post implantation in adjusted analyses. The evolution in physical ( $p=0.0503$ ) and mental QoL scores ( $p=0.3772$ ) during follow-up was similar for both cohorts, as indicated by the non-significant interaction effect for ICD system *by* time. Both patients with an S-ICD system and a TV-ICD system experienced significant improvements in physical and mental QoL between time of implant and 3 months (both  $ps<0.0001$ ) and between time of implant and 6 months (both  $ps<0.0001$ ) but not between 3 and 6 months (both  $ps>0.05$ ). In conclusion, these first results show that the QoL of patients with an S-ICD versus TV-ICD system is similar, and that patients with either system experience improvements in QoL on the short-term.

**KEYWORDS:** Implantable cardioverter defibrillator; quality of life; registry; subcutaneous; transvenous

## INTRODUCTION

The clinical efficacy of implantable cardioverter defibrillator (ICD) therapy is well established<sup>1,2</sup>, but due to risk of lead complications associated with the transvenous ICD (TV-ICD) system - referred to as the *Achilles' heel* - the entirely subcutaneous ICD system (S-ICD™ system) was developed as an alternative<sup>3</sup>. The international **E**valuation of **F**actors Impacting **C**linical Outcome and Cost **E**ffectiveness of the S-ICD (EFFORTLESS S-ICD) Registry was initiated in 2011 to evaluate the S-ICD system with respect to its clinical and system performance and its impact on patients in the 'real world'<sup>4</sup>. The first clinical results based on data from 29 clinical sites across Europe and New Zealand demonstrate comparable performance of the S-ICD system with the TV-ICD system with respect to clinical conversion efficacy of discrete episodes of spontaneous ventricular tachycardia (VT) and ventricular fibrillation (VF) and inappropriate shock rates<sup>5</sup>. The S-ICD system is now recommended in the 2015 European Society of Cardiology guidelines with a Class IIa indication in patients who are not dependent on pacing therapy for bradycardia, anti-tachycardia or resynchronization pacing<sup>6</sup>. In the current study, we compared (i) the QoL of patients with an entirely S-ICD system to an unrelated cohort of patients with a TV-ICD system, and (ii) the influence of the type of ICD system relative to symptomatic heart failure, personality, and shocks on QoL during 6 months' follow-up, using data from the EFFORTLESS Registry.

## METHODS

The EFFORTLESS S-ICD Registry is an international, observational, prospective, non-randomized, standard of care evaluation that includes both retrospective and prospective patients. However, the QoL substudy was designed to include only prospective and first-time implant patients that were recruited from 29 sites in the Czech Republic, Denmark, Germany, Italy, the Netherlands, New Zealand, Portugal, and the United Kingdom between the period of March 2011 to July 2014. Patients were eligible for inclusion if they were implanted with a *first generation* S-ICD system per local clinical guidelines due to a primary or secondary

prevention indication, and were willing to participate and provide written informed consent. Patients were excluded, if they participated in another study that was considered to interfere with interpretation of the results from the EFFORTLESS S-ICD Registry, had previously been implanted with an ICD, experienced incessant ventricular tachycardia and/or spontaneous, frequently recurring VT that could reliably be terminated with anti-tachycardia pacing, and if they had a bradycardia indication or cardiac resynchronization therapy (CRT).

The QoL substudy of the EFFORTLESS S-ICD Registry was designed to use the MIDAS (**M**ood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter **D**efibrillator: **A** prospective **S**tudy) cohort as a unrelated comparison group<sup>4</sup>. MIDAS is a prospective observational study prior to the S-ICD era that recruited consecutively implanted patients with a first-time TV-ICD system between August 2003 and February 2010 at the Erasmus Medical Center, Rotterdam, the Netherlands<sup>7,8</sup>.

At each participating center, a member of staff approached patients for study participation at the time when patients were scheduled for the S-ICD implantation. All patients received oral and written information about the study. If willing to participate, they provided written informed consent. Patients would receive a reminder questionnaire if they did not return the first questionnaire. Similarly to the procedure in EFFORTLESS, patients from the MIDAS cohort were approached by a cardiologist or nurse about study participation. All patients received oral and written information about the study, and signed an informed consent form if they were willing to participate.

The protocol for the EFFORTLESS S-ICD Registry was approved by the relevant medical ethics committees in each participating country. The Registry was conducted according to the Helsinki Declaration and ISO 14155:2009, and registered on <http://www.ClinicalTrials.gov> (NCT01085435). The protocol for the MIDAS cohort was approved by the medical ethics committee of the Erasmus Medical Center, Rotterdam, the Netherlands (MEC # 231.491/2003/148 - September 9, 2003).

Information on clinical and demographic variables captured from the patients' medical records was entered into an online case record form. As information on particular

demographic variables, such as education, marital status, participation in cardiac rehabilitation, and treatment for psychological problems are not entered standardly in patients' medical records, these were included as purpose-designed questions in the questionnaire package containing the standardized and validated measures.

QoL was assessed with the standardized and validated 12-Item Short-Form Health Survey (SF-12) at baseline, 3- and 6-months post implant<sup>9</sup>. The 12 items contribute to a Physical Component Summary (PCS) and a Mental Component Summary (MCS) score, with a range between 0-100 (0 = poorest possible QoL; 100 = best possible QoL) <sup>9</sup>. Both PCS and MCS combine the 12 items in such a way that they compare to a national norm with a mean score of 50.0 and a standard deviation of 10.0.

To control for the potentially confounding influence of personality on QoL, patients completed the Type D Scale (DS14) at baseline. The DS14 is a 14-item measure tapping into negative affectivity (e.g. *'I often feel unhappy'*) and social inhibition (e.g. *'I am a closed kind of person'*) <sup>10</sup>. Items are rated on a 5-point Likert scale from 0-4 (score range for both subscales is 28), with a score of  $\geq 10$  on both traits indicating a Type D personality <sup>10,11</sup>. The DS14 is a valid and internally consistent measure (Cronbach's alpha: 0.80 for negative affectivity and 0.86 for social inhibition) <sup>10</sup>. Type D personality is a vulnerability factor for poorer QoL, life-threatening arrhythmias and premature mortality in patients with an ICD <sup>12-14</sup>.

Prior to propensity score matching, patients from the MIDAS cohort who had an indication for bradycardia or CRT, or with a secondary prevention indication due to monomorphic VTs were excluded from analyses, as these patients are not eligible for an S-ICD system. EFFORTLESS and MIDAS patients were matched 1:1 using propensity score matching on the following a priori selected variables: Gender, age, indication for ICD (primary versus secondary), ischemic versus non-ischemic etiology and baseline physical QoL and mental QoL. Propensity score matching was performed using the greedy matching algorithm with the recommended caliper width by Austin <sup>15</sup>. Multivariable modelling with repeated measures was used to analyze physical QoL and mental QoL across the visits, baseline, 3- and 6 months post implantation. The time *by* ICD system (S-ICD versus TV) interaction was

also considered in the multivariable modeling, if statistically significant at the 0.05 level. In a first model, a priori based on the literature, we choose to adjust for the following factors that might serve as potential confounders on QoL in multivariable analysis: Low education, NYHA functional class III-IV, amiodarone, cardiac rehabilitation attendance, treatment for psychological problems, Type D personality, and shocks during the 6 months' follow-up period. In a second model, we adjusted additionally for all baseline factors that were significantly different between the EFFORTLESS and MIDAS cohorts despite matching. Data were analyzed using SAS version 9.2.

## RESULTS

Of the 419 EFFORTLESS patients prospectively enrolled, 95% (397/419) consented to participate. Of these patients, 17% (68 of 397) were excluded due to previous implantation with a TV-ICD system or pacemaker, while 20% (80 of 397) patients were excluded due to insufficient QoL data. After matching EFFORTLESS patients with patients from the MIDAS cohort using propensity score matching, data from 167 patients with an S-ICD and 167 patients with a TV-ICD system were used for analyses. A flowchart of the patient selection is shown in **Figure 1**.

Baseline characteristics of the 2 cohorts are presented in **Table 1**. Despite propensity score matching on a priori selected variables, the EFFORTLESS and MIDAS cohorts differed on some baseline characteristics. EFFORTLESS patients were less likely to have VF as index arrhythmia, to be prescribed statins and diuretics, but more likely to have a lower QRS duration as compared to the MIDAS patients. EFFORTLESS patients were more likely to have VT as index arrhythmia, and to have diabetes and heart failure than MIDAS patients. There were no systematic differences on any of the other characteristics, including personality and baseline QoL (the latter was one of the matching criteria).

During the 6 months' follow-up period, in the matched cohort of equal size (n=167) and equal follow-up (6 months), 19 episodes were treated with a shock in the Effortless cohort as compared to 29 in the MIDAS cohort.

Multivariable modelling examining the effect of ICD system, time, and ICD system *by* time interaction showed that the interaction was neither statistically significant for physical QoL ( $p=0.0503$ ) nor mental QoL ( $p=0.3772$ ), indicating that the evolution in QoL scores during the 6-months of follow-up was similar in patients with either an S-ICD or a TV-ICD system.

Therefore, analyses were run again including only the main effects for ICD system and time. These unadjusted analyses (without the interaction effect) showed no statistically significant main effects for ICD system (S-ICD versus TV) neither on physical ( $p=0.1707$ ) nor on mental QoL ( $p=0.3364$ ) across baseline, 3- and 6 months post implantation. When adjusting for a priori determined potential confounders (i.e., low education, NYHA functional class III-IV, amiodarone, cardiac rehabilitation attendance, treatment for psychological problems, Type D personality, and shocks during the 6 months follow-up period), the model estimate when comparing the 2 cohorts was statistically significant for physical QoL ( $p=0.0324$ ) but not for mental QoL ( $p=0.2232$ ) (**Table 2 - Model 1**). The mean score differences on physical and mental QoL between the 2 cohorts were largest at baseline with 2.32 (on a scale from 0-100) with the MIDAS cohort experiencing a slightly better QoL. For mental QoL, the same pattern was seen, although the highest mean score difference between the 2 cohorts was at 6 months with a mean score difference of 1.26 (on a scale from 0-100). When adding also differences between the 2 cohorts on baseline characteristics to the variables entered in Model 1, the largest mean difference between the 2 cohorts was reduced to 0.29 for physical QoL and to 0.14 for mental QoL (**Table 2 – Model 2**). Neither the model estimate for differences in physical ( $p=0.8157$ ) nor mental QoL ( $p=0.9080$ ) between the 2 cohorts was statistically significant. Shocks during follow-up were neither associated with physical QoL ( $p=0.5648$ ) nor mental QoL ( $p=0.5161$ ) in Model 2, which was fully adjusted.

The main effect for time was statistically significant, indicating that both cohorts improved in physical ( $p>0.0001$ ) and mental QoL ( $p>0.0001$ ) during the 6-months of follow-

up. Test for differences between time intervals for physical QoL, including a priori specified factors and baseline differences between the 2 cohorts, showed that both patients with an S-ICD system and a TV-ICD system experienced significant improvements in physical QoL between the time of implant and 3 months ( $p < 0.0001$ ) and between the time of implant and 6 months ( $p < 0.0001$ ) but not between 3 and 6 months ( $p = 0.8239$ ). We found similar results for mental QoL, with both patients with an S-ICD system and a TV-ICD system experiencing significant improvements between the time of implant and 3 months ( $p < 0.0001$ ) and between the time of implant and 6 months ( $p < 0.0001$ ) but not between 3 and 6 months ( $p = 0.3912$ ).

Absolute differences in the unadjusted physical and mental QoL scores at baseline, 3- and 6 months, stratified by ICD system, symptomatic heart failure, personality, and shocks during 6 months of follow-up are shown in **Figures 2a-b**. When evaluating mean score differences in physical and mental QoL scores across baseline, 3- and 6 months follow-up between patients (i) with an S-ICD versus a TV-ICD system, (ii) NYHA class I-II versus III-IV, (iii) Type D versus a non-Type D personality, and (iv) shocks versus no shocks during follow-up, there is the least differentiation between the 2 ICD systems both in physical (range: 0.10-2.70) and mental QoL scores (range: 0.30-2.30) across the 3 time points (**Figure 3**). For physical QoL, the largest difference was seen between patients with NYHA class I-II versus III-IV, with a mean score difference range of 9.10-10.90, while for mental QoL the largest differentiation was between patients with a Type D versus non-Type D personality, with a mean score difference range of 8.9-9.7. This indicates that the type of ICD system has less of an impact on patients' physical and mental QoL relative to symptomatic heart failure (NYHA class III-IV), personality, and shocks during follow-up.

## DISCUSSION

In the current article, we present the first results of the multi-center, international EFFORTLESS QoL substudy comparing patients with an entirely S-ICD system to an unrelated control cohort of patients with a TV-ICD system. We found a statistically significant but minimal mean difference of 2.32 points in physical but not mental QoL between the 2



cohorts, with this difference disappearing after adjustment for confounders. Thus, overall, the physical and mental QoL of patients with an S-ICD and a TV-ICD system are similar across baseline, 3- and 6 months post implantation, and both cohorts improved in physical and mental QoL over time, with the evolution of changes in QoL scores over time being similar.

These findings emphasize that the type of device, and in this case also the difference in size and weight between the pulse generator of the S-ICD versus the TV-ICD system - the S-ICD is considerably larger and weighs almost the double (145 g) of the TV-ICD system <sup>16</sup> - has negligible impact on patients' well-being and QoL at least up to 6 months of follow-up. In part, the concern with respect to size may be more on the physician side, as they know the difference in size between a TV-ICD versus S-ICD, while patients with an S-ICD in most cases are unlikely to be able to make this comparison. There is also no indication that the mean QoL scores found both in the S-ICD and MIDAS cohorts differ systematically from those reported in other TV cohorts <sup>17,18</sup>. Similarly, as in previous studies of patients with a TV-ICD system (excluding previously published findings from the MIDAS cohort), we found that other factors, in particular symptomatic heart failure and personality, may be more important determinants of QoL than the type of device itself and having a device <sup>19-22</sup>.

The results of this study should be interpreted with the following limitations in mind. The MIDAS patients used as controls cohort for the EFFORTLESS S-ICD patients was obtained from a single center and recruited over a period of 7 years as compared to 3 years for EFFORTLESS patients. Nevertheless, the mean QoL scores of the MIDAS patients did not differ systematically from other TV-ICD cohorts from Denmark and China <sup>17,18</sup>. Given that the eligibility criteria for the S-ICD system differ from those for a TV-ICD system, we had to exclude some of the MIDAS patients from the comparison cohort prior to matching, reducing the number of patients available. In addition, a priori we had decided to match the 2 cohorts on pre-selected baseline characteristics. Although the matching eradicated some of the differences between the 2 cohorts, they still differed on some baseline characteristics, in particular on medication prescription. However, we adjusted statistically for these differences in statistical analyses. As there is no disease-specific measure to tap into the QoL of patients

with an ICD, we used the SF-12, a generic and international standard of QoL that has been used either in its short- (SF-12) or long form (SF-36) in the seminal primary and secondary prevention trials, such as DEFINITE <sup>23</sup> and SCD-HEFT <sup>24</sup>. Although this generic measure may be less sensitive to demonstrate changes over time and differences between groups, DEFINITE demonstrated almost equivalent changes in scores on the SF-12 and the Minnesota Living with Heart Failure questionnaire.

This study also has several strengths. First, it evaluates the patient perspective by asking patients to evaluate the impact of a new device on their well-being and QoL. Such a patient-centered approach has not only been advocated by the Institute of Medicine in the US <sup>25</sup>, but also the American Heart Association <sup>26</sup> and the European Society of Cardiology <sup>27</sup>. Second, EFFORTLESS patients were included from 29 clinical sites not only across Europe but also New Zealand. Third, both the EFFORTLESS and MIDAS cohorts were well described not only in terms of their demographic and clinical characteristics but also their psychological profile. Fourth, final statistical models were fully adjusted including adjustment for differences in baseline characteristics that were not resolved via matching and shocks during follow-up as a time-varying variable.

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## **CONFLICTS OF INTEREST**

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**Table 1.** Baseline characteristics for the EFFORTLESS (S-ICD) and MIDAS (TV-ICD) cohorts

Characteristics	EFFORTLESS (S-ICD system) (n = 167)	MIDAS (TV-ICD system) (n = 167)	<i>p</i>
Men	122 (73%)	120 (72%)	0.8065
Age, mean $\pm$ SD (years)	54 $\pm$ 16	55 $\pm$ 13	0.8831
Low education (<13 years)	73 (45%)	90 (55%)	0.0597
Primary prevention indication	123 (74%)	115 (69%)	0.3334
Ventricular fibrillation as index arrhythmia	32 (20%)	50 (30%)	<b>0.0480</b>
Ventricular tachycardia as index arrhythmia	8 (5%)	2 (1%)	<b>0.0426</b>
Atrial fibrillation	36 (22%)	30 (18%)	0.4097
Diabetes mellitus	31 (19%)	16 (10%)	<b>0.0183</b>
Heart failure	69 (41%)	28 (17%)	<b>&lt;0.0001</b>
NYHA III-IV	20 (12%)	24 (15%)	0.5313
Renal failure (60 ml/kg/1.73m <sup>2</sup> )	13 (8%)	23 (14%)	0.0841
Transient ischemic attack or stroke	13 (8%)	8 (5%)	0.2781
Dilated cardiomyopathy	25 (15%)	39 (23%)	0.0516
Ischemic cardiomyopathy	12 (7%)	12 (7%)	1.0000
Hypertrophic cardiomyopathy	22 (13%)	18 (11%)	0.5002
QRS duration	105 $\pm$ 21	112 $\pm$ 27	<b>0.0071</b>
Previous myocardial infarction	66 (40%)	68 (40%)	0.8223
Previous percutaneous coronary intervention	32 (19%)	42 (25%)	0.1877
Previous coronary bypass	17 (10%)	17 (10%)	1.0000
Amiodarone	15 (9%)	12 (7%)	0.5470
Beta-blockers	125 (75%)	133 (80%)	0.2964
Digoxin	10 (6%)	17 (10%)	0.1600
Statins	50 (30%)	75 (45%)	<b>0.0047</b>
Angiotension converting enzyme inhibitors	92 (55%)	106 (64%)	0.1190
Diuretics	80 (48%)	57 (34%)	<b>0.0105</b>
Cardiac rehabilitation	7 (4%)	11 (7%)	0.3593



Treatment for psychological problems <sup>†</sup>	9 (5%)	14 (8%)	0.2798
Type D personality	44 (27%)	35 (21%)	0.2461
Baseline physical quality of life (PCS), mean $\pm$ SD	41 $\pm$ 12	41 $\pm$ 11	0.9787
Baseline mental quality of life (MCS), mean $\pm$ SD	42 $\pm$ 12	43 $\pm$ 12	0.8697

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<sup>†</sup> Currently seeing a social worker, psychologist or psychiatrist for psychological problems

**Table 2.** Physical and mental quality of life of patients with an S-ICD system versus a TV-ICD system during the course of 6-months follow-up post implant

	<b>EFFORTLESS (S-ICD system)</b>	<b>MIDAS (TV-ICD system)</b>	
	<i>Mean [95% CI]</i>	<i>Mean [95% CI]</i>	<i>p-value</i>
<b>Model 1<sup>a</sup></b>			
<b>Physical QoL (PCS)</b>			
Baseline	39.35 [37.75-40.95]	41.61 [40.02-43.19]	0.032
3 months	42.42 [40.87-43.98]	44.68 [43.15-46.21]	
6 months	42.33 [40.72-43.93]	44.58 [43.00-46.17]	
<b>Mental QoL (MCS)</b>			
Baseline	41.60 [40.00-43.19]	42.84 [41.27-44.42]	0.2232
3 months	45.12 [43.53-46.71]	46.37 [44.80-47.93]	
6 months	44.52 [42.85-46.20]	45.78 [44.12-47.41]	
<b>Model 2<sup>b</sup></b>			
<b>Physical QoL (PCS)</b>			
Baseline	40.48 [38.69-42.27]	40.77 [39.12-42.42]	0.8157
3 months	43.56 [41.79-45.34]	43.85 [42.22-45.48]	
6 months	43.45 [41.63-45.26]	43.74 [42.06-45.41]	
<b>Mental QoL (MSC)</b>			
Baseline	42.39 [40.60-44.19]	42.25 [40.59-43.92]	0.9080
3 months	45.86 [44.04-47.68]	45.72 [44.04-47.40]	
6 months	45.19 [43.29-47.09]	45.05 [43.28-46.81]	

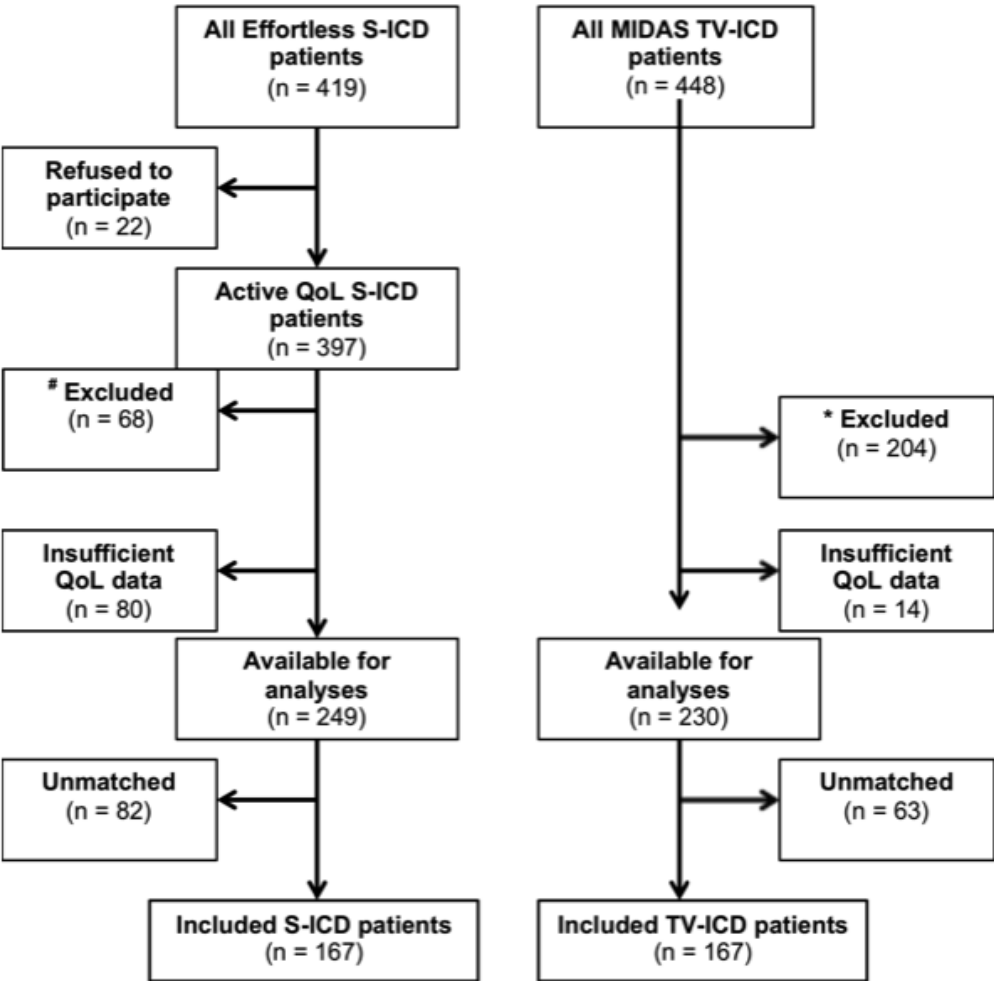
\* adjusted for a priori selected covariates

† adjusted for a priori selected covariates and baseline differences between the two cohorts

**Figure 1.** Flowchart of patient selection

TOP

**Figure 1.**



# if patients had had a prior TV-ICD or pacemaker implanted

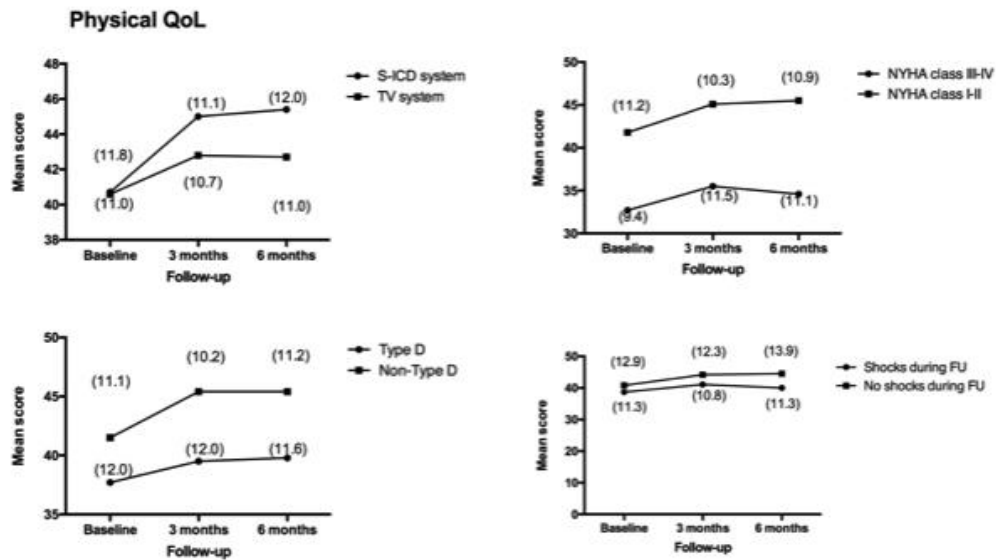
\* if pacemaker dependent, ICD with cardiac resynchronization therapy (CRT-D), or secondary prevention indication due to monomorphic ventricular tachyarrhythmias, as these patients are not eligible for an S-ICD system

**Figure 2.** Comparison of mean physical and mental QoL scores at baseline, 3- and 6-months follow-up, stratified by ICD system, symptomatic heart failure, personality, and shocks during follow-up (unadjusted analysis)\*

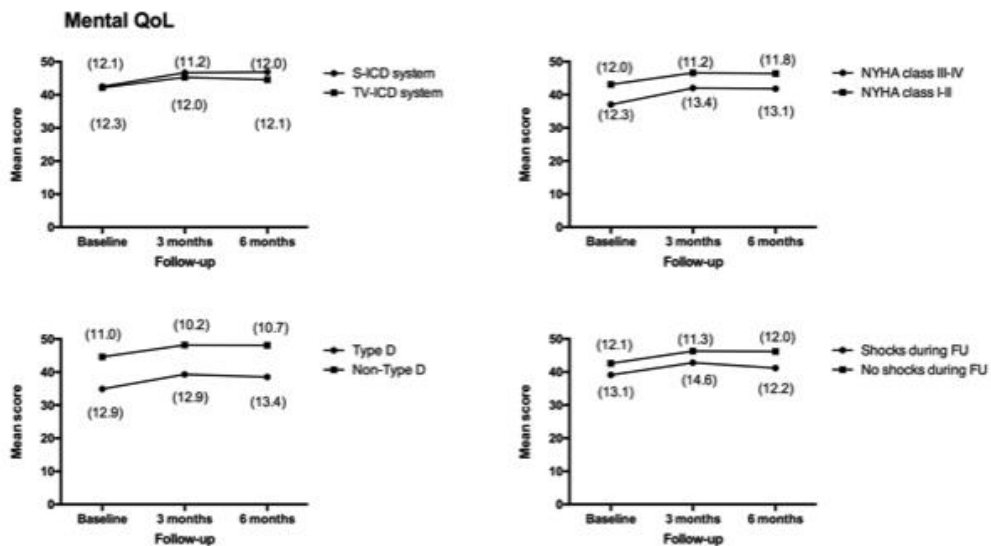
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**Figure 2.**

(a)



(b)



\* Standard deviations are listed in brackets; score range 0-100, with 100 indicating the best QoL.

**Figure 3.** Mean physical and mental QoL score differences at baseline, 3- and 6 months stratified by ICD system, symptomatic heart failure, personality, and shocks during follow-up (unadjusted analysis)\*

Figure 3.

