Longevity of the Subcutaneous Implantable Defibrillator: Long-Term Follow-Up of the European Regulatory Trial Cohort

Running title: Theuns et al.; Longevity of the S-ICD

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Abstract:

Background - The recent advent of subcutaneous implantable cardioverter defibrillators (S-ICDs) has provided investigators with a safe and effective new therapy in patients at risk of sudden cardiac death. At present, no data are available with regard to the longevity of these new devices. This study evaluated the longevity of the S-ICD system.

Methods and Results - All patients enrolled in the European Regulatory Trial were included in the analysis. During follow-up, time and causes of device replacement or explantation were assessed and categorized. Device longevity was estimated using Kaplan-Meier analysis. Fifty-five patients were followed for a median of 5.8 years. During follow-up, 26 (47%) patients underwent device replacement and 5 (9%) device explantation. Median time to replacement was 5.0 years (Q1-Q3, 4.4 - 5.6 years). Replacement was caused by battery depletion in 25 patients (92%), of which 5 within 1.5 years due to premature battery depletion, and by infection in 1 patient (2%). Replacement for a transvenous ICD system was required in 4 patients (7%), due to ineffective defibrillation in 1 (0.003 per patient-year), need for resynchronization therapy in 2 (0.01 per patient-year) and for anti-bradycardia pacing in 1 (0.003 per patient-year). At 5 years follow-up, 71% of devices were still in service.

Conclusions - This study provides the first estimate of S-ICD system longevity since its introduction in clinical practice. Median longevity of the first generation S-ICD system was 5.0 years. The majority of devices were replaced due to battery depletion.

Clinical Trial Registration - URL: http://www.clinicaltrials.gov. Unique identifier: NCT01117792.

Keywords: implantable cardioverter-defibrillator, subcutaneous implantable defibrillator, device longevity, replacement, battery
Introduction

Several large randomized trials have shown the efficacy of the implantable cardioverter-defibrillator (ICD) in reducing mortality in selected patients at high-risk of arrhythmic death from ventricular arrhythmias.\(^1\text{-}^4\) Despite the proven mortality benefit, the ICD has been associated with morbidity due to short and long-term complications with transvenous leads.\(^5\text{-}^7\) These complications include pneumothorax, cardiac perforation, systemic infections, acute and chronic lead displacement, insulation breaches and conductor breaks. Removal of infected or failed transvenous leads is associated with considerable morbidity and mortality.\(^8\text{-}^9\) These complications are part of the rationale to develop an entirely subcutaneous ICD (S-ICD) system with no leads within or on the heart and preservation of the central venous circulation.\(^10\) The feasibility and safety of the S-ICD system were established in early human studies.\(^11\text{-}^13\) The safety and effectiveness of the S-ICD system for the treatment of ventricular arrhythmias were proven in the investigational device exemption (IDE) trial.\(^14\) Recently, an interim analysis of the EFFORTLESS registry presenting ‘real–world’ data of patients implanted with the S-ICD system regarding clinical data has been published.\(^15\) However to date, there are no data present about the longevity of the S-ICD. The aim of this study was to analyze longevity of the subcutaneous ICD.

Methods

Study population

The study cohort of the European Regulatory Trial consisted of 55 patients who underwent implantation in Europe and New-Zealand between December 2008 and February 2009. All patients were eligible candidates for S-ICD implantation among the patients referred for ICD implantation at each participating center. The inclusion criterion of the trial was a class I, II-a, or
II-b indication for ICD therapy. None of the patients had an indication for bradycardia pacing, cardiac resynchronization therapy, ventricular tachycardias with rates < 170 bpm or documented monomorphic ventricular tachycardias which could be terminated by antitachycardia pacing. The study protocol of the European Regulatory Trial was approved by the ethics committee at each participating institution. All study participants provided written informed consent.

**Device description**

The S-ICD system consists of a pulse-generator, which is implanted near the left mid-axillary line, and a subcutaneous lead, which is placed 1 to 2 cm parallel to the left mid-sternal line. The device weighs 145 grams and has a volume of 69 cc. The device delivers non-programmable 80-J biphasic transthoracic shock and has the capability to provide ventricular bradycardia pacing up to 30 seconds post-shock at a rate of 50 bpm. Automatic capacitor reformation is performed 3 times per year. Based on this capacitor reformation, the projected longevity of the device is 5 years. Each additional charge reduces longevity by 21 days.

**Definition of device replacement**

Device longevity was defined as the time from implantation to surgical replacement, and thus not necessarily to elective replacement indication (ERI). Reasons for replacement were ERI, premature ERI due to excessive battery drainage, malfunction of device or infection. Permanent removal of the implanted S-ICD system was defined as explantation. Reasons for explantation were for example a change to a transvenous ICD system due to development of an indication for bradycardia pacing, cardiac resynchronization therapy or antitachycardia pacing. Premature ERI was defined as ERI within 36 months after implantation, which is based on the value given in the warranty. All other replacements based on battery depletion after more than 36 months service time were defined as normal ERI. End of follow-up with administrative censoring of longevity of
devices still in service was set at December 1st, 2014.

Data analysis
Continuous variables are presented as mean ± SD or as median with 25th and 75th percentiles, where appropriate. Categorical data are presented as counts and percentages. Event-free rates from device replacement were calculated with the Kaplan-Meier method. Event-free rates were expressed with a 2-sided 95% confidence interval (CI). Patients who reached the end of follow-up without ERI were censored for administrative reasons. Patients who died prior to ERI were treated as censored observations. To evaluate the relation between ICD shocks and elective device replacement, Cox regression analysis was applied with number of delivered shocks as time-varying covariate. Statistical analysis was performed using SPSS version 21 (IBM Corp, Somers, NY). Statistical significance was defined as P < 0.05 (two-tailed).

Results
Clinical characteristics of the patients enrolled in the European Regulatory Trial are presented in Table 1. Among the patients, 44 (80%) were male, and 37 (67%) had ischemic heart disease. Primary prevention was the indication for ICD placement in 43 (78%) patients. The number of patients who died prior to ICD replacement was 8 (15%); 3 cardiac and 5 non-cardiac deaths. None of the deaths were related to the S-ICD system or implant procedure.

During a median follow-up of 5.8 years (5.7 – 5.9 years), 26 (47%) devices were replaced and 5 (9%) were explanted. The indications for device replacement and explantation are presented in Figure 1. Of the total cohort, four (7%) patients had the S-ICD explanted and received a transvenous ICD system. Two of them developed an indication for cardiac resynchronization therapy (CRT) due to symptomatic heart failure (NYHA class III)(0.01 per patient-year), one patient had an indication for bradycardia pacing due to symptomatic
bradycardia (0.003 per patient-year), and one patient received a transvenous ICD system as specified by protocol of the European Regulatory Trial in case of ineffective defibrillation testing. One device was explanted due to infection.

The majority of devices (81%) were replaced based on ERI. Overall, the median time to device replacement was 5.0 years (4.4 – 5.6 years). Event-free rates for device replacement were 94% (95% CI, 83% - 98%) after 2 years, 89% (95% CI, 76% - 96%) after 4 years, and 30% (95% CI, 15% - 46%) after 6 years (Figure 2). However, premature ERI due to rapid battery depletion was observed in 5 devices (9%) with a mean service time of 1.5 ± 0.7 years. Considering the manufacturer-projected device longevity of 5 years, 71% of devices were actually still in service at 5-years follow-up.

We analyzed whether elective device replacement was associated with shock delivery. During follow-up, a total of 119 delivered shocks in 16 individual patients (29%) were recorded. Of these patients, the majority (69%) received fewer than 5 shocks. Proportionally, the occurrence of shock delivery was not different between devices with ERI versus those without ERI (32% versus 27%). The relation between ICD shocks and elective device replacement was further evaluated by Cox regression analysis. Considering the number of shocks as a time-varying covariate in Cox regression analysis, no association between number of shocks and elective device replacement was found (HR 1.01, 95% CI 0.98 – 1.04; P = 0.29).

**Discussion**

This is the first study to analyze the longevity of the subcutaneous ICD since its clinical introduction. The primary results of this analysis indicate that the median longevity of the S-ICD is 5 years as projected by the manufacturer. The majority of devices were replaced because of battery depletion, and approximately 7% of the devices were explanted due to a non-battery-
related indication.

Nowadays, the majority of ICDs are implanted on account of primary prevention of sudden death. The majority of these primary prevention patients is expected to survive their first ICD and will probably need one or more device replacements.\textsuperscript{16} Device longevity is an important factor to improve the cost-effective application of ICD therapy. According to several studies, device longevity increased from a mean of 19 months in the late 1980-ies to approximately 60 months at present.\textsuperscript{17-20} When analyzed per type of contemporary transvenous ICD, single-chamber ICDs have a mean longevity of 5.5 years and dual-chamber ICDs 5.8 years.\textsuperscript{20}

Compared to contemporary transvenous ICD systems, longevity of the first generation S-ICD is slightly shorter with a median longevity of 5.0 years. During follow-up of the first implanted S-ICD cohort, premature ERI due to rapid battery depletion was observed in 5 devices (9%). Analysis identified a battery manufacturing issue and led to a field safety notification issued at the time of the IDE trial. No adverse clinical outcomes were reported as a result of premature battery ERI, and the replacements were uneventful. In subsequent S-ICD studies, premature battery depletion was observed in 2 cases (0.6%) in the IDE trial and in 1 case (0.2%) in the EFFORTLESS registry.\textsuperscript{14, 15} When considering transvenous ICD systems, premature ERI has been reported in 9\% of transvenous devices.\textsuperscript{21} Battery malfunctions were the most common cause of device failure in a meta-analysis of device registries.\textsuperscript{22}

A concern with the S-ICD system may be the inability to pace. Obviously, the S-ICD system is not indicated for patients with bradycardia or need for cardiac resynchronization. The number of ICD recipients who require bradycardia pacing during their follow-up is low, 3\% of patients in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) and 4\% in the Dual Chamber and VVI Implantable Defibrillator (DAVID) study.\textsuperscript{3, 23} Heart failure is usually a
progressive condition and patients initially implanted with an ICD might later on develop an indication for CRT. The upgrade rate of ICD recipients to CRT varies among studies. In a retrospective single centre study, 3.8% of patients had their device upgraded to CRT during a follow-up of 4 years. While in the European Cardiac Resynchronization Therapy Survey on CRT implant procedures, 28.2% were identified as upgrade from ICD to CRT-D. In a recent sub study of the Resynchronization-defibrillation for Ambulatory heart Failure Trial (RAFT) study, 12.3% of ICD patients had an attempted upgrade to CRT. In our analysis, approximately 7% of the S-ICD systems were explanted and replaced by a transvenous ICD system due to the need for bradycardia pacing or CRT. The interim analysis of the EFFORTLESS registry reported a low explant rate of the S-ICD, occurring in 3.7% of patients mainly due to infection. In 1% of patients, the S-ICD was replaced for a transvenous ICD system due to recurrent ventricular arrhythmias or patient decision.

Limitations
There are several limitations to this study. The number of patients is low compared to the IDE trial and the EFFORTLESS registry. However, the median follow-up of the first implanted S-ICD cohort is over 5 years warranting an analysis of longevity of the subcutaneous defibrillator. Device longevity was defined as the time from implantation to replacement and thus not the day of detection of ERI. Overestimation of longevity can be neglected because replacement is performed within 1 to 2 weeks after detection of ERI.

Conclusion
The longevity of the first generation S-ICD systems is slightly less compared to single- and dual-chamber ICDs. The majority of devices were replaced because of battery depletion. During a median of 5 year follow-up, the need for a transvenous ICD system replacement was rather low.
Conflict of Interest Disclosures DAMJT has received institutional grant and consulting fee from Boston Scientific. MAH has received lecture honoraria, institutional grant, and consulting fees from Boston Scientific. RC has equity and intellectual property rights from Cameron Health, a subsidiary of Boston Scientific, and lecture honoraria, institutional grant, and consulting fees from Boston Scientific. REK has institutional grant from Boston Scientific. AHM receives lecture honoraria from Boston Scientific. LVAB receives lecture honoraria and consulting fees from Boston Scientific. All other authors have none.

References:


Table 1: Baseline clinical characteristics of the study cohort (n=55)

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>56 ± 13</td>
</tr>
<tr>
<td>Male gender, n(%)</td>
<td>44 (80)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>173 ± 8</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>83 ± 14</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28 ± 5</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>34 ± 13</td>
</tr>
<tr>
<td>NYHA functional class I – II, n(%)</td>
<td>48 (87)</td>
</tr>
</tbody>
</table>

**Underlying cardiac disease**

- Ischemic heart disease, n(%) 37 (67)
- Nonischemic cardiomyopathy, n(%) 10 (18)
- Congenital heart disease, n(%) 2 (4)
- Other, n(%) 6 (11)

**Indication for ICD therapy**

- Primary prevention, n(%) 43 (78)
- Secondary prevention, n(%) 12 (22)

Continuous data are presented as mean ± SD
BMI = body mass index; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association
Figure Legends:

Figure 1: Proportions of the indications for device replacement and explantation. ERI = elective replacement indication; TV-ICD system = transvenous ICD system.

Figure 2: Event-free rates for device replacement because of normal and premature battery depletion. Regarding the curves, devices were censored in case of explantation for reasons other than battery depletion.
Device longevity

Years

N at risk  55  47  42  39  38  31  4
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