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**Innovations in Cardiac Implantable Electronic Devices
and post-market surveillance**

Erik F.J. Oosterwerff

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Thesis, UVA University, Amsterdam, The Netherlands

Innovations in Cardiac Implantable Electronic Devices
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Illustration: Björn de Vries

Chapter 1

General Introduction

Report of a case

A 55-year-old man with non-ischemic cardiomyopathy presented at the emergency room with multiple inappropriate shocks of his eight years old implantable cardioverter-defibrillator (ICD) with a Linox (Biotronik, Berlin, Germany) lead. Later at the outpatient clinics he elucidated the impact of the inappropriate shocks and he suffered from persistent psychological distress and fear.

This heartbreaking clinical presentation demonstrates the need for improvement of cardiac implantable electronic devices (CIED's) therapy. Unexpected ICD lead failures have caused serious problems in the past. What lessons have we learned from earlier incidents? Can we push the field towards modular, extravascular device therapy? What challenges accompany the introduction of these new devices? And last but not least, how appropriate is the current post-market surveillance?

Cardiac implantable electronic devices

The use of implantable devices for cardiac electrical stimulation was first reported in 1959 and became a fundamental treatment for bradyarrhythmia's. (1) Since the early 1990s transvenous implantable cardioverter defibrillators (TV-ICD) were introduced and became an important treatment tool for patients who are at risk of ventricular tachyarrhythmias. The use of CIED's for both bradycardia and tachycardia has increased over the last decades.

Despite the obvious clinical benefits, CIED therapy still causes serious complications like pocket infections and lead failure. (2) (see figure 1) A Danish population-based study found that 9.5% of patients experienced complications within six months post-implantation. (3) These results are in line with the Dutch DO-IT trial, a large-scale registry of 1442 patients receiving ICD's as primary prevention for sudden cardiac death in cases of structural heart disease with reduced left ventricular function. Over a two-year follow-up, 228 complications were reported in 195 patients (13.6%), with 7.8% experiencing major complications, defined by specific criteria of life-threatening or significant medical intervention needs. (4) The most common complications in these two large cohorts are lead-related. (3,4) In the early days, up to 30% lead-related complications were observed within five years of follow-up. (5-7) Technical advances, such as multilumen design to avoid mechanical stress, have resulted in a dramatically decreased risk of lead failure and complications. The annual lead failure rate of a defibrillator lead is currently around 0.5% within five years of follow-up. (8)

However, experience with lead and generator recalls have led to a highly critical examination of performance. Device reliability and vigilance is still of utmost importance for patients.



Figure 1 Complications of transvenous pacemakers

A: Pacemaker pocket infection with extensive pus. B: Perforated pulse generator C: Explanted lead with adherent fibrotic tissue Adapted from Beurskens et al. HeartRhythm 2019 (2)

Supervision of post-market surveillance

The deployment of CIED's, classified as high-risk medical devices, is subject to stringent regulations. Recently, the European Commission updated the former European Medical Device Directive (MDD) and is now called the Medical Device Regulation (MDR). Once a device is approved, compliant with the MDR's requirements, it receives a CE certification (Conformité Européenne). After market approval, manufacturers of medical devices are responsible for post-market surveillance. The complete pathway of approval and monitoring is illustrated in Figure 2. (9)

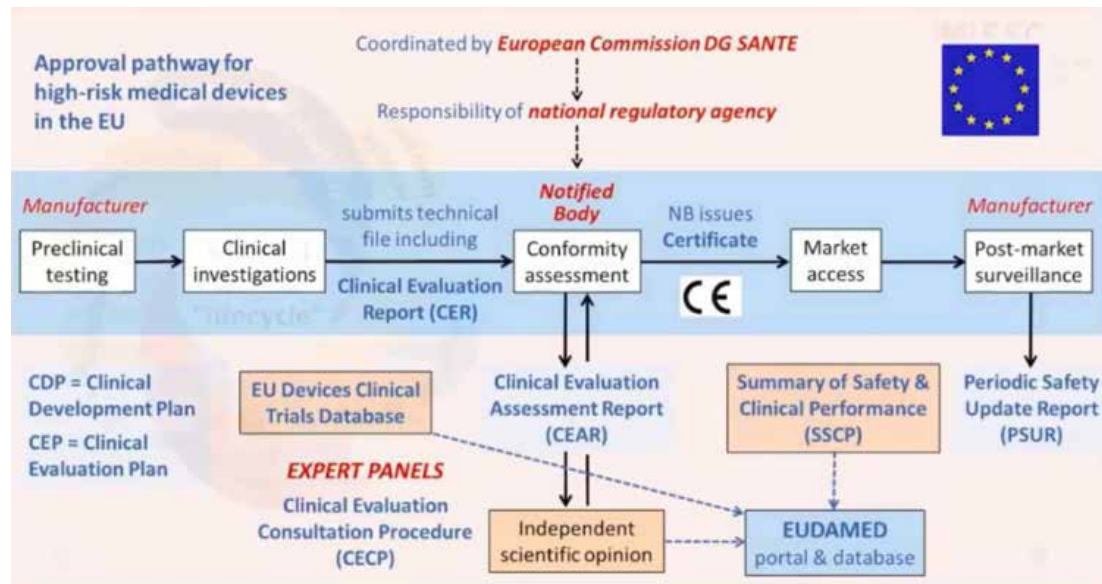


Figure 2. Modified with permission from E Wierda et al. *Eur Heart J Qual Care Clin Outcomes*. 2022 Jan 5;8(1):1-3.

A major change with the launch of MDR is the start of a central European Databank on Medical Devices (EUDAMED). While EUDAMED is under development the manufacturers must report adverse reactions with Field Safety Notice (FSN) to supervising authorities. FSN is defined in the MDR as communication sent by a manufacturer to users or customers in relation to a corrective action taken by the manufacturer for technical or medical reasons to prevent or reduce the risk of a serious incident in relation to a device made available on the market. It is the responsibility of manufacturers to register all serious incidents involving devices and report to the supervising authorities. (9, 10)

Safety issues in recent pacemakers

The Nanostim leadless pacemaker (LP) (Abbott/St. Jude Medical, St. Paul, MN, USA) was introduced in 2012 as a capable alternative to avoid complications inherent to transvenous pacing systems. (see Figure 1)

However, while leadless pacing introduced a significant advance-

ment, it also presented unforeseen challenges. Shortly after its clinical deployment, early battery failures of the Nanostim LP were reported. In October 2016, Abbott issued an advisory acknowledging that seven out of 1,423 implanted Nanostim devices (0.5%) exhibited sudden battery depletion before the anticipated minimum battery life of 8.8 years. (11) Because of this unexpected high rate of premature battery depletions, the manufacturer recalled Nanostim devices and all implantations were ceased immediately. Moreover, patients with Nanostim devices were advised to undergo device interrogation every three months to monitor battery performance.

Oosterwerff et al. (12) describes the experience with the follow-up and extraction of Nanostim LP pacemakers at risk of malfunction. (see Chapter 2) The incidence of early battery failure in Nanostim LP's during further follow-up was excessively higher as initially reported (37% vs. 0.5% respectively and 12%/year vs 0.02%/year). This specific battery problem does not occur in the later introduced Micra VR LP (Medtronic, Minneapolis, MN, USA) and is thus not expected to be inherent to leadless pacing per se.

Breeman et al. (13) provides further context offering the first real-world long-term results of LP therapy in a general LP population. The long-term safety (excluding advisory-related complications) and efficacy of LP's was considered to be adequate. These recent examples underline the importance of unbiased data. Non-industry-related studies of good scientific quality are crucial for a better insight in real-world pacemaker performance.

Recent reports of safety issues in ICD's

Over the past decades, two ICD leads have been subject to significant safety issues resulted in an FSN. The real world reported annual failure rate was 4.8% for Sprint Fidelis (Medtronic, Minneapolis, MN, USA) and 4.9% for Riata/Riata ST leads (St. Jude Medical, St. Paul, MN, USA). (14-15) Similar long-term failure of a third ICD lead, namely the Linx ICD lead family (Biotronik, Berlin, Germany) was found in a recent Dutch nationwide study. (16) (see Chapter 5). The high failure rates observed

in this physician-driven, multi-center study in a large real-life contemporary cohort, with long and complete follow-up, confirmed the results of earlier manufacturer-independent smaller registries (16-25), but are remarkably higher than the numbers in the last Biotronik product performance report. (26) While the higher-than-expected failures of the Sprint Fidelis and the Riata prompted a recall, this was remarkable not the case with the Linux family leads.

Recent example of the third ICD lead with significant safety issues highlights the importance of continuous evaluation of lead performance in real-world populations. Moreover, it demonstrated that transvenous systems are still associated with specific risks of lead failure and subsequent increased morbidity and mortality. Subcutaneous ICD system like the S-ICD by Boston Scientific (St. Paul, MN, USA) and the more recently introduced EV ICD by Medtronic (Minneapolis, MN, USA) could potentially decrease these risks, due the stability of the subcutaneous lead position. (27, 28)

The outline of this thesis

Although clear clinical benefits, CIED therapy is associated with serious complications. This thesis aims to advance understanding of CIED limitations by collecting physician-driven real-world data to provide insight into CIED performance. Additionally, a proof-of-concept study for introducing a new approach to CIED design is presented. One limiting factor in S-ICD use is the size of the pulse generator (PG), as significant size reductions necessitate PG's that deliver less energy. In this research, we explore the feasibility of a modified S-ICD system, adding a second shock coil to lower the defibrillation threshold.

- * Part I addresses post-market surveillance of leadless pacemakers (LP's) in the Netherlands. Chapter 2 details the management of malfunctioning Nanostim LP's, including premature battery depletion, which was observed at a higher rate than initially reported. Chapter 3 examines real-world long-term battery longevity in Micra LP's, and Chapter 4 presents the first real-world long-term results of LP therapy in a general LP patient population.

- * Part II focuses on ICD's. Chapter 5 analyzes transvenous systems, highlighting a high and accelerating failure rate for a commonly used ICD lead. Chapter 6 evaluates the performance of an alternative ICD system, the S-ICD, in a typical ICD patient population. Chapter 7 delves further into the S-ICD, presenting a proof-of-concept study that introduces a second coil to influence the defibrillation threshold.
- * Part III provides a summary of the findings and offers a comprehensive discussion in English (Chapter 8) and Dutch (Chapter 9). This thesis ultimately seeks to contribute critical insights to the advancement of CIED therapy and to highlight areas for further development in device safety and efficacy.

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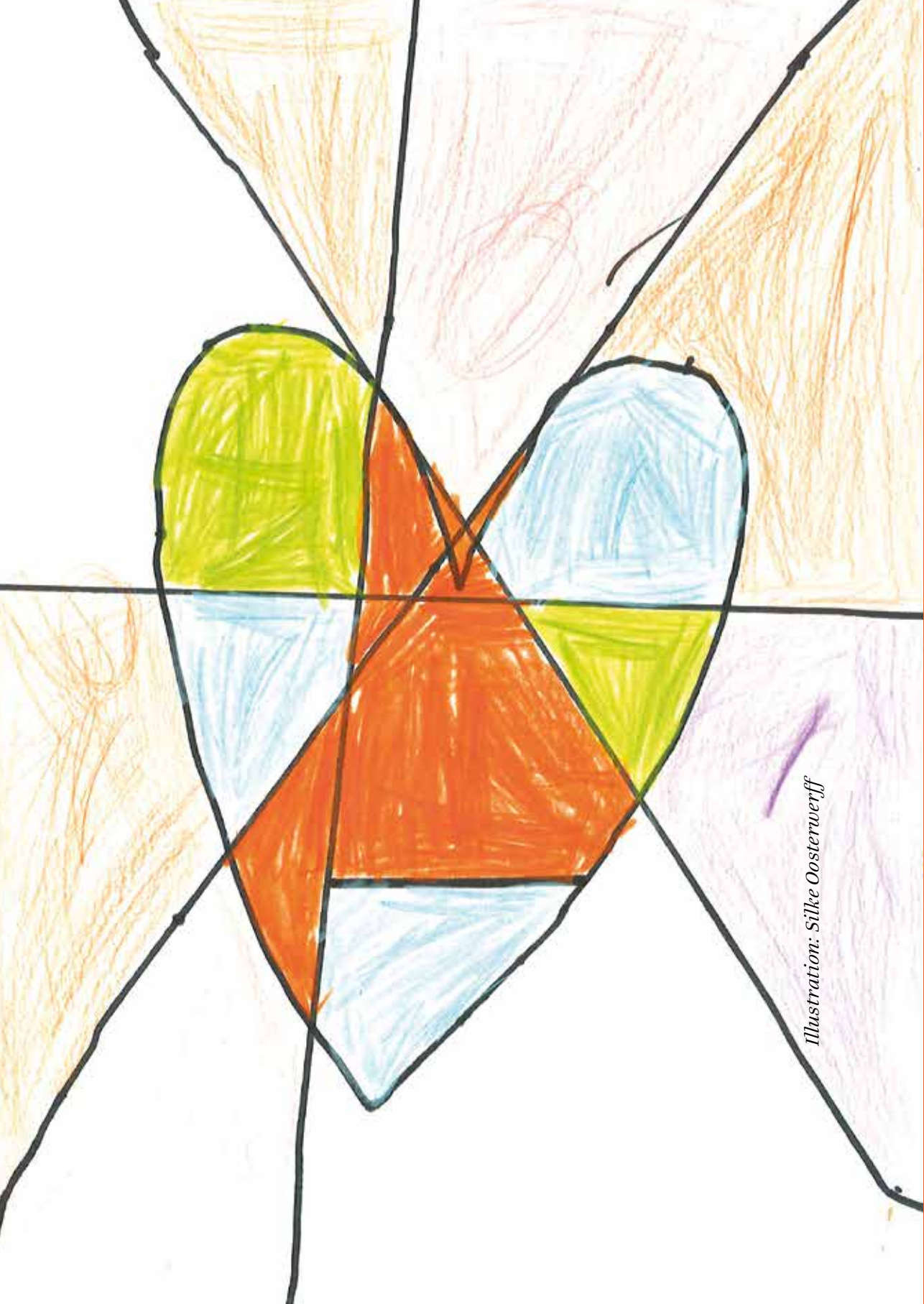


Illustration: Silke Oosterwerff

Part I

Post-market surveillance of leadless pacemakers

Chapter 2

Experience with Malfunctioning Leadless Pacemakers:
troubleshooting and management during medium term follow-up

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Peter Paul Delnoy, Ahmet Adiyaman, and Arif Elvan

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Heart Rhythm. 2022 Jun;19(6):894-900

Abstract

Background

The Nanostim leadless pacemaker (LP) was launched in 2012. However, the use of Nanostim LP was suspended due to safety.

Objective

The aim of this study was to report our experience with the management of malfunctioning Nanostim LP's, including premature battery depletion.

Methods

Fifty-one consecutive patients (age 83 ± 10 , 65% male) who underwent Nanostim LP implantation between 2014 and 2016 at Isala Hospitals were identified. Two patients were excluded from analysis due to incomplete follow-up. Mean follow-up duration was 1114 ± 560 days.

Results

Nanostim LP malfunction occurred in 20/49 (40.8%) patients. Premature LP battery failure was observed in 18/20 (90%) of the affected patients. Furthermore, malpacing/malsensing was observed in 1 patient and mechanical dislocation of the Nanostim LP occurred in 1 patient.

Of note, 17/18 (94%) Nanostim LP's with premature battery depletion showed normal device parameters three months prior to the diagnosis of (impending) premature battery failure. In 12 patients Nanostim LP's with a mean device age at the time of extraction of 1040 ± 467 days was successfully extracted without complications. Implantation of another LP or a transvenous device was successfully performed in all 20 patients with Nanostim LP malfunction. All known cases of early-life battery failure were identified during the 3-monthly follow-up consultations.

Conclusion

The incidence of Nanostim LP early-life battery failure was higher than previously reported. Nanostim LP extraction in an older population seems to be safe and effective. Three monthly follow-up seems to be effective at preventing in-between Nanostim LP related hospitalization.

Introduction

The Nanostim leadless pacemaker (Abbott/St. Jude Medical, St. Paul, MN, USA) was launched in 2012 as a promising less invasive alternative for conventional transvenous cardiac pacemakers. (1) Tjong et al concluded that Leadless Pacemakers (LP) are less susceptible to various procedural and long-term complications associated with conventional pacemakers. (2) Reported short term complication rate in patients implanted with conventional pacemakers ranged from 9.5% to 12.6% based on data derived from large nationwide multicenter cohort studies conducted in Denmark and the Netherlands. (3,4) These complications were mainly related to pacing leads but also include pneumothorax, cardiac perforation, and pocket infection or hematoma.

Initial clinical trials showed promising results with the LEADLESS observational study reporting 97% implantation success and 90-day complication free survival in 94% of implanted patients. (5) Subsequently, the LEADLESS II study reported 95.8% implantation success whilst reporting device-related serious adverse events in 6.7% of implanted patients. Furthermore, this latter study estimated the Nanostim LP to have a projected battery longevity of 15.0 ± 6.7 years. (6)

In the years following introduction for clinical use, enhanced Nanostim LP early-life battery failures were reported and in October 2016 Abbott released an official advisory stating that seven out of the 1423 implanted devices (0.5%) displayed battery failure before reaching the projected minimal 8.8 years of battery life. (7) Consequently, the manufacturer recalled Nanostim devices due to a high rate of premature battery failure and all implantations ceased immediately. The manufacturer advised to follow all patients on a 3-monthly basis with interrogation of the device. In addition, Abbott released a second advisory in April 2018 stating a 0.28% docking button detachment rate which causes the Nanostim LP to be irretrievable. (8)

Safe and effective management of patients implanted with Nanostim LP's is of paramount importance. In particular, sudden battery failure can be life threatening for pacing dependent patients.

Limited real-life data is available regarding the long-term perfor-

mance of Nanostim LP's and management of premature battery failure. Furthermore, there is a scarcity of data regarding safety and efficacy of extraction of Nanostim LP's. Currently, there are only six database studies published on Nanostim LP extraction. (Table 1). Furthermore, only one study from Lakkireddy et al. addressed the management of Nanostim LP's following the Nanostim advisory. (9) Previous studies described problems such as; encapsulation of the pacemaker, faulty docking ports, mechanical dislodgement and irretrievable LP's due to proximity of the docking button to the tricuspid valve. (9, 12-16)

The aim of this study is to address the following three questions: 1) What is the real-life incidence of Nanostim LP's premature battery failure during medium term follow up? 2) Is Nanostim LP extraction and subsequent pacemaker reimplantation safe and effective in an elderly patient population? 3) Is three monthly follow-ups under the Nanostim advisory effective at preventing Nanostim LP related in-between hospitalizations?

Methods

Data were retrospectively collected from medical records in all consecutive patients implanted between 2014 and 2016 with a Nanostim LP at the Isala Hospitals (Zwolle, the Netherlands), Department of Cardiology, a tertiary high volume referral center. All Nanostim LP patients were implanted with participation in the Leadless observational study (NCT02030418). (6) Inclusion and exclusion criteria for implantation were derived from the Leadless observational study. Additionally, patients lacking written consent for study participation and complete follow-up care at Isala Hospitals were excluded from this study. All research activities were conducted according to the principles of the Declaration of Helsinki as revised in 2013. (10) Ethical approval was obtained by the Medical Ethics Committee at the Isala Hospital, the Netherlands.

Advisory management plan

Before October 2016, all patients were subject to follow-up consultations at 90 days and six months post implantation. After this, patients were scheduled for follow-up consultations every six months until the last included patient completed five years of follow-up. However, after the release of the 2016 Nanostim advisory all Nanostim patients at Isala hospital were followed with three monthly consultations in order to timely identify Nanostim LP's at risk of impending early-life battery failure. (7)

Nanostim LP retrieval

The Nanostim LP was designed to be a retrievable self-containing unit with a dedicated retrieval catheter which comes in a single or a triple snare configuration.

Prior to retrieval, chest x-ray was performed to identify the position of the Nanostim pacemaker which was compared to the post-implant chest x-ray. The procedure started with right ventricular fluoroscopy to identify the intact docking button and the free movement of the Nanostim LP during one full cardiac cycle. Percutaneous access through the right femoral vein was the preferred point of entry for extraction. Subsequently, in most cases the Nanostim LP retrieval catheter was introduced through an 23F Medtronic sheath. Fluoroscopic imaging was used to advance the catheter to the junction of the inferior vena cava and the right atrium. The deflectable retrieval catheter was exposed by withdrawing the protective sleeve. The catheter was deflected subsequently advanced into the right ventricle where the snare was moved into the position to grasp the docking button. The device was snared and docked to the catheter after which a sleeve was advanced over the distal part of the device. The Nanostim LP was unscrewed under fluoroscopy through two full counter clockwise turns. Subsequently, the protective sleeve was advanced over the full length of the device after which the Nanostim LP was withdrawn from the body. Then, a new (leadless) pacemaker was inserted during the same procedure.

Outcome variables

Two independent observers retrospectively reviewed leadless pacemaker technical data and medical records. Data recorded in our registry included: patient characteristics, cardiovascular history, pacing indication and pacemaker data and patient outcomes. Early-life battery failure was defined as (impending) loss of telemetry, loss of contact, unusual parameters in Nanostim LP's with a device age under the minimal 8.8 years of advertised battery longevity. (1) Pacemaker indication was categorized according to the guidelines of the European Society of Cardiology. (11)

Endpoints

The study's primary endpoints for the three research questions were defined as the following:

1) Early-life Nanostim LP battery failure was defined as (impending) failure of a Nanostim LP's battery before the minimal advertised battery longevity. 2) Nanostim LP dysfunction was defined as a (partial) loss of function of an LP before the minimal advertised product age. 3) Nanostim LP extraction success and safety is formulated as the percentage of successful extractions and subsequent successful reimplantation without severe adverse events. 4) The effectiveness of the Nanostim advisory follow-up regimen was defined as the absence of in between follow-up hospitalizations that are pacemaker related.

Statistical analysis

Data are presented as means \pm standard deviations, median and interquartile range where appropriate and categorical variables are presented as proportions or percentages. Clinical data were collected until 12-12-2020 which was taken as the last moment of follow-up. We used a Kaplan-Meier curve to display Nanostim LP dysfunction free survival. Statistical and descriptive analyses were performed using IBM SPSS Statistics version 25.0 (IBM, Armonk, New York).

Results

Patient characteristics

Fifty-one consecutive patients who underwent Nanostim LP implantation at Isala Hospitals, Department of Cardiology, a tertiary heart center (Zwolle, The Netherlands) were identified. Two patients were excluded from further analysis due to incomplete follow-up data. The remaining 49 patients were included in this study. Mean follow-up duration was 1114 ± 560 days. Patient characteristics are summarized in Table 2.

Clinical Presentation of Nanostim LP malfunction

Twenty Nanostim LP's became dysfunctional. (figure 1) Most common reason for Nanostim LP malfunction was battery failure 90% (18/20); in one patient there was malsensing and mechanical dislocation of the Nanostim LP occurred in another patient. The incidence of early-life battery failures in our patient cohort was 37% (18/49) during a follow up of 3 years. Figure 2 depicts the Kaplan-Meier Nanostim LP malfunction free survival curve.

Early Nanostim mechanical dysfunction occurred at 65 days post-implantation due to a dislocation of the device. The first premature battery malfunction was observed at 770 days post implantation and the last patient had a premature battery malfunction 1854 days post-implantation. The mean device age at the time of (impending) premature battery failure was 1221 ± 377 days. During the consultation prior to being diagnosed as (impending) early life battery failure 44% of pacemakers (8/18) had a "Beginning of Life" battery status and 56% (10/18) had a "Middle of life" battery status. All known cases of battery failures in Nanostim LP's were identified during the regular follow-up consultations. All but one Nanostim LP showed no prior signs of impending battery failure.

Currently, two elderly frail patients with a dysfunctional Nanostim pacemaker refused an extraction/reimplant procedure. Moreover, after shared decision four patients chose to implant a conventional TVP alongside the abandoned dysfunctional Nanostim.

Nanostim LP extraction efficacy and safety

Twelve out of the 15 (80%) attempted extractions were successful and pacemaker reimplantation was successful in all patients. Table 3 summarizes the details of the Nanostim LP extraction procedures. No major complications were observed during the extraction procedures. The three patients with unsuccessful extraction procedures were successfully converted to implantation of conventional TVPs due to concerns that a second LP might interact with the abandoned Nanostim LP. No interactions/complications were observed during follow-up consultations in patients who were implanted with a conventional TVP alongside an abandoned Nanostim LP (N=3). The mean device age during extraction was 1040 days (± 467). The mean procedure time was 102 minutes (± 55) with a mean fluoroscopy time of 19:34 minutes ($\pm 12:45$). The Micra leadless pacemaker was chosen as a replacement in 10/15 procedures followed by a conventional TVP (4/15) and Nanostim LP (1/15).

The attempted extraction of the oldest Nanostim LP at a device age of 1863 days eventually resulted in a peri-procedural abandonment (procedure 2). The LP was implanted at a mid-septal level and the docking button was identified during fluoroscopy. However, the operator attempted to snare the LP for a total of 30 minutes during which the snare slid of the body of the LP and would not grasp the docking button. The operator noted the docking button was probably encapsulated and converted the procedure to a conventional TVP implant procedure. Extracting a Nanostim LP with a device age of 1495 days proved to be difficult due to encapsulation of the Nanostim LP's docking button/body (procedure 15). The docking button was snared after multiple attempts after which the protective sleeve couldn't be advanced over the distal half part of the Nanostim LP's body due to encapsulation of the device. The Nanostim LP was finally detached from the septum through 30 turns. This phenomenon of Nanostim LP encapsulation was observed in other successful extraction procedures at Isala Hospitals. (Figure 3)

In a 83 year old female with a device age of 934 days snaring was unsuccessful due to the proximity of the docking-button directly un-

der the tricuspid valve. Nanostim LP was abandoned and conventional TVP was implanted. (Procedure 9)

In a 74-year-old male with a device age of 912 days, fluoroscopy prior to the procedure revealed absence of the docking-button. The procedure was converted to a conventional VVI TVP which was successfully implanted. (procedure 8)

Of note one Nanostim LP that was extracted after 71 days post-implantation was dislocated into the pulmonary artery. This patient consulted the treating cardiologist after experiencing progressive dyspnea on exertion (procedure 6). Interrogation of Nanostim LP revealed no ventricular capture. Subsequent chest x-Ray and CT-thorax imaging showed a Nanostim LP in the right pulmonary artery (supplementary file). The extraction procedure was carried out six days later during which the LP was swiftly captured with a Goose Neck snare. Afterwards, a new Nanostim LP was successfully implanted during the same procedure.

Discussion

This report describes our experience with the follow-up and extraction of Nanostim LP pacemakers at risk of malfunctioning including (impending) battery failure.

Our main finding is that the incidence of early-life battery failure in Nanostim LP's during medium term follow-up was much higher than previously reported data with shorter follow-up (37% vs. 0.5% respectively). (7) All known cases of early-life battery failure in Nanostim LP's were identified during regular three monthly Nanostim advisory follow-up consultations.

The incidence of early-life battery failure in our cohort increased over time which could explain the higher incidence of early-life battery failure than the 0.5% published in the Nanostim advisory of 2016. (7) Moreover, Lakkireddy et al. reported a lower percentage of battery failures (2.39%) in their population of 1423 patients occurring at 2.9 ± 0.4 years with no instances of associated patient injury (9). The lack of

prior signs of impending battery failure, and the higher than previously known percentage of early-life battery failures, emphasizes the importance of careful follow-up and management of Nanostim LP's. Furthermore, pre-emptive replacement of functional Nanostim LP's should be considered in pacemaker-dependent patients since acute early-life battery failure without prior warnings remains a risk.

Since no serious adverse events were observed, Nanostim LP extraction and subsequent pacemaker reimplantation seems to be safe (and effective (80% retrieval success and 100% reimplant success) in our series with a predominantly elderly population (mean age 80 years). Similar studies report a slightly higher extraction success when compared to our study (90% versus 80%). However, the mean device age of Nanostim LP's that underwent attempted extraction in our study was higher when compared to previous reports (1040 vs 256, 556 and 620 days). (9, 12-15) Only Breeman et al. (16) reported results of extraction with similar device age (1080 days). Their success rate was 93% and they assessed the histopathology of adherent tissue and obtained clinical characteristics. They showed that thrombus formation, thrombus organization, and a fibrotic response around LP's are a common feature. Over time, the fibrosis matures and likely encapsulates the LP similarly to transvenous leads, the timing of which is variable. This phenomenon could be responsible for some difficult extraction procedures. Moreover, one Nanostim LP was abandoned due to the proximity of the docking button to the tricuspid valve. This finding is in line with a report from Asirvatham et al. who stated that proximity of the docking button within 1 cm of the tricuspid valve increases the risk of peri-procedural abandonment of the Nanostim LP. (12) An additional finding was that one of the Nanostim LP's that underwent attempted extraction had a detached docking button. Detachment of the docking button carries risks such as embolization of the docking button. This finding is in line with the 2018 Nanostim advisory in which Abbott stated that 0.85% docking buttons were detached in Nanostim LP's that underwent attempted extraction. There is currently no clinical evidence that prophylactic imaging is effective at identifying docking button detachments (8). For different reasons a conventional pacemaker was

implanted besides a Nanostim LP. In this cohort, there were no pacing issues or sensing issues due to interaction with Nanostim LP during follow-up.

Since removal of the Nanostim LP is not always possible, it is imperative to inform these patients on the risks of extraction including the possibility of a peri-procedural Nanostim LP abandonment and subsequent conversion of the procedure to a different pacemaker. The mean procedure time of an attempted Nanostim LP extraction and subsequent reimplantation was 102 minutes (± 55) with a mean fluoroscopy time of 19:34 (minutes:seconds, $\pm 12:45$). Asirvatham et al. reported both a higher mean procedure time (205 min ± 49) and a higher mean fluoroscopy time (37 min ± 19) in their series of 9 attempted Nanostim LP extractions. (12)

We recognize several strengths and limitations to our study. As mentioned in the introduction, there are currently only six database studies available on Nanostim LP extraction with only one describing the management of Nanostim LP's at risk of early-life battery failures. In our cohort, we abandoned the dysfunctional Nanostim LP and placed a second device without complications in 7 patients. Probably we could have further limited the number of extractions. The risk benefit assessment and decision to extract the Nanostim LP was left to the discretion of the patient and implanting physician. Our study is the first to describe the modes of clinical presentation during medium term follow-up and management of dysfunctional devices including extraction of Nanostim LP's. There are several limitations inherent to the retrospective design of the current study. The single center design and limited number of patients are important limitations. The results should be regarded as hypothesis generating. A long term independent multi-center follow-up study on Nanostim LP extractions is needed to allow firm and valid conclusions. Second, we could not verify the accuracy of the data due to the retrospective nature of the study. All out of hospital deaths were captured in the registry but the cause of death often remains unknown since autopsy is rarely performed in this elderly population. Therefore, we could not assess potential deaths due to dysfunctional Nanostim LP's.

Conclusion

This “real world” registry indicates that the percentage of Nanostim LP’s that develop early-life battery failure during medium term follow-up is higher than previously reported. The most common indication for Nanostim LP extraction was battery malfunction. Nanostim LP extraction was safe and effective. Three-monthly follow-up under the Nanostim advisory seems to prevent PM related in-between follow-up hospitalizations. Finally, prophylactic replacement of a functional Nanostim LP’s should be considered in pacemaker-dependent patients since premature battery failure without prior warning remains a risk.

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Table 1. Overview of existing literature on Nanostim extraction/management (9, 12-16)

Leadless Pacemaker	Year of Publication	First Author	Number (n)	Time LP <i>in situ</i>	Extraction Success	Source (Organization, hospital, trial)
Nanostim	2021	Breeman (16)	15	1080 (mean)	93%	AMC, Amsterdam, The Netherlands
Nanostim	2020	Asirvatham (12)	9	554 (mean) days	89%	Mayo Clinic, Rochester, USA
Nanostim	2020	Dar (13)	73	256 (median)	90%	Leadless II
Micra			40	46 (median) days	100%	Manufacturer data
Nanostim	2017	Gonzalez (14)	3	983-1048-1070 days	100%	Hospital Universitario La Paz, Madrid, Spain
Nanostim	2017	Lakkireddy (9)	73	1,7 years (mean)*	90%	Leadless, Leadless II, Evolution of a new Pacemaker
Nanostim	2016	Reddy (15)	5	<6 weeks	100%	Leadless, Leadless II, Evolution of a new Pacemaker
			11	>6 weeks	91%	

* Article only specified mean in-situ time of the 53 LP's extracted after the 2016 October battery advisory.

Table 2. Nanostim patient characteristics

	Nanostim LP (n=49)		Nanostim LP (n=49)
Patient Characteristics		NYHA-Class	
Follow-up duration (Days)	1114 ± 560	1	83,7%
Age (Years)	83 ± 10	2	8,2%
Sex (Male)	65,3%	3	8,2%
BMI (kg/m ²)	26,6 ± 3,97	4	0%
Indication category*		Medication	
Chronic atrial fibrillation with high-grade AV-block or slow ventricular response	38,8%	ACE-Inhibitor or ARB	57,1%
Sinus rhythm with high grade AV-block	34,7%	Betablocker	38,8%
Sinus bradycardia with infrequent pauses including brady-tachy syndrome	24,5%	Calcium-antagonist	14,3%
Symptomatic bradycardia not specified	2%	Digoxin	6,1%
Ablation and pacing	0%		
Cardiovascular risk factors			
Hypertension	44,9%		
Hypercholesterolemia	30,6%		
Diabetes Mellitus	22,4%		
Familiar history	14,3%		
Smoking	2%		
Cardiovascular history			
Atrial fibrillation	53,1%		
Previous myocardial infarction	20,4%		
Previous CABG	18,4%		
Previous PCI	16,3%		
Previous Transvenous Pacing System	4,1%		

*Class I or II indications for cardiac pacing according to the ESC guidelines (11)

AV-block = Atrioventricular block.

BMI = Body Mass Index

CABG = Coronary Artery Bypass Grafting

PCI = Percutaneous Coronary Intervention

Table 3. Attempted Nanostim extraction procedures

Proce- dure	Age Year	Gender	Extraction indication	RVP%	Implant duration days	Proce- dure time, min	Dose Area Product Gycm ²	Retrieval attempts	Reimplant	
1	90	M	Battery	28	1191	87	5,8	I	Micra	
2	72	F	Battery	28	1863	178	10	**	TVP	
3	88	F	Battery	85	892	70	11	I	Micra	
4	74	M	Patient	2	534	123	2,7	I	TVP	
5	85	M	Battery	88	1438	90	8,8	I	Micra	
6*	73	M	Dislocation	97	71	188	29,8	I	Nanostim	
7	79	M	Sensing	3	711	202	13	I	Micra	
8*	74	M	Battery	100	912	160	15	**	TVP	
9	83	F	Battery	39	934	107	8,5	**	TVP	
10	74	M	Battery	96	927	60	10	I	Micra	
11	89	F	Battery	2	1060	49	5,1	I	Micra	
12	76	M	Battery	0,3	1028	63	6,2	I	Micra	
13	84	F	Battery	22	772	40	7	I	Micra	
14	75	M	Battery	84	1778	45	7,2	I	Micra	
15	86	M	Battery	96	1495	73	16,7	I	Micra	
Mean:				Mean:	Mean:	Mean:	Mean:	Mean:		
80 SD				51 SD	1040 SD	102 SD	10 SD			
± 6,51				± 41	± 467	± 55	± 6,5			

* Denotes same patient

** Unsuccessful

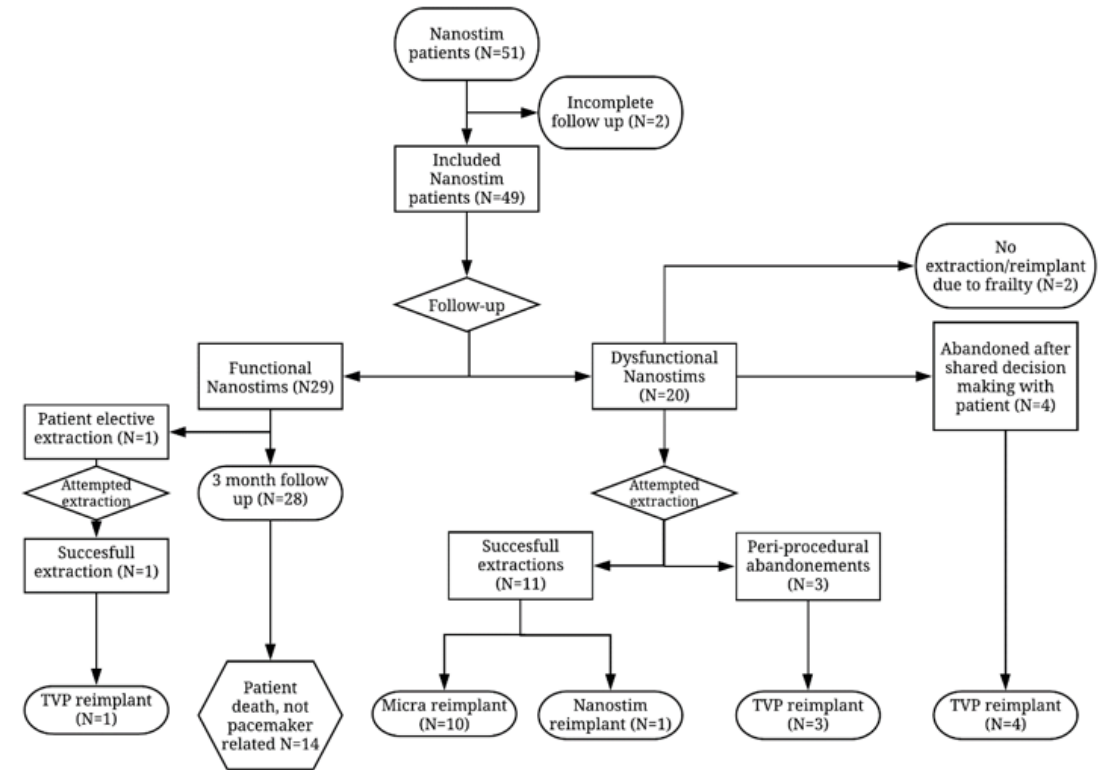
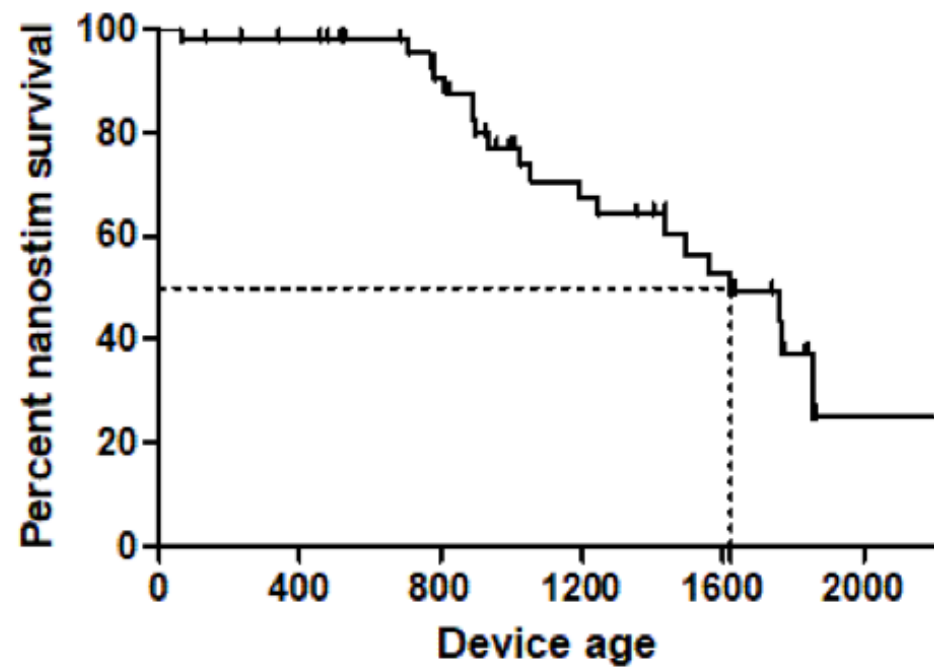


Figure 1. Management of Nanostim LP's at risk of early-life battery failure under the Nanostim advisory



Patients at risk: 49 45 36 22 15 2

Figure 2. Nanostim LP dysfunction survival curve, dotted line denotes 50% device survival rate at 1623 days

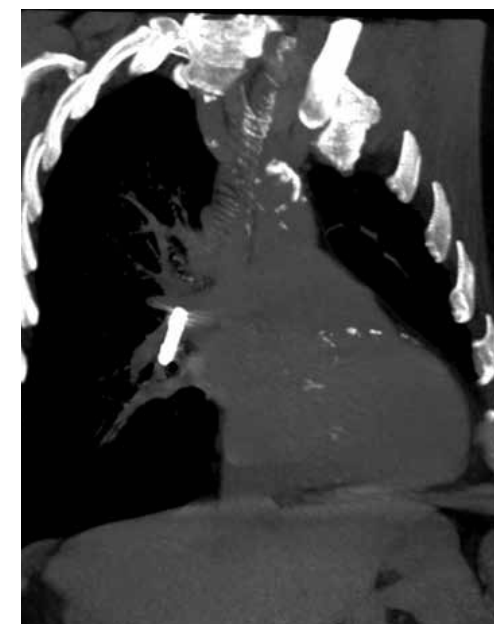
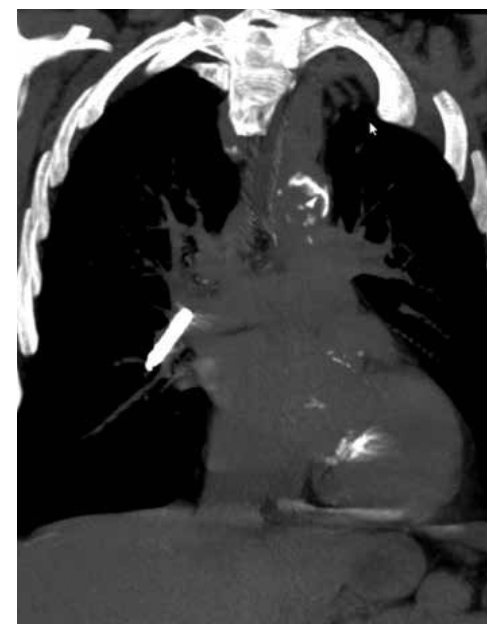


Device age: 1191 days



Device age: 711 days

Figure 3. Nanostim LP's extracted at Isala Hospital showing various degrees of encapsulation on the docking button. Pictures courtesy of Abbott.



Supplementary file
CT imaging of the dislocated Nanostim (red arrow) situated in the right pulmonary artery.

Chapter 3

Real-World Long-Term Battery Longevity of Micra Leadless Pacemakers

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Leadless pacemakers (LP's) are a guideline-directed option for patients with bradyarrhythmias. The currently most implanted LP (>150,000 implantations) is the Micra VR (Medtronic, Minneapolis, USA). Mid-term safety and efficacy were proven, but long-term data is lacking. (1) Long-term safety will largely depend on battery longevity, as battery depletion is the main reason for replacements with a concomitant complication risk. However, real-world battery longevity does not always match the predicted values. For instance, premature battery depletion of Nanostim LP's starting 2 years after implantation resulted in a large number of (prophylactic) re-interventions. (2, 3) The mean battery longevity of the Micra VR predicted by the manufacturer is 12 years, which is comparable to transvenous pacemakers. (4) This prediction held true after one year in 630 patients. (5) We sought to determine the mid- and long-term battery longevity.

Consecutive patients with Micra VR implantation at two large-volume LP implanting hospitals from January 2014 to September 2021 were included. Baseline characteristics and electrical parameters including expected battery longevity were assessed during all yearly follow-up visits (visit at 0 years was between 1-6 months to allow for early programming changes). Expected battery longevity is the projected time until recommended replacement time and is based on battery voltage, time since implant, programmed parameter settings and pacing percentage. Maximum expected battery longevity is displayed as '>8 years. Mixed models were used to assess changes in electrical parameters over time. If pacing capture threshold (PCT) was not available at 0.24ms (nominal pulse width), it was estimated using the energy formula ($E=V^2/R*d$). This study was approved by the local ethics committees.

153 patients (105 [69%] male, age 80 ± 9 years) were included. Pacing indications were atrial fibrillation with slow conduction (78 [51%]), third-degree AV-block (24 [16%]), incomplete AV-block (15 [10%]), sinus node disease (35 [23%]) and unexplained syncope (1 [1%]). At implantation, PCT, impedance and R-wave amplitude were $0.72 \pm 0.61V$ (147 at 0.24ms, 6 at 0.4ms), $775 \pm 205\Omega$ and $11.6 \pm 5.2mV$, respectively. Lower rate was programmed 50-60/min in 128 (84%), <50/min in 16 (10%) and >60/min in 9 (6%); rate-responsive pacing was programmed on in 64 (42%).

Pacing percentage at the first follow-up visit was median 35% (IQR 6-95%). Median follow-up was 35 months (IQR 21-57 months). PCT and pacing percentage remained constant ($-0.02V/year$, $p=0.28$; $+0.64%/year$, $p=0.14$, respectively), impedance decreased ($-49\Omega/year$, $p<0.001$) and R-wave amplitude increased ($+0.73mV/year$, $p<0.001$).

Up to 5 years, expected battery longevity was the maximum value (>8 years) in the majority of patients (Figure 1, A). At 7 years, expected battery longevity ranged from 4.1 years to >8 years ($n=6$). Added to the dwelling time at those visits, >13 years battery longevity is expected in the majority of patients. Battery voltage was mean $3.14 \pm 0.03V$ at implantation and decreased by $0.03V/year$ ($p<0.001$). No premature battery failures were seen. Two LP's were replaced (2/153, 1.3%; Figure 1, B). One after 1.7 years at an expected battery longevity of 7 months due to high PCT ($1.75V@0.24ms$ at implant which increased to $2.13V@0.4ms$ at 1.7 years), slightly low impedance (460Ω at implant which remained low) and high pacing percentage (84% at 1 year), while programmed vVIR with lower rate 50/min. The other was replaced after 3.7 years at an expected battery longevity of 4 months due to high PCT ($0.63V@0.24ms$ at implant which increased to $1.25V@0.4ms$) and high pacing percentage (>95% from implant to replacement), programmed vVIR with lower rate 50-60/min. The dwelling time and expected battery longevity at the latest follow-up visit (median 1.5 years after implant) added up to below 7 years (median 6 years, range 5.0-6.6 years) in 6 other patients. There were multiple energy-consuming factors: high PCTs in 5/6 (83%), low impedances in 2/6 (33%), high pacing percentages in 4/6 (67%) and high lower rates in 2/6 (33%).

These results imply that up to 7 years post-implantation, the manufacturer's predicted mean battery longevity of 12 years still holds. In practice, real-world battery longevity of transvenous pacemakers does often not match the predicted values, which contrasts with our study. Possibly, the battery longevity in this study was as predicted due to the favorable electrical parameters (relatively high impedance, low PCT). Both battery failures were not deemed premature in light of the projected values based on accelerated discharge data and device modeling(6). Of note, the nominal pulse width of the Micra VR was chosen near chronaxie (0.24ms); hence, increased pulse width importantly

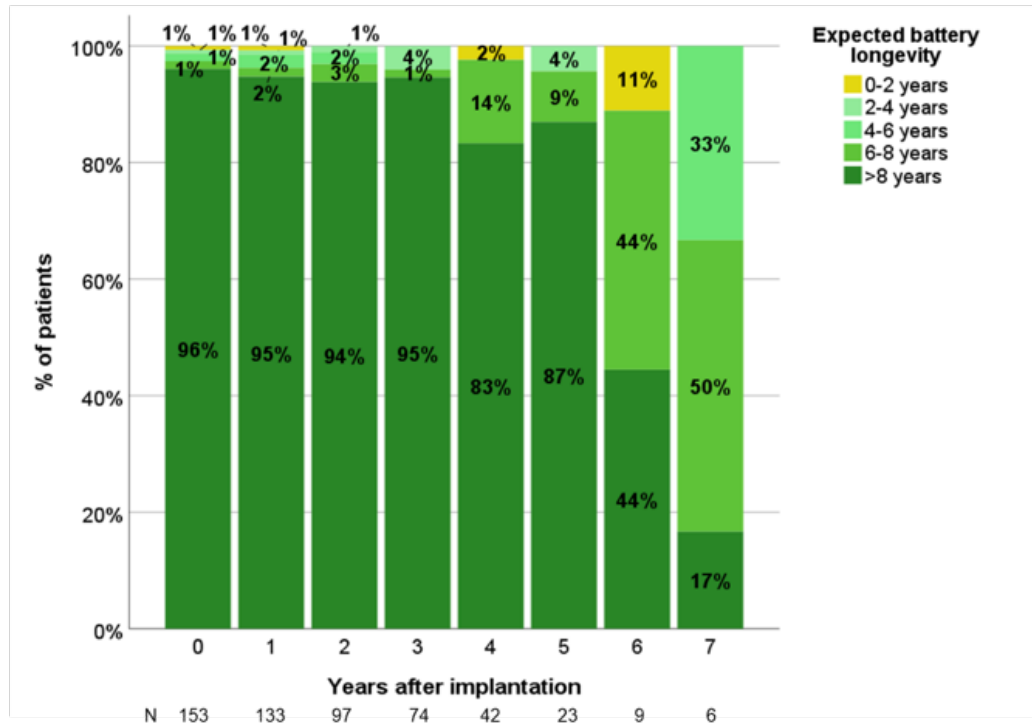
reduces expected battery longevity. The projected battery longevity of <7 years in 6 LP's was also in line with projected values. This study was limited by lack of the exact expected battery longevity when over 8 years.

In conclusion, these long-term real-world data suggest that the battery longevity of the Micra VR will match the manufacturer's predicted battery longevity. Data from larger registries is necessary to confirm these results.

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A. Expected battery longevity up to 7 years after implantation



B. Battery survival up to 7 years after implantation

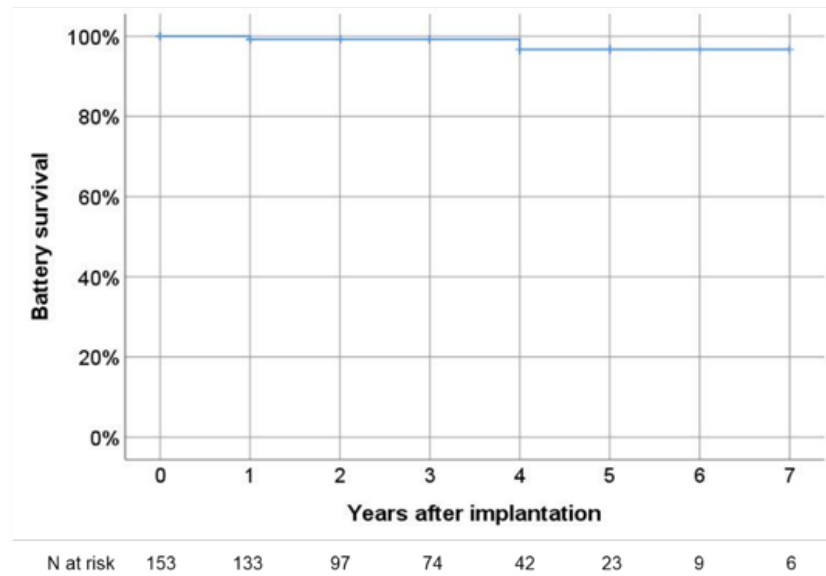


Figure 1. Expected battery longevity (A) and battery survival (B) and up to 7 years after implantation.

Chapter 4

Five-year safety and efficacy of leadless pacemakers in a Dutch cohort

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Abstract

Background

Adequate real-world safety and efficacy of leadless pacemakers (LP's) has been demonstrated up to three years after implantation. Longer-term data is warranted to assess the net clinical benefit of leadless pacing.

Objective

To evaluate the long-term safety and efficacy of LP therapy in a real-world cohort.

Methods: In this retrospective cohort study, all consecutive patients were included with a first LP implantation from December 21, 2012 to December 13, 2016 in six Dutch high-volume centers. The primary safety endpoint was the rate of major procedure- or device-related complications (i.e., requiring surgery) at five-year follow-up. Analyses were performed with and without Nanostim battery advisory-related complications. The primary efficacy endpoint was the percentage of patients with a pacing capture threshold of ≤ 2.0 V at implantation and without ≥ 1.5 V increase at the last follow-up visit.

Results

179 patients were included (mean age 79 ± 9 years), 93 (52%) with a Nanostim and 86 (48%) with a Micra VR LP. Mean follow-up duration was 44 ± 26 months. Forty-one major complications occurred, of which seven not advisory-related. The five-year major complication rate was 4% without advisory-related complications and 27% including advisory-related complications. Not advisory-related major complications occurred median 10 days (range 0-88 days) post-implantation. The pacing capture threshold was low in 163/167 (98%) and stable in 157/160 (98%).

Conclusion

The long-term major complication rate without advisory-related complications was low with LP's. No complications occurred after the acute phase and no infections occurred, which may be a specific benefit of LP's. The performance was adequate with a stable pacing capture threshold.

Introduction

For patients with bradyarrhythmias, pacemaker therapy is the cornerstone of treatment. (1) Transvenous pacemakers have been the standard treatment for decades. This pacemaker type, however, is associated with an important rate of complications, in particular lead- and pocket-related. (2, 3) To circumvent those complications, leadless pacemakers (LP's) have been developed. LP's are small capsule-like pacemakers that are implanted via the femoral or jugular vein and are fully contained in the right ventricle. Initially, two LP models were commercially available: the Nanostim LP (Abbott Medical Inc., Abbott Park, IL, USA) with a helix-based fixation mechanism and the Micra VR LP (Medtronic, Minneapolis, MN, USA) with a tine-based fixation mechanism and with a smaller length (42 mm vs. 26 mm). (4, 5) Nanostim LP implantations were halted due to premature battery failures. Without battery-related complications, however, mid-term safety and efficacy were adequate (6). Large-scale, real-world data of Micra VR LP's demonstrated adequate safety and efficacy, with follow-up durations up to three years after implantation in selected populations. (7-9) Compared to transvenous pacemakers, more acute perforations occurred but fewer device-related complications. Because the needed duration of pacemaker therapy is much longer than three years in most patients, the net clinical benefit of leadless pacing can only be assessed with long-term data. Although Nanostim LP's are currently not implanted, long-term data of this model is warranted, as its successor, the Aveir VR (Abbott Medical Inc., Abbott Park, IL, USA) has a similar fixation mechanism and shape. In the Netherlands, LP technology was adopted early on, resulting in the availability of a unique cohort with long-term follow-up data.

Our aim was to evaluate the safety and efficacy of LP therapy on the long-term in this real-world cohort.

Methods

Design, patients and procedures

In this retrospective cohort study, all consecutive patients were included that were implanted with a primary LP (Nanostim LP or Micra VR LP) from December 21, 2012 to December 13, 2016 in six Dutch high-volume centers. All patients provided informed consent. The study was approved by the local Ethics Institutional Committee on Human research. The implantation procedure of both LP's has been described previously. (4, 5) Baseline characteristics, procedural details and follow-up data were collected from patient files up to July 1, 2022. The management of patients with Nanostim battery failures at the Isala Clinics (Zwolle, The Netherlands) was reported before. (10)

Outcomes

The primary safety endpoint was the rate of major procedure- or device-related complications during five years of follow-up after implantation. The classification of complications was as follows: minor complications were defined as complications requiring no action and potentially observation; intermediate complications were defined as complications requiring a non-surgical medical intervention (e.g. drugs or transfusion); major complications were defined as complications requiring surgery. The secondary safety endpoint was the rate of all procedure- or device-related complications through 5 years after implantation.

The primary efficacy endpoint was the percentage of patients with a pacing capture threshold (PCT) of $\leq 2.0V$ at implantation at the nominal pulse width (Nanostim LP LP 0.40ms; Micra VR LP 0.24 ms) and without $\geq 1.5V$ increase at the last follow-up visit. Secondary efficacy endpoint was the electrical performance (PCT, impedance and R-wave amplitude) during follow-up.

Complication status and electrical parameters were retrospectively collected from patient files. Data from implantation and follow-up visits at pre-hospital discharge, 3 months after implantation and yearly after implantation were included in this study.

Battery advisory-related complications

During the study, an advisory was issued for the Nanostim LP due to premature battery failures. This led to several events that met the complication criteria: replacement for a different (leadless) pacemaker due to battery failure or prophylactic replacement in pacemaker-dependent patients were defined as major complications, battery failure without replacement pacemaker as a minor complication. This specific battery problem does not occur in the Micra VR LP and is thus not expected to be inherent to leadless pacing per se. Therefore, we performed separate analyses: with and without complications related to this technical problem.

Statistical analysis

Summary statistics are presented as follows: continuous variables as mean \pm standard deviation or median and interquartile range, and categorical variables as frequencies. Kaplan-Meier estimates were used to estimate the rate of complications at five years after implantation. Patients were censored at death, replacement of the LP, battery depletion without replacement LP, or end of study. Changes in parameters of electrical performance were assessed using mixed models. Differences in groups were tested for using the Student's T test for continuous, normally distributed variables and Mann Whitney U test for continuous, non-normally distributed variables. The association between extraction success and time to extraction was estimated with logistic regression.

Results

Clinical characteristics

A total of 179 patients were included with an implantation before December 13, 2016 from six high-volume centers in the Netherlands. The baseline characteristics are summarized in Table 1. The cohort reflects a common single-chamber pacemaker population with an average age at implantation of 79 ± 9 years and the primary pacing indication being mostly persistent or permanent atrial tachyarrhythmia with slow ventricular rate (40%) or with complete AV-block (17%). Sixty-two (35%) of the patients were female.

Procedural details

Details of the implantation are described in Table 2. Of the 179 implanted LP's, 93 (52%) were Nanostim LP's and 86 (48%) Micra VR LP's. The majority of patients used anticoagulants (70%), which were discontinued during the implantation in most patients. Repositioning was required in 24%.

Safety

Mean follow-up duration was 44 ± 26 months, with 66 patients having five or more years follow-up. A total of 41 major complications occurred in 41 patients: 7 not advisory-related and 34 advisory-related. The Kaplan-Meier estimate for major complications at five-year follow-up without advisory-related major complications was 4% (95%-confidence interval 1%-7%) (Figure 1A). Including advisory-related major complications, the five-year Kaplan-Meier estimate for major complications was 27% (95%-confidence interval 19%-35%) (Figure 1B). All major complications are shown in Table 3. The seven not advisory-related complications occurred median 10 days (range 0-88 days) after implantation: three during the hospitalization for implantation and four during follow-up. During implantation, two Nanostim LP's dislocated without embolization, after which the LP's were retrieved and another Nanostim implanted. There was one case of pericardial effusion on the day of implantation in a patient with a Micra VR LP, and percutaneous drainage was successfully performed. During follow-up, there were two patients with loss-of-capture of their Nanostim LP. In both cases, the LP was retrieved and another Nanostim LP implanted. Also, one patient presented 65 days post-implantation with dyspnea due to embolization of the Nanostim LP to the proximal pulmonary artery. The LP was retrieved using a gooseneck snare and another Nanostim LP was implanted successfully. Lastly, there was one case of pacemaker syndrome due to unexpected return of sinus rhythm in a patient with a Micra VR LP. Atrial flutter was re-induced during an electrophysiology study with subsequent symptom resolution. The occurrence of major complications without advisory-related complications did not differ significantly between patients with a Nanostim LP or Micra VR LP (Supplementary table 1). The 34 advisory-related complications included

27 replacements due to (impending) battery failure and 7 prophylactic replacements in pacemaker-dependent patients, after median 1150 days (range 304-2909 days).

All device-related complications are shown in Supplementary table 2. The Kaplan-Meier estimate of five-year complications was 10% (95%-confidence interval 5%-14%) without advisory-related complications and 37% (95%-confidence interval 28%-45%) including advisory-related complications (Supplementary figure 1). There were no intermediate complications. The not advisory-related minor complications included groin bleedings ($n=7$), arrhythmias during implantation ($n=2$) and worsening tricuspid regurgitation potentially due to the LP ($n=1$). The advisory-related minor complications included five cases of premature battery depletion where, in consultation with the patients, no replacement device was implanted. Three of those patients no longer met a guideline indication for pacing therapy and two had a low ventricular pacing burden.

Efficacy

The PCT was $\leq 2V$ at implantation in 163/167 (98%) with available PCT at nominal pulse width. PCT was stable ($\leq 1.5V$ increase) up to the last follow-up visit in 157/160 (98%). Of the six patients not reaching the efficacy endpoint, three had a PCT $> 2V$ at implantation, two a rise of $> 1.5V$ (one with loss of capture after 88 days), and one a PCT $> 2V$ at implantation with loss of capture after nine days. In 12 (7%) subjects, no implantation PCT was available at the nominal pulse width: there was one Micra patient with a PCT of 3.25V at 0.4ms, two patients with no available PCT, and in the other nine, PCT ranged from 0.25V to 1.1V at 0.5ms to 1ms. In 19 (11%) of subjects, the difference in PCT could not be estimated exactly due to differences in pulse widths or unavailable data. In two of those subjects, there may have been an increase of $> 1.5V$: at implantation, the PCT was 0.75V at 0.4ms in both and at the last follow-up visit, the PCTs were 0.75V and 1V, both with a pulse width of 1.5ms. PCTs of both Nanostim and Micra LP's were stable (respectively $p=0.066$ and $p=0.390$), R-wave amplitude increased over time ($p=0.002$), and impedance decreased over time ($p<0.001$; Figure 2A-D). The rate-response feature was activated in 60 (40%) patients at one year. The lower rate

was programmed <50/min in 17 (11%), 50-60/min in 127 (82%) and >60/min in 10 (7%) at 1 year. Ventricular pacing percentage was 0-25% in 70 (47%) patients, 25-50% in 21 (14%) patients, 50-75% in 14 (10%) patients and >75% in 43 (28%) patients at one year, and is shown over time in Supplementary figure 2. During follow-up, three LP's (Nanostim LP, n=1; Micra VR LP, n=2) were replaced due to battery depletion (after mean 60 ± 13 months) that was not deemed premature.

Replacement strategies

During this study, a replacement strategy (extraction, co-implantation or deactivation and no further action) was required for non-dislocated LP's in 48 patients. Figure 3 demonstrates different strategies that were taken. As mentioned, in five patients with a Nanostim LP with premature battery depletion, the LP was deactivated and no further action was taken. Extraction was attempted in 34 and was successful in 30 (88%). All 34 LP's were Nanostim LP's, time to extraction was mean 37 ± 22 months. There was no significant difference in time to extraction between the successful and unsuccessful extractions (36 ± 22 months vs. 45 ± 19 months, $p=0.49$). Extraction success by time to extraction is shown in Figure 4. Of the unsuccessful retrievals, three were due to incapability to snare the docking button. This was deemed to be due to the position of the docking button behind the TV (n=1), due to adhesions (n=1) or due to one of both (n=1). In the other unsuccessful retrieval, catheter rotations were not converted to pacemaker rotations due to fibrotic overgrowth. The 9 patients with no extraction attempt (Micra VR LP's n=3, Nanostim LP's n=6) were all co-implanted with another device. No intermediate or major complications occurred during replacement or co-implantation.

There were different clinical scenarios requiring a replacement strategy. The most common was (impending) premature battery failure due to the Nanostim battery or pacemaker-dependency with a Nanostim in situ (n=39, of which 5 patients without reimplantation). Further, in four patients, the device was replaced for a transvenous device due to a change of indication. One was replaced for an ICD due

to the occurrence of ventricular tachycardias, one for a CRT-D due to deterioration of left ventricular function after myocardial infarction and one for a CRT-P due to high ventricular pacing percentage (77%) and heart failure with midrange ejection fraction. In the last patient, the LP was replaced for a dual-chamber pacemaker on patient's request due to highly atypical chest symptoms. There were three patients with a replacement due to recommended replacement time (mentioned in 'Efficacy'). Extraction was attempted in one, and the LP was successfully replaced with a Micra VR LP. The remaining two were co-implanted, one with a Micra VR LP and the other with a transvenous VVI pacemaker. Two LP's were replaced due to loss of capture, also described in 'Safety' and 'Efficacy'.

End of follow-up

Of 179 patients, 96 reached end of follow-up before either having a complication or reaching the end of the study. Eighty-three (46%) died mean 34 ± 23 months after implantation, none of which were deemed to be device-related. There were seven (4%) device replacements that were unrelated to a complication (recommended replacement time n=3, change of indication n=4). Follow-up was lost in six (3%) patients.

Discussion

These real-world results in a general LP population demonstrate a low major complication rate, with all complications unrelated to the battery advisory occurring before 90 days, and a stable performance up to seven years after implantation. Multiple replacement strategies were feasible and extraction was successful in 88% with a time to extraction of approximately 3 years and without declining success rate over time. This study confirms previous results of industry-initiated studies and studies with selected populations.

In this study, we focused on major device-related complications defined as those requiring surgery, as those are thought to be most

important to the patient. The most common were perforation (0.6%), dislodgement (1.7%) and loss-of-capture (1.1%). These complications occurred at a rate very comparable to early LP studies, which was to be expected as this study included LP's implanted early in the worldwide adoption. (4, 5) The rate of their occurrence did not differ between the two studied LP types, although all dislodgements and cases of loss-of-capture occurred in patients with Nanostim LP's. Potentially, differences between the two LP types such as the different fixation mechanisms may have played a role. Compared to transvenous pacemakers, the perforation rate of LP's is known to be higher, although it is decreasing due to more refined implantation techniques and the operator learning curve. (7, 8) The incidence of dislodgements and loss-of-capture is similar for LP's and transvenous pacemakers. (2) Of note, in this study, 2/3 (66%) dislodgements were during implantation and therefore posed less risk to the patient than out-of-hospital dislodgements. Another important complication of pacemaker therapy that may require surgery, device infection, did not occur in this study, which is in line with previous studies on LP's. (11) Further, an important finding of this study is the absence of complications requiring surgery between 88 days and seven years post-implantation. In comparison, there was a 4% reintervention rate after two months in a large transvenous pacemaker study. (2) As most of the transvenous pacemaker complications requiring reintervention are pocket- and lead-related, the low major complication rate after the acute phase may be a specific benefit of LP therapy.

Our results also demonstrate stable pacing parameters on the long-term, confirming earlier studies with shorter follow-up. (6, 7) The efficacy endpoint was met in nearly all patients. Importantly, the PCT remained stable up to seven years post-implantation. In contrast, the PCT of transvenous pacemakers rises slowly over time. (12) Of note, the rate of procedural repositioning was 24% in our cohort, reflecting the early implementation phase of LP's. This rate may be lower in current clinical practice, as PCTs proved to decrease often after LP implantation. (13) Further, the results of this study add to the little available

experience on the feasibility and risks of different replacement strategies. First, we demonstrated a good long-term extraction success without a decline with longer time to extraction. Second, our results emphasise that it is of utmost importance to reassess the pacemaker indication before extraction, as there can be significant changes to the pacemaker indication on the long-term (e.g. the progression of brady-tachy syndrome to permanent atrial fibrillation eliminating the pacemaker indication).

This study has certain limitations. First, the design was retrospective, introducing the risk of information bias. Second, there may have been differential attrition among patients, as patients with more comorbidities or higher age may have been more likely to drop out of the study. Third, we did not collect data on the safety and efficacy of LP's or transvenous devices that replaced primary LP's. Hence, we are not able to provide data on the strategy of LP implantation and subsequent revisions as a whole. Fourth, as data was collected from all follow-up visits without standard echocardiographic examinations, we are not able to provide the exact number of patients with pacing-induced cardiomyopathy.

This study reports the first real-world long-term results of LP therapy in a general LP population. Long-term results are very important because pacemakers are a long-term therapy. Our expectation is that the reported complication rate will hold for the lifetime of LP's given the encapsulation of LP's which probably diminishes the risk of dislodgements and perforations, and the stable threshold shown in this study and others. (7, 14) The inclusion of Nanostim LP's is important as the use of LP's with a helix-based fixation mechanism has returned with the Aveir VR, and long-term results of the Aveir VR will not be available in the upcoming years. The use of helix-based fixation mechanism LP's may become even greater, as the first dual-chamber LP, the Aveir DR, consists of the Aveir VR and a similar atrial LP. The clinical study of the Aveir DR is currently in progress (15). Now the results of this study are derived from two LP models with different morphologies, this study provides a more robust reflection of LP therapy in general.

Conclusion

In conclusion, the long-term safety (excluding advisory-related complications) and efficacy of LP's was adequate. No complications occurred later than three months after implantation, which may be a specific benefit of LP's. The pacing threshold of LP's is stable over time, in contrast to the gradually rising threshold of transvenous pacemakers. Our findings confirm previous studies and are promising for longer-term data on leadless pacing.

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Table 1. Baseline characteristics.

Characteristic	Total (n=179)
Sex, female, n (%)	62 (35%)
Age at implantation, years	79±9
Body mass index, kg/m ²	26±4
Pacing indication, n (%)	
Persistent/permanent atrial tachyarrhythmia with slow ventricular rate	71 (40%)
Persistent/permanent atrial tachyarrhythmia with complete AV-block	31 (17%)
AV-block	36 (20%)
Sinus node dysfunction	35 (20%)
Other	6 (3%)
Pacemaker-dependent, n (%)	26 (15%)
Previous cardiac rhythm device, n (%)	
VVI(R) pacemaker	7 (4%)
DDD(R) pacemaker	11 (6%)
DDD(R) ICD	3 (2%)
CRT-P	1 (0.6%)
Cardiomyopathy, n (%)	
Dilated	1 (0.6%)
Hypertrophic	6 (3%)
Ischemic	11 (6%)
Restrictive	1 (0.6%)
Other	4 (2%)
Coronary artery disease, n (%)	53 (30%)
Prior CABG, n (%)	21 (12%)
Prior PCI, n (%)	28 (16%)

Table 1 continued

Prior valve surgery, n (%)	
Aortic	31 (17%)
Pulmonary	0
Mitral	12 (7%)
Tricuspid	5 (3%)
Hypertension, n (%)	94 (53%)
Diabetes mellitus, n (%)	35 (20%)
Renal failure, n (%)	
Yes, without dialysis	40 (23%)
Yes, dialysis	5 (3%)
Stroke, n (%)	14 (8%)
Peripheral artery disease, n (%)	13 (7%)
COPD, n (%)	19 (11%)

BMI: missing in 21 pts, CMP missing in 5 pts, renal failure missing in 2 pts, pm dependent missing 2

Table 2. Procedural characteristics.

Characteristic	Total (n=179)
Model leadless pacemaker	
Nanostim LP	93 (52%)
Micra VR LP	86 (48%)
Anticoagulation during implant	
VKA	108 (60%)
DOAC	13 (7%)
Therapeutic heparin	5 (3%)
Anticoagulation management*	
Discontinued	65 (68%)
Discontinued, bridged with LMWH/heparin	2 (2.1%)
Continued	29 (30%)
Venous access site**	
Right femoral vein	159 (89%)
Left femoral vein	5 (3%)
Right jugular vein	1 (0.6%)
Reposition required, n (%)	42 (24%)
Implant location, n (%)***	
Apex	88 (49%)
Septum	38 (21%)
Apicoseptal	29 (16%)
Other	12 (7%)

*missing in 30

**missing in 14 pts;

***missing in 12,

Table 3. Major device-related complications.

Complication	Total (n=179)	
	Advisory-related complications excluded	Advisory-related complications included
Implantation-related	3 (1.7%)	3 (1.7%)
Periprocedural dislocation	2 (1.1%)	2 (1.1%)
Pericardial effusion	1 (0.6%)	1 (0.6%)
Device-related	4 (2.2%)	4 (2.2%)
Loss-of-capture	2 (1.1%)	2 (1.1%)
Dislocation during follow-up	1 (0.6%)	1 (0.6%)
Pacemaker syndrome	1 (0.6%)	1 (0.6%)
Advisory-related complications	-	34 (19%)
Replacement due to (impending) battery failure	-	27 (15%)
Prophylactic replacement	-	7 (3.9%)
Total	7 (3.9%)	41 (23%)

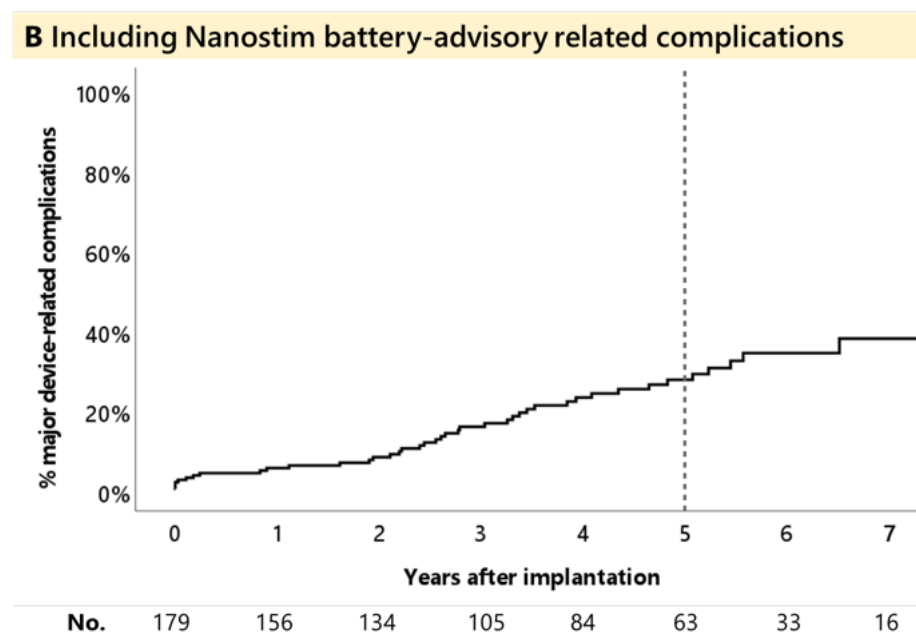
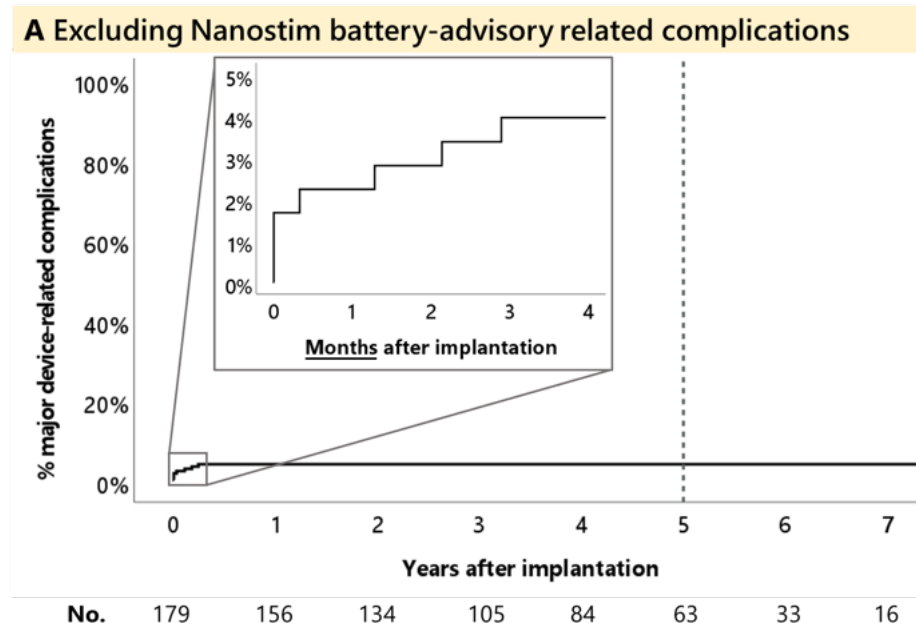


Figure 1. Major device-related complications, (A) without Nanostim battery advisory-related complications and (B) including Nanostim battery advisory-related complications.

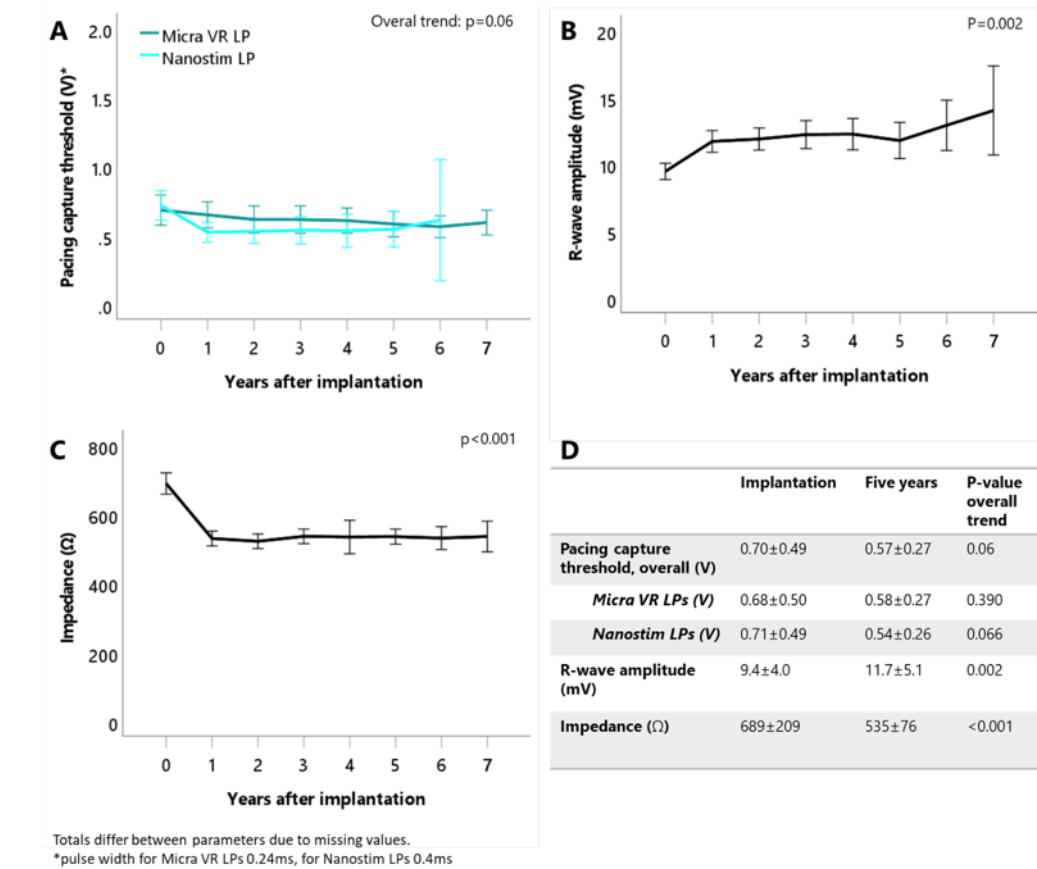


Figure 2. Electrical parameters over time, vertical lines represent the 95% confidence intervals (PCT for Micra VR LP's and Nanostim LP's separately due to different pulse widths).

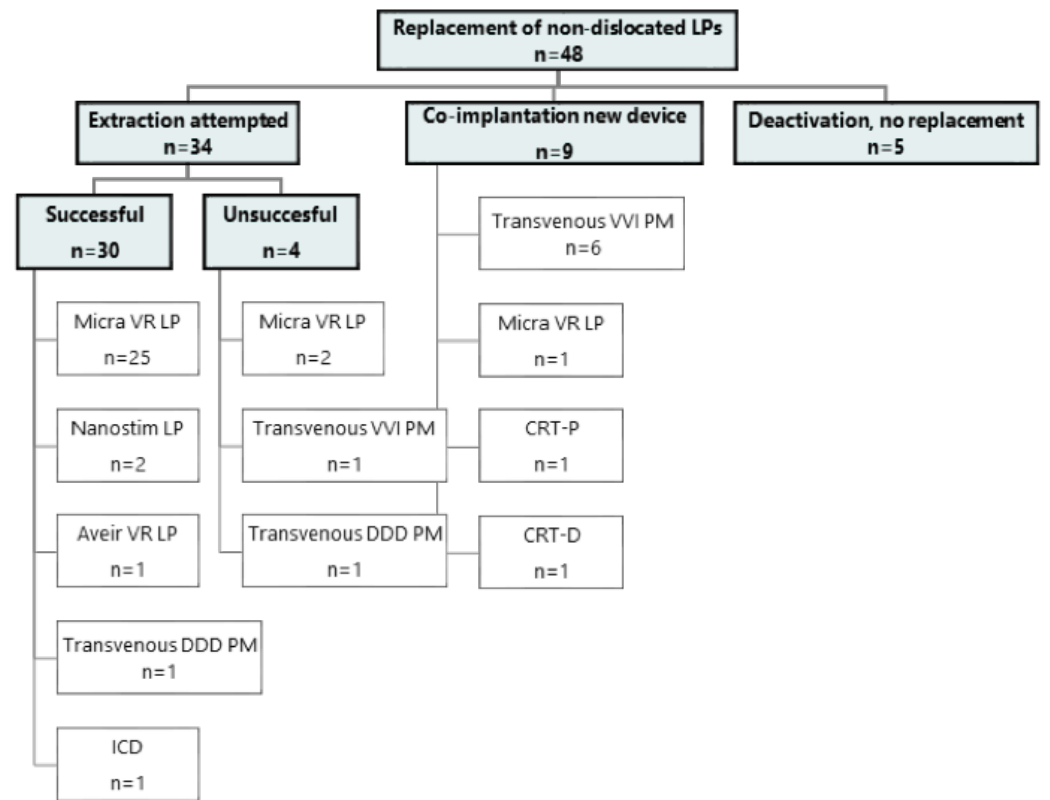
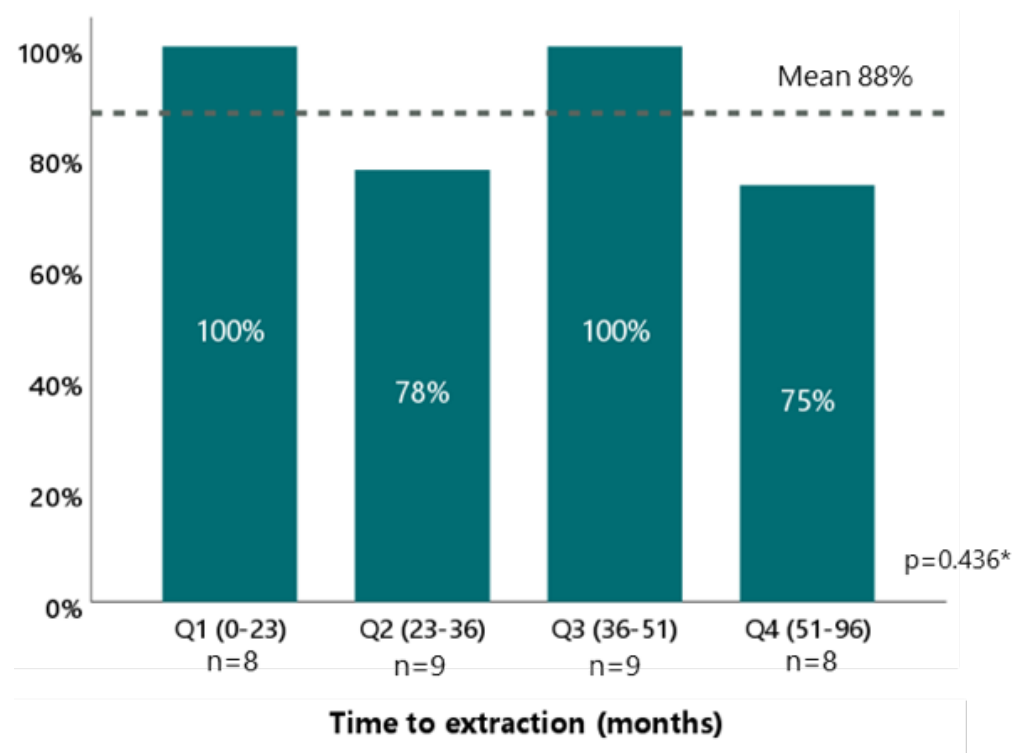


Figure 3. Diagram of different replacement strategies taken in this study, including the device types that were implanted after extraction or co-implanted with the primary implanted leadless pacemaker.



*Using time to extraction as continuous variable

Figure 4. Extraction success by time to extraction (months). Time to extraction is shown in quartiles with cut-off points at 23 months, 36 months and 51 months.

Supplemental material

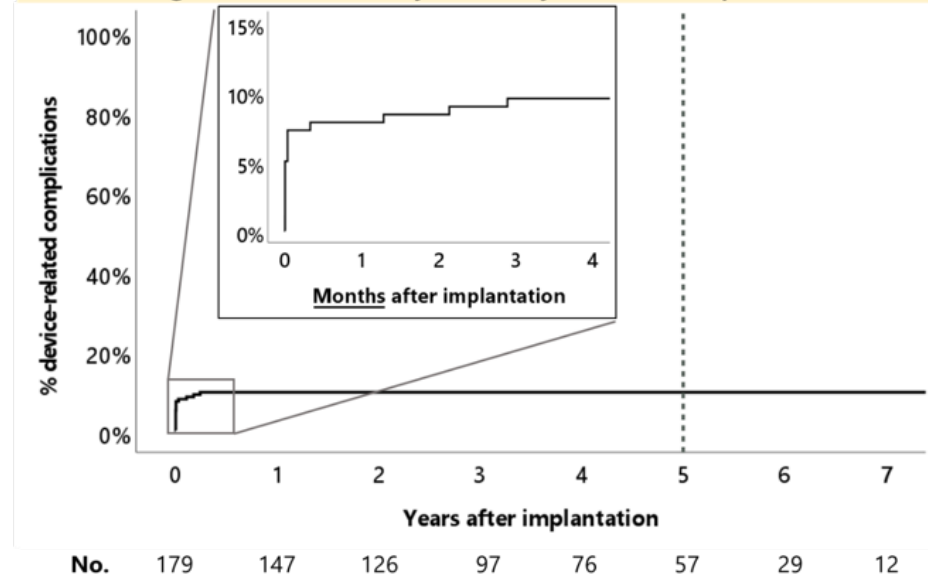
Supplementary table 1. Major device-related complications per LP type (non-advisory related).

Complication	Total (n=179)		P-value
	Nanostim LP (n=93)	Micra VR LP (n=86)	
Implantation-related			
Periprocedural dislocation	2 (2.2%)	1 (1.2%)	0.498
Pericardial effusion	0	1 (1.2%)	0.480
Device-related			
Loss-of-capture	2 (2.2%)	0	0.498
Dislocation during follow-up	1 (1.1%)	0	>0.99
Pacemaker syndrome	0	1 (1.2%)	0.480
Total	5 (5.4%)	2 (2.3%)	0.446

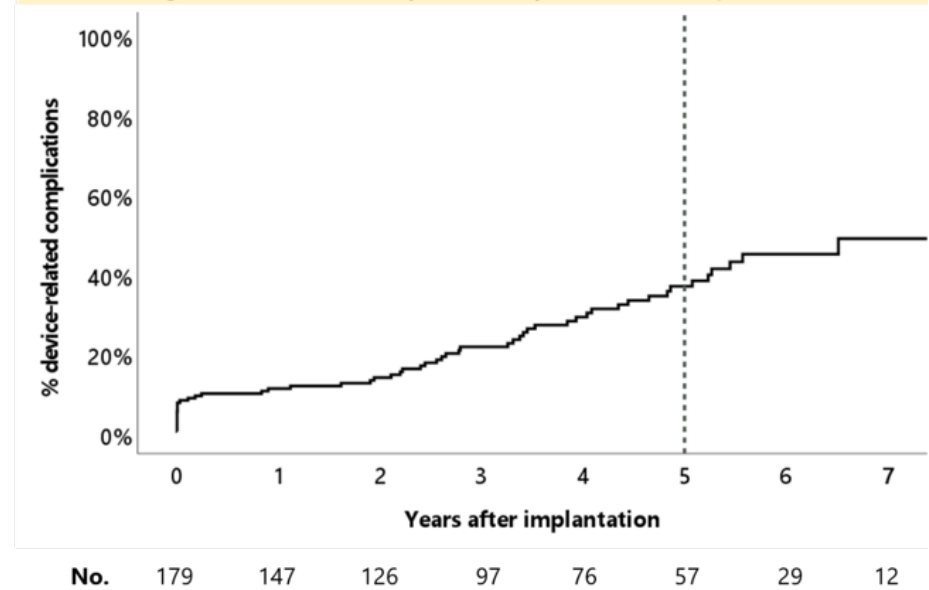
Supplementary table 2. All device-related complications.

Complication	Total (n=179)	
	Advisory-related complications excluded	Advisory-related complications included
Implantation-related	12 (6.7%)	12 (6.7%)
Periprocedural dislocation	2 (1.1%)	2 (1.1%)
Pericardial effusion	1 (0.6%)	1 (0.6%)
Ventricular arrhythmia requiring cardioversion	1 (0.6%)	1 (0.6%)
Atrial flutter	1 (0.6%)	1 (0.6%)
Groin bleeding	7 (3.9%)	7 (3.9%)
Device-related	5 (2.8%)	5 (2.8%)
Loss-of-capture	2 (1.1%)	2 (1.1%)
Dislocation during follow-up	1 (0.6%)	1 (0.6%)
Pacemaker syndrome	1 (0.6%)	1 (0.6%)
Tricuspid regurgitation potentially due to LP	1 (0.6%)	1 (0.6%)
Advisory-related complications	-	39 (21.8%)
Replacement due to (impending) battery failure	-	27 (15.1%)
Prophylactic replacement	-	7 (3.9%)
Battery failure without replacement pacemaker	-	5 (2.8%)
Total	17 (9.5%)	56 (31%)

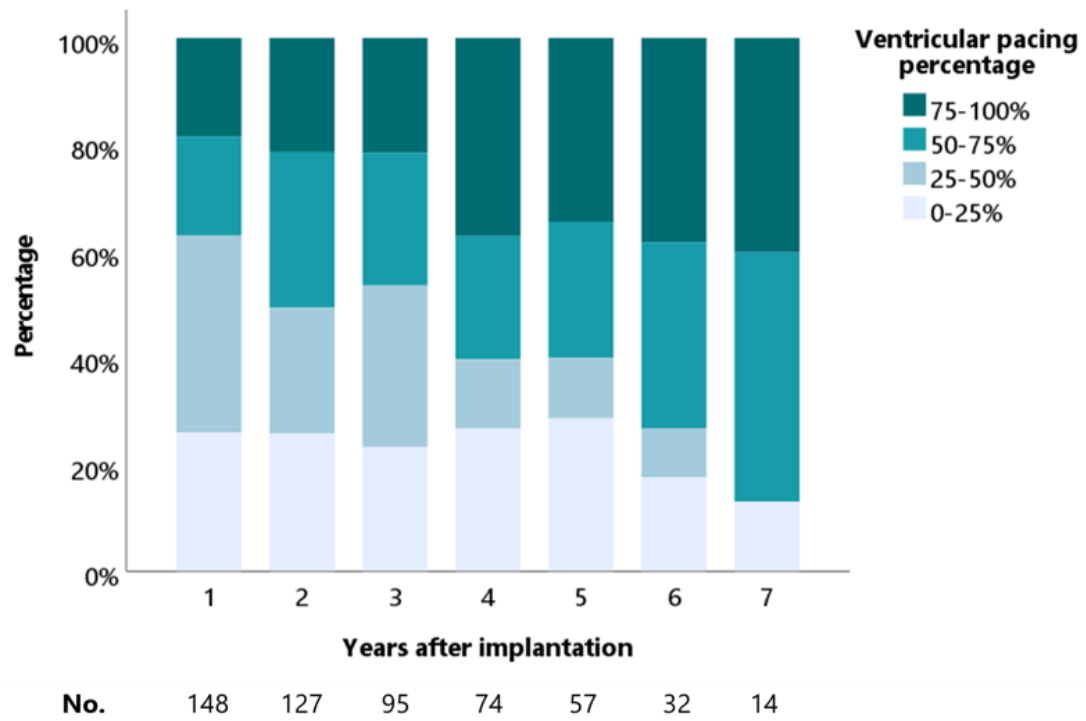
A Excluding Nanostim battery-advisory related complications



B Including Nanostim battery-advisory related complications



Supplementary figure 1. Device-related complications, excluding Nanostim battery advisory-related complications (A) and including Nanostim battery advisory-related complications.



Supplementary figure 2. Ventricular pacing percentages over time.



Illustration: Milou Oosterwerff

Part II

Innovations in implantable cardioverter-defibrillators and post-market surveillance

Chapter 5

Remarkably high and accelerating failure rate of a widely used implantable cardioverter-defibrillator lead: a large-scale manufacturer-independent multicenter study with long accurate follow-up

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Abstract

Background

High annual failure rate of the Linx family defibrillator lead (Biotronik SE & Co. KG, Berlin, Germany) was reported in various small single-center studies. No independent multicenter long-term performance information exists for this lead.

Objective

Our aim was to assess the longevity of Linx family leads and to evaluate clinical variables and adverse events associated with failure.

Methods

This 4-center study included adults >18 years of age who received Linx family leads for the prevention of sudden cardiac death. From November 2006 to November 2016, a total of 3993 high-voltage leads of the Linx family were implanted and followed up on.

Results

The absolute failure rate was 10.6% (dwell time to lead failure of $6.3 \pm$ SD 3.4 years). Multivariate analysis confirmed younger age (for every 5 years younger than 65 years), HR 1.09, 95% CI (1.05 to 1.14), $p < 0.001$) subclavian access HR 1.46, 95% CI (1.18 to 1.81), $p < 0.001$) as independent risk factors for lead failure. Patients frequently presented themselves with inappropriate shocks (20% in patients with lead failure) due to detection of non-physiological high-rate signals/noise.

Conclusion

This is the largest physician-driven multicenter study on the very long-term performance of Linx family leads. Our data reports a remarkably high failure rate of these leads. Our findings have significant implications for the management of patients. Monitoring by remote care should be available for all active Linx family leads.

Keywords failure rate, lead failure, long-term performance, Linx, implantable cardioverter defibrillator (ICD)

Introduction

Implantable cardioverter defibrillators (ICD's) are widely used for primary and secondary prevention of sudden cardiac death after several landmark trials have shown the efficacy of these devices. (1, 2) Generally ICD systems including electrodes are considered to be safe, with an accepted annual lead failure rate of 0.5%. However, ICD therapy has been associated with a number of short- and long-term complications. (3-6) The Achilles heel of a transvenous (ICD) system remains the right ventricular (RV) high-voltage lead. In the last two decades, two ICD leads have been subject to a significant safety issue. The Sprint Fidelis (Medtronic, Minneapolis, MN) was prone to fractures and the Riata/Riata ST (St. Jude Medical, Sylmar, CA) were found to have insulation failures, with the protective coating degrading over time. These higher-than-expected failures prompted a recall, an increased scrutiny of ICD lead design and the introduction of new algorithms to postpone inappropriate shocks. (7, 8)

The Biotronik Linx ICD lead family (Biotronik SE & Co. KG, Berlin, Germany) has also been associated with a high failure rate but this was only made public through a number of small, manufacturer-independent registries. (9-16) After introduction in 2006 a few changes in lead design were made. Since 2010, the Linx series have been substituted by the LinxSmart series, covered with an additional Silglidec surface coating, a surface treatment which ensures lubricious coating, improved gliding, low friction and reduces the risk of abrasion. In a similar manner, Riata ST and Durata St. Jude Medical models were provided with an additional abrasion-resistant silicone-polyurethane co-polymer (OptimTM). Silicone rubber is inert and more biostable compared to polyurethane, but has a higher coefficient of friction and is more vulnerable to abrasion and breaches. (17) The second difference concerned the lead body of the DF-1 connector exit, which has been modified to have an increased diameter to strengthen this section. Although there has been concern amongst device cardiologist because of the occurrence of lead failures in daily practice, no larger scale studies became available and Biotronik did not issue an FSN. For that reason, the Device Advisory Committee of the Netherlands Heart Rhythm As-

sociation decided to pool the data from the four largest Biotronik ICD implanting centers in the Netherlands, in order to determine the true extent of Linx family ICD lead failures, whether predictive factors can be identified and how failures affect patients.

Methods

Study population

The four Dutch high-volume ICD implanting centers retrospectively identified all consecutive patients, implanted with a high-voltage lead of the Linx family. Data obtained from the review of medical records were demographics (age and gender), lead model, serial number, date of implant, and implant procedural data. All research activities were conducted according to the principles of the Declaration of Helsinki as revised in 2013. The study was approved by the local Ethics Institutional Committee on Human research. This was a retrospective cohort analysis of patients with a clinical indication for ICD therapy. The need for written informed consent was waived.

Description of high-voltage defibrillation leads

The Biotronik silicone-insulated Linx defibrillator lead was introduced in 2006. It is a 7.8F single- or dual-coil active or passive fixation, steroid-eluting quadripolar lead with a silicone insulation. The pace/sense cable conductor is made of 7×7 filars of MP35N R® (a nickel-cobalt based proprietary alloy) material and the shock coil cable conductor is made of 7×7 filars of MP35N R®/silver. The pace/sense and shock coil cable conductors are wrapped with a Teflon™ Perfluoroalkoxy (PFA) coating. The inner conductor is a 4 filar wire conductor made of MP35N R®. The Linx family has 4 cable lumens to provide a symmetric cross-sectional design. Since 2010, the Linx series have been substituted by the LinxSmart series. After being approved as MRI conditional, LinxSmart was named LinxSmart Pro MRI without any change in its technical design. A more stable lead-to-can connection (DF-4 connector) was developed for the newer generation Biotronik

ICD leads, such as the Protego lead, but this was not yet available in the Linx family leads. (17-19) The design of the Protego lead was the basis for Plexa's lead body design. Plexa and Protego are very similar with isodiametric lead body design and Silglide. The main differentiator making Plexa one-of-a-kind is the new helical design, which reduces stress on the lead body. Figure 1 presents the different lead designs.

Definition of lead failure

In the current analysis, lead failure was defined if one (or more) of the following criteria were met: (1) presence of non-physiological signals on the intracardiac ventricular electrogram, unrelated to external interference; (2) the sudden occurrence pacing impedance outside the interval 200–2000 Ω or $>100\%$ increase or $>50\%$ decrease of the stable baseline impedance; (3) change in high-voltage impedance to >200 or $<25 \Omega$; (4) a sudden or intermittent increase in right ventricular threshold and/or decrease in R-wave amplitude, without alternative explanation. Lead dislodgment, perforation, T-wave oversensing, R-wave sensing <3.0 mV or $>50\%$ reduction, physiological oversensing, gradual increase of impedance and header problems were not considered as lead failures. Gradually increasing impedance was excluded as it is not thought to be associated with lead failure but rather with fibrosis and calcifications at lead/endocardial surface. The presence of any inappropriate shock associated with lead failure was recorded. All cases associated with lead failure were reviewed and adjudicated by authors EO, DAT, LvE, and AHM. Follow-up started at the time of ICD implantation. In all four centers, in-office device interrogation was performed every 6 to 12 months or after symptomatic events. In addition to in-office follow-up, 1323 patients (33%) used remote monitoring of their implanted ICD system.

All patient deaths were recorded. If no lead failure had occurred during follow-up, the date of the last known device interrogation was recorded as the last follow-up date for the Kaplan-Meier analysis. The administrative censoring date was set at June 1, 2022.

Statistical Analysis

Normality of distribution was determined using the Shapiro-Wilk test. Normally distributed continuous variables are expressed as mean \pm SD and compared by Student t test. Non-normally distributed variables are expressed as median with 25th and 75th percentiles and compared using Kruskal-Wallis H test. Categorical data are expressed as numbers and percentages and compared by the chi-square test or Fisher exact test. Cumulative lead failure rates and cumulative hazard were calculated by the Kaplan-Meier method, and curves were compared by the use of the log-rank test. In addition, the incidence rate of lead failure was calculated using time at risk from implantation to last follow-up. Incidence rates were expressed per 100 patient-years with a 2-sided 95% confidence interval (CI). Comparative analysis was performed by estimating the incidence rate ratio. To assess the change in lead failure risk over time, a log-log plot of the cumulative hazard function (log H vs log t) was constructed. Based on the transition of the cumulative hazard in the log-log plot, conditional survival probabilities of Linx leads functioning normally past the transition point were calculated. Linear regression analysis using the least-squares method was performed to estimate the slope of the conditional survival on the log H vs log t plot. If the slope of the conditional survival log H versus log t approximated 1 (i.e., constant lead failure rate over time), linear regression analysis was performed on the cumulative hazard plot (H vs t) to define the lead failure rate per year. Lead failure rates are expressed per 100 patient-years with a 2-sided 95% confidence interval (CI). Patient deaths or lead explants not related to true lead failure were treated as censoring events. Patients who were lost to follow-up were censored at the time of the last follow-up visit at our clinics. The clinical predictors of lead failure were assessed using a Cox proportional hazards model. Any variable with a P value \leq 0.2 in a univariate analysis was included in a subsequent multivariate Cox proportional hazard model. Two-sided P values of \leq 0.05 were considered significant. Statistical analysis was performed using Stata/SE 16.1 for Windows (StataCorp LP, College Station, TX) and SPSS version 28 (IBM Corp., Somers, NY).

Results

Study population

Between November 2006 and November 2016, a total of 3993 high-voltage leads of the Linx family were implanted in 3903 patients. Ninety patients received multiple leads of the Linx family due to infection or dysfunction. A total of 2268 (57%) were the original Linx and 1725 (43%) were LinxSmart. The various implanted subtypes of the Linx family are summarized in Table 1. Of the study population, 75% were male (n=2924) and the mean age of the total population was 65 years (IQR 56 to 73 years). Most patients had a primary prevention indication (n=2870 (74%)) and a minority also had a bradycardia pacing indication (n=810 (21%)). Venous access was obtained through subclavian puncture for most leads (n=2559, 64%). In the remaining 1434 cases (36%) the cephalic approach was used. Patient characteristics at implant are listed in Table 2. Follow-up was until June 2022 and 1824 (46%) Linx family leads were still functional. Of these functional leads there were 878 original Linx and 946 with LinxSmart. The median dwell time was 9.1 yrs (IQR 7.2 to 11.1 yrs) with a significant difference in dwell time between the Linx without Smart and the later introduced LinxSmart (11.1 years (IQR 6.0 to 12.3 years) versus 8.4 years (IQR 7.4 to 9.6 years), (P < 0.001)).

Lead failure

At the 1st of June 2022, a total of 422 (10.6%) lead failures had been reported with a dwell time to lead failure of 6.3 ± 3.4 years. There was no difference in absolute failure between Linx without Smart (n = 252 (11.1%)) and LinxSmart (n = 170, 9.9%) (p=0.21), but the dwell time to lead failure was significantly shorter with LinxSmart (5.4 ± 2.9 years vs. 6.9 ± 3.6 ; p < 0.001) (Figure 2a)

Linx without Smart

The cumulative failure rates of the Linx without Smart high-voltage lead were 5.4% and 14.1%, at 5- and 10-years follow-up, respectively.

Statistical analysis demonstrated a transition of the cumulative failure rate of Linx ICD leads at 11 years follow-up. First, all Linx ICD

leads up to 11 years follow-up were analyzed to assess whether risk of lead failure changed over follow-up to 11 years. Based on the log-log plot, transition of the cumulative hazard occurs at $\log t = 0.22$ which corresponds to a follow-up time of 1.25 years. Based on this, conditional survival for Linx leads functioning normally at 1.25 years up to 11 years was calculated. Linear regression analysis yielded a straight line with perfect fit ($R^2 = 0.97$; $p < 0.0001$). Linear regression analysis of the cumulative hazard obtained for functional Linx leads without Smart up to 11 years follow-up yielded a yearly failure rate of 1.3% (95% CI (1.3% – 1.3%), $R^2 = 0.97$). (Figure 2b)

For Linx without Smart leads functioning normally after 11 years follow-up ($n=556$), linear regression analysis yielded a straight line with perfect fit ($R^2 = 0.99$; $p < 0.0001$). For functional Linx leads from 11 years of follow-up onward, a yearly failure rate of 5.3% (95% CI, 5.1 – 5.5%, $R^2 = 0.99$) was observed. (Figure 2c)

LinxSmart

The cumulative failure rates of the LinxSmart high-voltage lead were 6% and 18.3%, at 5- and 10-years follow-up, respectively. Statistical analysis of this lead demonstrated a transition in the cumulative failure rate at 8.7 years of follow-up. Based on the log-log plot, transition of the cumulative hazard occurs at $\log t = 0.14$ corresponding to a follow-up of 1.15 years. The conditional survival for Linx Smart leads functioning normally at 1.15 years up to 8.7 years follow-up was calculated. Linear regression analysis of the cumulative hazard obtained for functional Linx Smart leads up to 8.7 years follow-up yielded a yearly failure rate of 1.3% (95% CI (1.2% – 1.3%), $R^2 = 0.99$). (Figure 2d)

For Linx Smart leads functioning normally after 8.7 years follow-up, linear regression analysis yielded a straight line with perfect fit ($R^2 = 0.99$; $p < 0.0001$). For functional Linx Smart leads at 8.7 years follow-up, the yearly failure rate was 5.1% (95% CI, 4.9 – 5.4%, $R^2 = 0.99$). (Figure 2e)

Clinical presentation

In 325 out of 422 lead failures (77%) there was one dominant mechanism. Figure 3 presents the overlapping presentations (23% ($n=97$)). Roughly two-third (63% ($n=267$)) of the patients with lead failure,

presented with non-physiological high-rate signals/noise. (see Figure 4 a,b, c and d) Most common was non-physiological high-rate signals/noise on the near field channel (90% ($n = 240$)). Of these patients, 32% ($n=85$) (2.1% of the total population) experienced inappropriate shocks. Despite remote care in 1323 patients, 31 patients still experienced inappropriate shocks. Lead failures because of significant changes of lead impedances (see figure 4e) occurred in 125 patients (30%). Significant threshold changes happened in 50 patients (12%). There were no differences in clinical presentation between early and late failures. The distribution of main clinical presentations like oversensing and impedance changes were equal in early and late failures (prevalence of noise Linx failure 62% (<8 years) versus 66% (>8 years), $p = 0.3$ and prevalence significant impedance change Linx failure 29% (<8 years) versus 31% (>8 years), $p = 0.82$). The pace-sense component is most prone for failure. Table 3 presents the details. Lead externalization was uncommon ($< 1%$ ($n = 3$)). We studied 49 of Biotronik returned product analysis (12% of total failure). Due to the extraction procedures the leads were damaged and the root causes were not always found. But in 44 cases it was assumed that the lead had been subject to severe mechanical stress in the implanted state. Interaction between the lead body and the tricuspid valve was mostly taken into consideration as root cause (22/44 = 50%). (see Table 3)

Predictors of lead failure

To identify factors associated with lead failure, we performed univariate and multivariate analysis of baseline characteristics (age, sex, indication), procedure-related variables (venous access and number of leads), and lead-related variables (number of coils). Younger age (for every 5 years younger than 65 years) (HR = 1.08, 95% CI ((1.04 to 1.12), $p < 0.001$) and subclavian access (HR = 1.08, 95% CI ((1.04 to 1.12), $p < 0.001$) were associated with lead failure in this study. Multivariate analysis confirmed younger age (for every 5 years younger than 65 years), HR 1.09, 95% CI ((1.05 to 1.14), $p < 0.001$) subclavian access HR 1.46, 95% CI ((1.18 to 1.81), $p < 0.001$) and single coil HR 2.15, 95% CI (1.43 – 3.23), $p < 0.001$) as independent risk factors for lead failure. Primary prevention was not associated with more lead failure, HR 0.89, 95% CI (0.72-1.10), $p = 0.27$) A summary is given in Table 4.

Discussion

This national, physician-driven, multi-center study on the Biotronik Linx family ICD lead performance in a large real-life population, with long accurate follow-up shows a remarkably high absolute lead failure of 10.6% (1.7%/year) and a mean dwell time to lead failure of 6.3 ± 3.4 years and becomes even higher on the long run. The Linx family ICD lead failure is notably higher in younger patients and with subclavian access. In case of lead failure, 63% presented with non-physiologic signals and were at risk for inappropriate shock, which actually occurred in about 1:3 of these patients.

The high failure rates observed in this study confirms the results of earlier manufacturer-independent smaller registries (9-16), but are remarkably higher than the numbers in the last Biotronik product performance report. These showed a 5-year failure rate of only 3.0% (0.6%/year) for the Linx ICD leads (19) An explanation for this difference in lead performance could depend on the type of analysis performed by Biotronik and other companies. Their analysis is mostly based on 'returned product', an inaccurate number because most leads never get returned. Furthermore, Biotronik, like other companies, depends on reporting by physician (e.g. battery depletions or lead complications) which leads certainly to underestimations of the true failure rates. This underestimation is further exacerbated since competing risk (i.e. mortality) is not taken into account, which means that the number of active leads is much lower than the number of implanted leads. In order to avoid underreporting, post-marketing registries have been performed. The estimated failure rate of the GALAXY and CELESTIAL registries of Biotronik was 3.7% at 5 years for Linx leads and thus still much lower than 10.6% at 6,3 years in the current study. (19) An important difference is the use of remote care. Data collected during remote monitoring visits were not used in the post-marketing registries of Biotronik, while in our registry 33% of the patients were on remote care. Moreover, the current study excels by long duration of follow-up, which was in the Biotronik post-marketing registries only 3.6 years for Linx leads and 2.3 years for LinxSmart leads. To further analyze the occurrence of lead failure changes over time, we performed a log-log

analysis of the cumulative hazard vs time. (20,21) This showed that the already high yearly failure rate of 1.3% further increased dramatically after 11 years for Linx to 5.3% and for LinxSmart even earlier, after 8.7 years, to 5.1%. This shows the importance of very long-term follow-up, which is typically not done by lead registries.

This study highlights the importance of continuous evaluation of lead performance in real-world populations. Post-marketing surveillance of lead performance should be a joint responsibility of patient groups, medical associations, healthcare professionals, medical device manufacturers, and European Union regulators. However, in daily practice, device cardiologists and technicians are too dependent on devices companies for quality surveillance. For us, medical professionals, to recognize a structural problem is already hard, but it is even more difficult to determine how to act, especially since implanted hardware is involved, whereas the potential complications of surgery are significant while having to be weighed against the risk of unwarranted shocks. Unbiased data from non-industry-related studies of good scientific quality is crucial. (22, 23)

A comparison with the Sprint Fidelis and the Riata/Riata ST lead issues is in order. The yearly failure rates were 4.8% for Sprint Fidelis and 4.9% for Riata/Riata ST leads. (7,8) Both leads showed accelerating failure, with a transition already around 4 years for both leads. (20,21). The accelerating failure of Linx family leads starts later (around 9 years) but annual failure rate is even higher and above 5%. The scope of the lead issues with the Linx family leads have similarities to that of the Sprint Fidelis and Riata. (20, 21, 24-26) Furthermore, the number of leads implanted worldwide is similar, estimated between 230.000-270.000 worldwide for each. (18, 20, 21, 24-26) It is remarkable that whereas the Sprint Fidelis as well as the Riata failures prompted an FSN and a recall for Medtronic and Abbott, respectively, Biotronik did not come to the same conclusion. This might be related to the underlying mechanisms of the occurring failure, which were multiple in case of the Linx, and therefore difficult to pinpoint. Mechanistically, lead stress due to fraction and movement, as well as abrasion of silicon between the lead and generator are probably the responsible causes for lead failure of Linx family leads. Insulation damage caused by

mechanical stress is time dependent. Therefore, lead failure becomes more common a problem in younger ICD patients and patients with better preserved left ventricular function who have a longer life expectancy. Insulation damage might also depend on the stability of the lead itself and silicone leads therefore also seem to be prone to insulation failure. (6) In some cases, non-physiological high-rate signals/noise were detected on both near-field and far-field electrograms (figure. 4a) which is suggestive for inner insulation breach with connection of de low-voltage and high-voltage conductors. In 2017 Biotronik introduced a different helical design Plexa lead but has not motivated the significant lead design change. The Linux family leads are no longer commercially available. Currently, an estimated 1800 study patients still have an active Linux family lead with a serious accelerating risk of failure rate. The number of patients worldwide be estimated to be 125.000.

In summary, the Linux family leads have a relatively high failure rate, that becomes even higher on the long run. While the higher-than-expected failures of the Sprint Fidelis and the Riata prompted a recall, this was remarkable not the case with the Linux family leads. Patients have suffered from the complications related to lead failure, most importantly inappropriate shocks and reoperation, with a severely negative impact on the quality of life. (27-29) Monitoring of electrical parameters by remote monitoring may prevent a subset of inappropriate shocks (30) and should be available for all active Linux family leads. Moreover, lead integrity alerts and lead noise algorithms could further help to minimize the clinical impact for the patients. Current generation Biotronik ICD's are capable of monitoring short intervals as an early sign of lead failure. This has been shown to be effectively reduce inappropriate shocks with Sprint Fidelis leads. (29) The use of an audible or tangible ICD alert function helps monitoring lead integrity by a remote monitor to secure safety. An app on the patient's mobile phone may replace the monitor in the coming decade, which will surely increase the patient's safety in case of unreliable hardware.

Study Limitations

Due to the retrospective nature of this study, it may be subject to a reporting bias. The mechanism of lead-abnormalities could be established/confirmed in a minority of all leads. In most cases an additional lead was implanted and the dysfunctional lead was not available for returned product analysis. Gradually increasing impedance was excluded because of the association with fibrosis and calcifications at lead/endocardial surface. We have collected limited baseline patient characteristics and cannot rule out other patient-based factors such as comorbidities affecting lead failure. Considering structural defects can be electrically silent for an extended period of time, some under-reporting of true-lead failure may have occurred. This study started in 2006 at that time remote care was not widely used in the Netherlands.

Conclusion

This is the largest physician-driven multicenter study about performance of Linux family leads. Our data reports a remarkably high failure rate of Linux family leads. Besides this, an increase in failure rate during longer follow-up has been shown. The majority of patients with lead failure are presented with nonphysiologic high-rate signals/noise with frequent inappropriate shocks. This study highlights the importance of continuous evaluation of lead performance in real-world populations in particular because early results of manufacturer's approval studies reported highly reliable lead performance.

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Table 1. Subtypes of the different Linnox without Smart and LinnoxSmart leads.

Subtype Linnox family	Number n (%)	Fixation	Coils	Insulation
Linnox without Smart	2268 (57)	-	-	Silicone
Linnox s65	1887 (47)	Active	Single	
Linnox SD65	343 (9)	Active	Dual	
Linnox s65 DX	21	Active	Single	
Linnox s75	1	Active	Single	
Linnox SD75	13	Active	Dual	
Linnox T65	2	Passive	Single	
Linnox TD65	1	Passive	Dual	
LinnoxSmart	1725 (43)	-	-	Silicone*
LinnoxSmart s60	3	Active	Single	
LinnoxSmart s65	472 (12)	Active	Single	
LinnoxSmart s65 DX	43 (1)	Active	Single	
LinnoxSmart SD65	75 (2)	Active	Dual	
LinnoxSmart s75	7	Active	Single	
LinnoxSmart SD75	2	Active	Dual	
LinnoxSmart T65	1	Passive	Single	
LinnoxSmart TD65	2	Passive	Dual	
LinnoxSmart pro MRI s65	868 (22)	Single	Active	
LinnoxSmart pro MRI s65 DX	229 (6)	Single	Active	
LinnoxSmart pro MRI SD 65	13	Dual	Active	
LinnoxSmart pro MRI s75	7	Single	Active	

*with Silglide® surface treatment

Table 2. Baseline Characteristics

	Patients with a Linux lead (n = 3903)
Age	Median 65 years (IQR 56 to 73 years)
Follow-up	Median 7.2 years (IQR 3.3 to 9.7 years)
Male	2924 (75 %)
Primary prevention indication	2878 (74 %)
Device	
Single-chamber	31 %
Dual-chamber	33 %
CRT	36 %

Table 3. Clinical presentation of a total of 422 lead failures

Clinical presentation	Number n (%)
Inappropriate shocks	85 (20)
Non-physiological high-rate signals/noise	267 (63)
Significant changes of lead impedances	125 (30)
Threshold/sense changes	50 (12)
Lead failure with multiple mechanism	97 (23)
Details non-physiological high-rate signals/noise	
Non-physiological high-rate signals/noise near field	240 (90)
Non-physiological high-rate signals/noise far field	5 (2)
Non-physiological high-rate signals/noise near field and far field	22 (8)
Details significant changes of lead impedances	
High-voltage component	42 (34)
Pace-sense components	83 (66)
Returned product analysis with considered root cause of failure (44/49 = 90%)	
Severe mechanical stress in the area of the tricuspid valve	22 (50)
Severe mechanical stress due to constant friction against generator	9 (20)
Severe mechanical stress in the area of clavícula-first rib	9 (20)
Severe mechanical stress due to constant friction against a nearby lead	4 (10)

Table 4. Univariate and multivariate analysis

	Failure n/(%)	No failure n/(%)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	P-value	HR (95% CI)	P-value
Age < 65 years	265 (64%)	1607 (46%)	1.08 (1.04 – 1.12)	< 0.001	1.09 (1.05 – 1.13)	< 0.001
Male gender	320 (76%)	2667 (75%)	1.09 (0.88 – 1.37)	0.43		
Primary prevention						
Single coil	397 (94%)	3147 (88%)	2.15 (1.43 – 3.23)	< 0.001	1.45 (1.17 – 1.80)	< 0.001
Subclavian access	301 (72%)	2258 (64%)	1.40 (1.13 – 1.73)	0.002	2.07 (1.37 – 3.12)	< 0.001
Single-chamber						
Dual-chamber	142 (34%)	1172 (33%)	1.04 (0.83 – 1.32)	0.73		
CRT-D						
Single-chamber	140 (33%)	1077 (30%)	Ref			
Dual-chamber	142 (34%)	1172 (33%)	1.04 (0.83 – 1.32)	0.73		
CRT-D	139 (33%)	1305 (37%)	0.89 (0.70 – 1.13)	0.33		

CI = confidence interval; CRT-D = cardiac resynchronization defibrillator;
HR = hazard rate

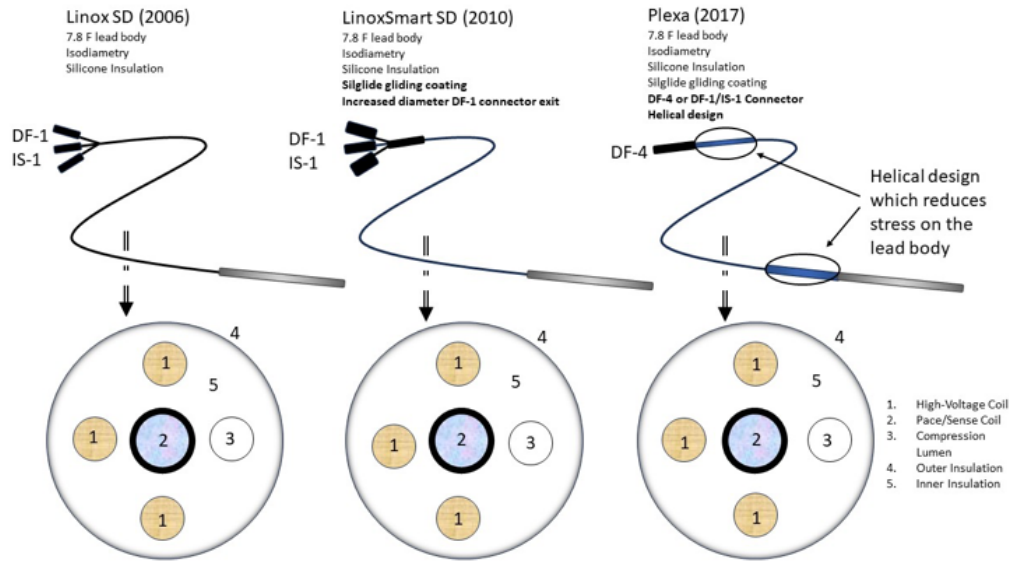


Figure 1. Lead design of the Linox, LinoxSmart and Plexa.

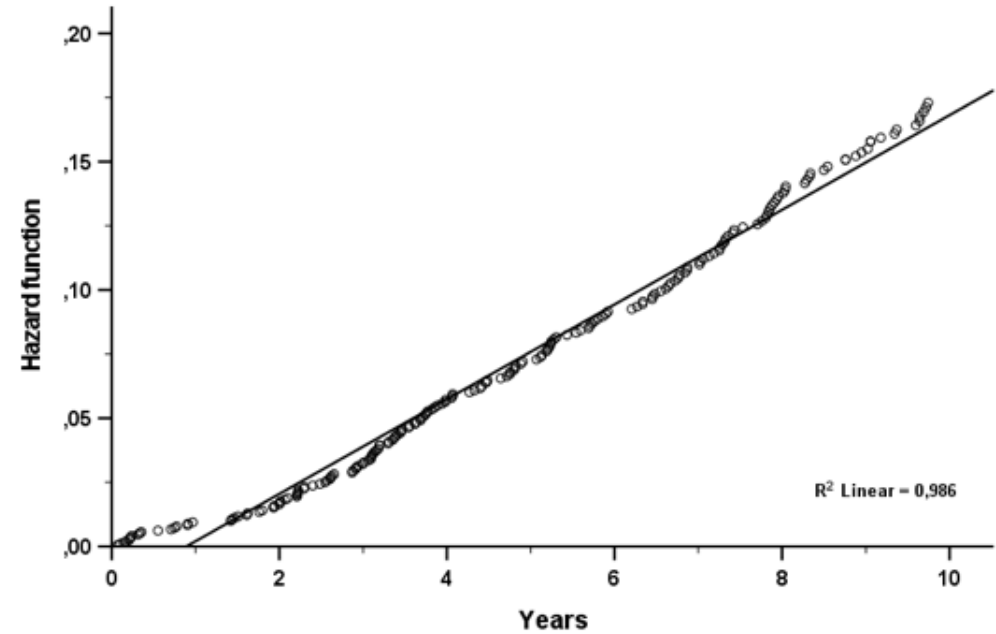


Figure 2b. Hazard function of conditional survival Linox without Smart after 1,25 yrs to 11 yrs. Annual failure rate 1.3%/ year, 95% CI (1.3% – 1.3%)

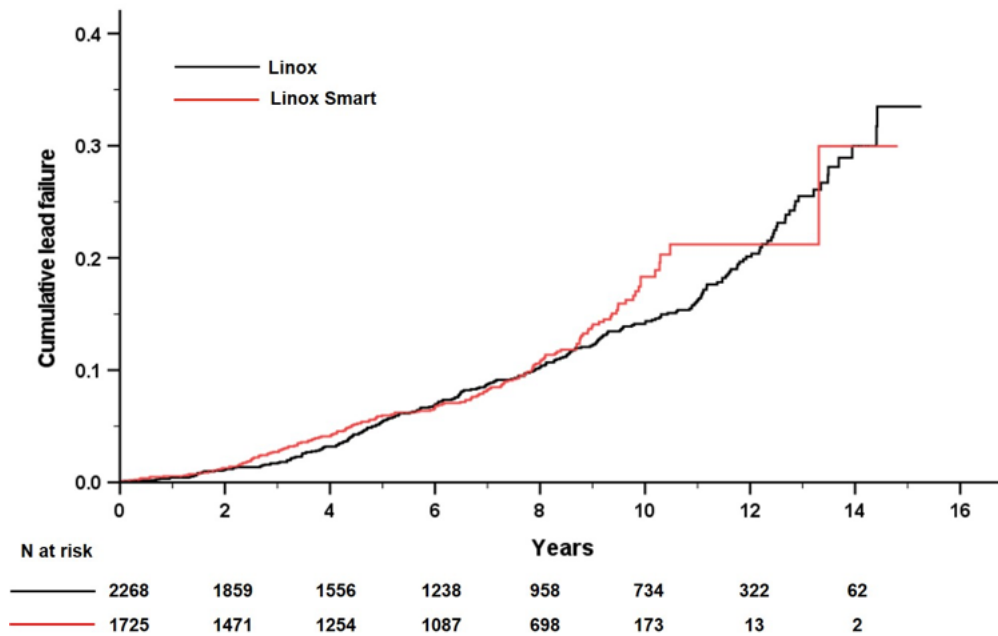


Figure 2a. Failure rate Linox without Smart and LinoxSmart ($p = 0.16$).

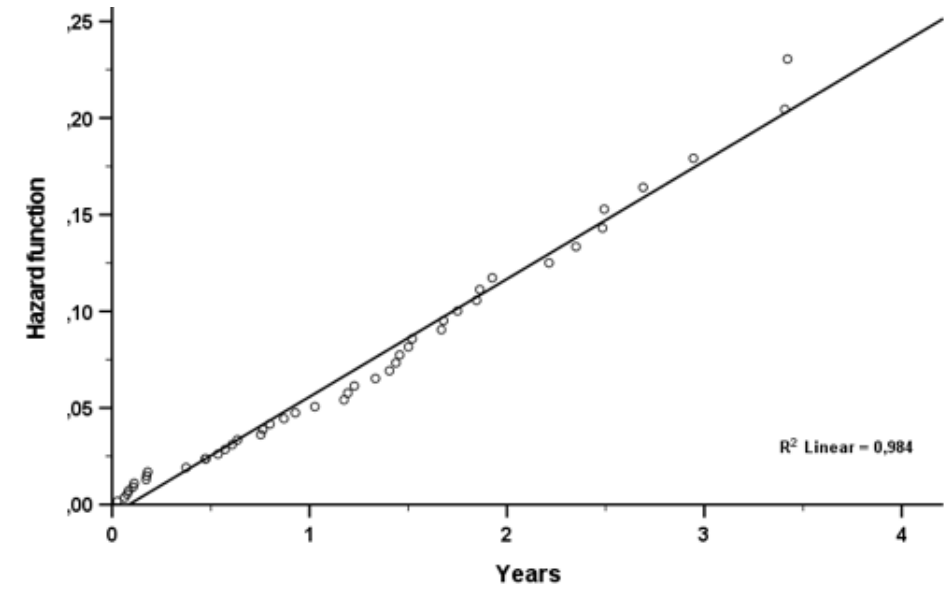


Figure 2c. Hazard function of conditional survival Linox without Smart after 11 yrs. Annual failure rate 5.3%, 95% CI (5.1% – 5.5%).

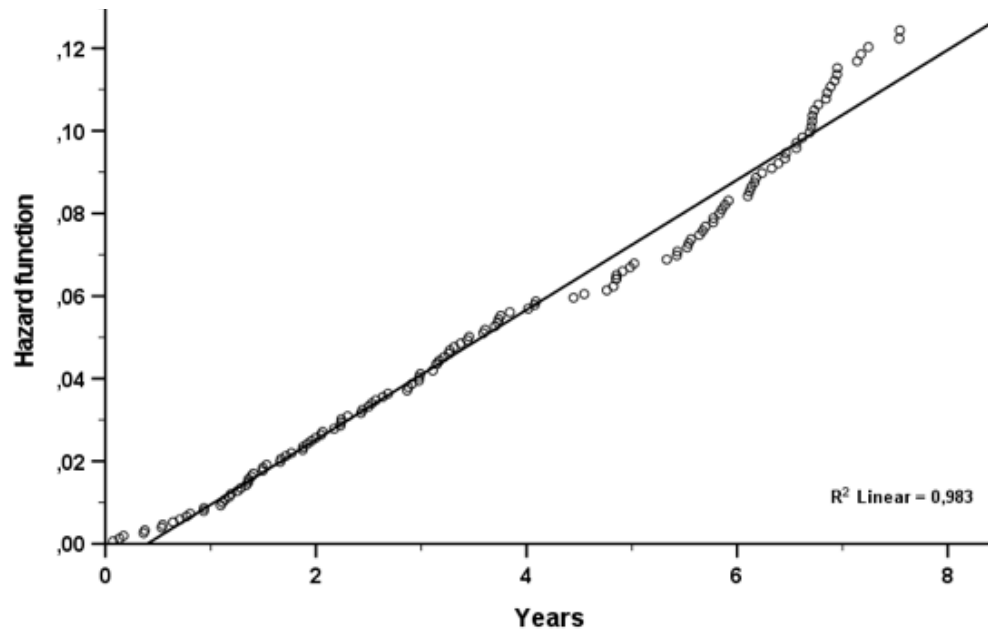


Figure 2d. Hazard function of conditional survival LincoSmart up to 8.7 years. Annual failure rate 1.3%, 95% CI (1.2% – 1.3%)

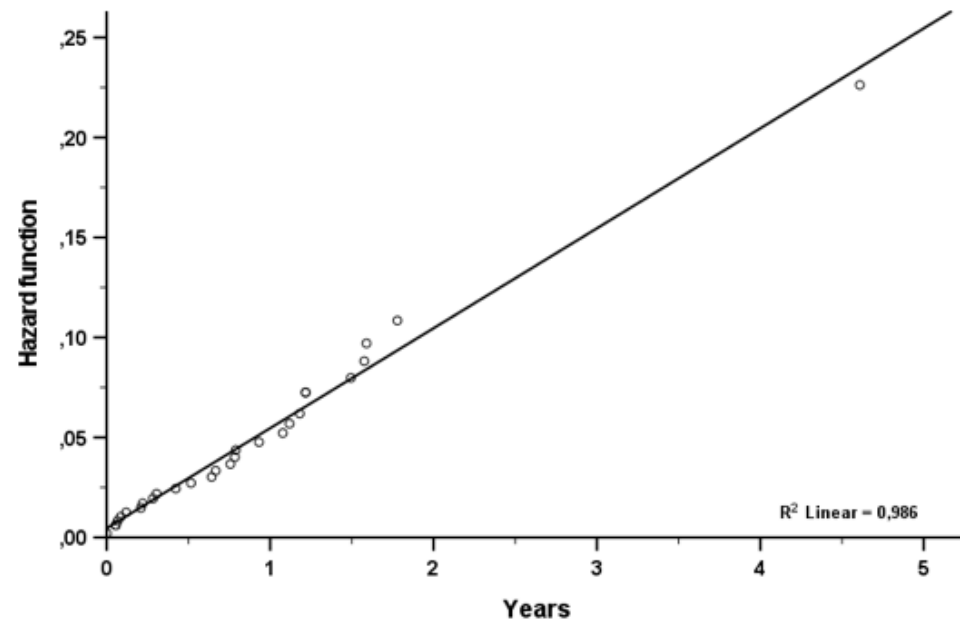


Figure 2e. Hazard function of conditional survival LincoSmart after 8.7 years. Annual failure rate 5.1%, 95% CI (4.9% – 5.4%).

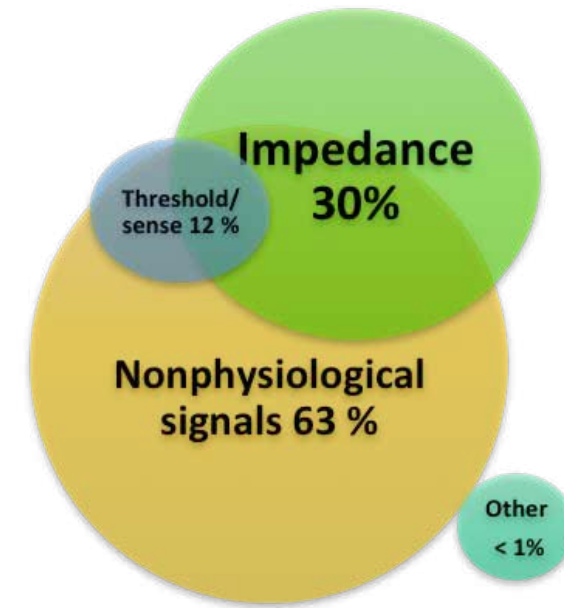


Figure 3. Venn Diagram showing Lead failure with multiple mechanism (n = 97 (23 %)). In particular significant threshold/sense changes presents with noise and/or impedance changes.

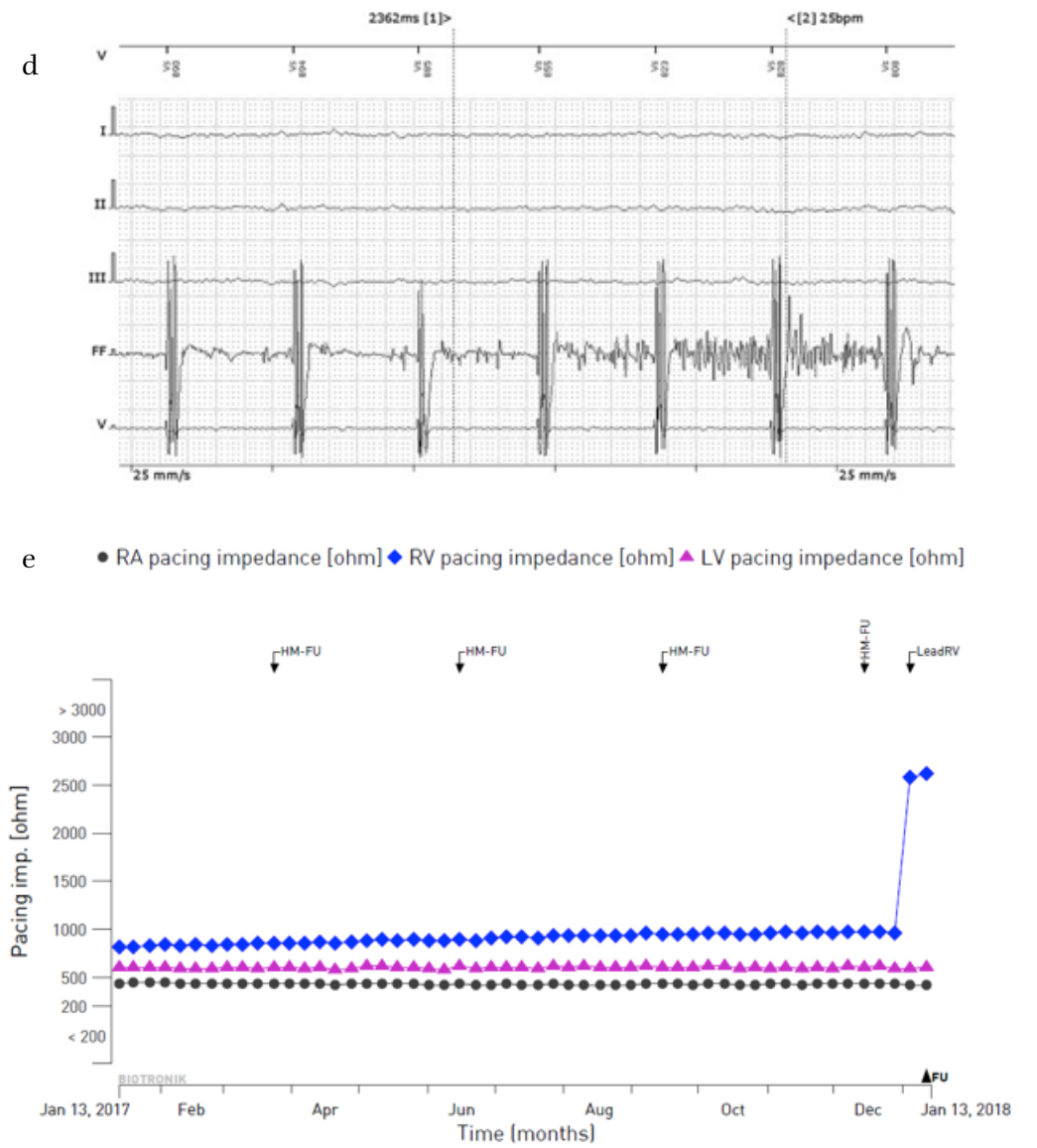
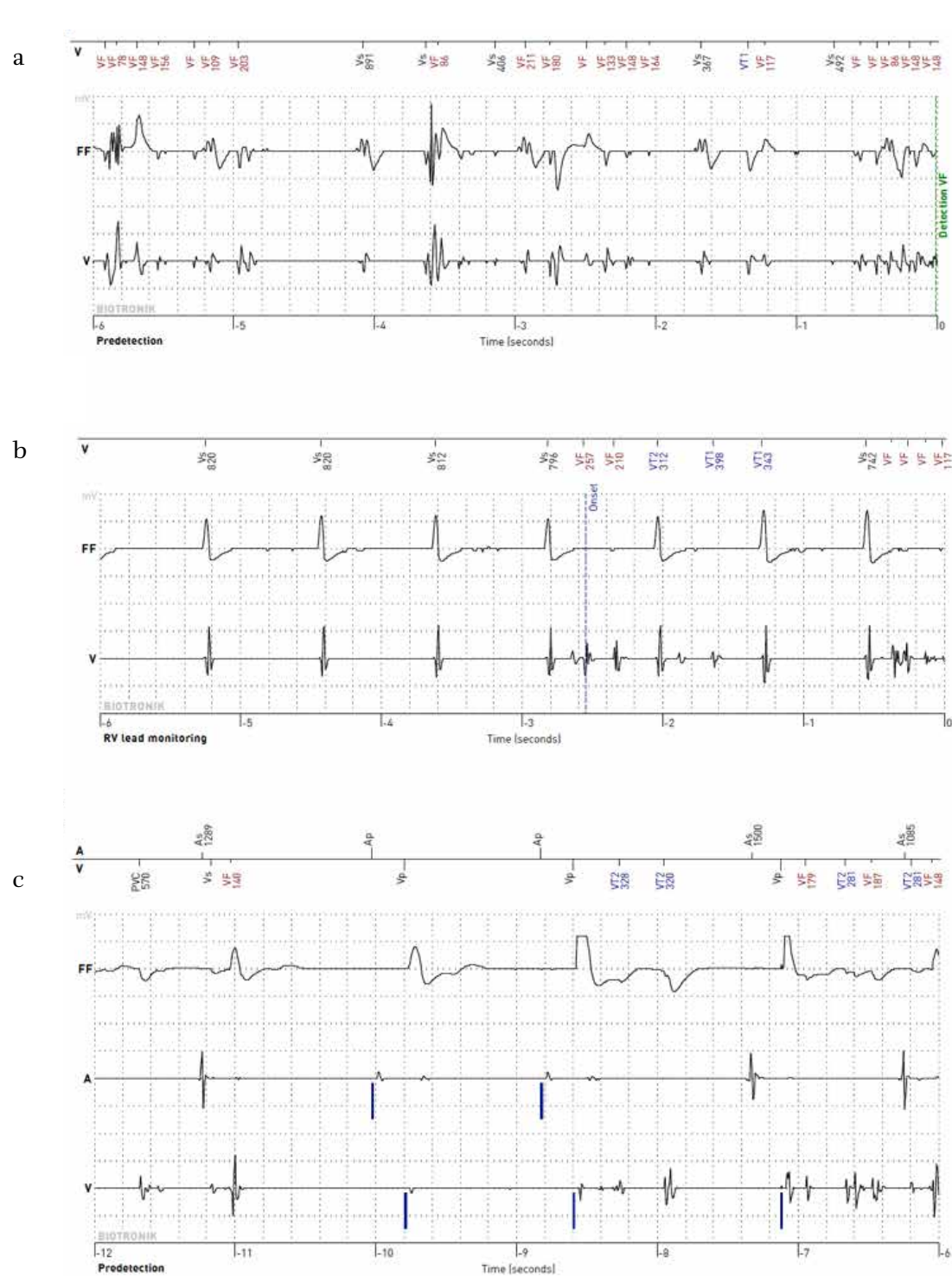


Figure 4.

- a: Nonphysiological signals on sensing and shock electrogram (EGM) suggest inner insulation breach.
- b: Nonphysiological signals on the sensing EGM
- c: Nonphysiological signals on the sensing EGM and only low amplitude signals on the shock EGM.
- d: Nonphysiological signals on the shock EGM.
- e: An example of significant changes of lead impedances. Remote care could be effective to detect these lead failures

Chapter 6

Significantly less inappropriate shocks in ischemic patients compared to non-ischemic patients.

The s-ICD experience of a high volume single-center

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Abstract

Background

The subcutaneous cardioverter-defibrillator (S-ICD) continues to be preferentially used in relatively young patients, with less advanced heart disease.

Objective

We therefore studied the short and long-term efficacy and safety of the S-ICD in subgroups of patients, which are underreported at present.

Methods

A total of 218 patients between November 2010 and February 2019 undergoing S-ICD with a follow up of at least 6 months implantation were included in a prospective registry. Mean follow up was 38 months.

Results

The most common indication for S-ICD implantation was ischemic cardiomyopathy (n = 106, 49%). Complication rate needing invasive intervention was 9 % (n = 21). Appropriate shock rate in patients with an S-ICD was 3.5%/year. A total of 30 inappropriate shocks (IAS) occurred in 19 patients (8.7%; 2.7%/year). The proportion of appropriate and inappropriate shock rates in patients with different cardiomyopathies shows remarkable variances. There were significant more IAS (3.6 %/year vs 1.7%/year, p = 0.048) in patients with non-ischemic cardiomyopathy versus patients with ischemic cardiomyopathy. Multivariate analysis identified, besides type of cardiomyopathy, atrial fibrillation as predictor for IAS.

Conclusion

In this real-world prospective registry we analysed S-ICD performance in the more traditional ICD patient. Patients with ischemic cardiomyopathy had significantly less inappropriate therapy compared to patients with non-ischemic cardiomyopathy and appear to be appropriate patients for this type of device.

Introduction

Implantable cardioverter-defibrillators (ICD's) are effective in prevention of sudden death from ventricular arrhythmias. (1) Transvenous (TV) systems are associated with specific risks of lead failure and systemic infection, and subsequent increased morbidity and mortality. (2,3) Annual lead failure rate in TV-ICD during long-term follow up reached 20% in 10-year-old leads. (4,5) The subcutaneous ICD system (S-ICD System, Cameron Health/Boston Scientific) could potentially decrease these risks, due to stable subcutaneous lead position. (6,7)

The EFFORTLESS (Boston Scientific Post Market S-ICD Registry) and the IDE (S-ICD System IDE Clinical Investigation) study concluded that the S-ICD was safe and effective in a selected cohorts of ICD patients. (6-9) These study populations however differ from classic TV-ICD trials, as the S-ICD populations were younger, less likely to have ischemic cardiomyopathy, and had better left ventricular systolic function. The S-ICD continues to be preferentially used in relatively young patients, with less advanced heart disease. Moreover, the impact of arrhythmic origin and ICD indication on appropriate and inappropriate ICD therapy is not studied specifically at present. We therefore studied the short and long-term efficacy and safety of the S-ICD in subgroups of patients, which are underreported at present.

Methods

The Isala Hospital (Zwolle, the Netherlands) is a high volume, tertiary heart center. All consecutive patients between November 2010 and February 2019 undergoing S-ICD with a follow up of at least 6 months implantation were included in a prospective registry. Patients participating in randomized trials were excluded (figure 1).

Indications for implantation were primary or secondary prevention of sudden cardiac death, according to the EHRA guidelines. Contraindications for S-ICD implantation were indications for Anti Tachy Pacing (ATP), need for permanent pacing or cardiac resynchronization

therapy. All research activities were conducted according to the principles of the Declaration of Helsinki.

Clinical data and s-ICD recordings were collected at implantation. The concomitant admission and at all visits (twice a year) thereafter were at our center or an allied center. Predefined endpoints were: rate of s-ICD complications, defined as device-related adverse events requiring invasive intervention; rate of inappropriate shocks, defined as shocks without recorded ventricular tachycardia (VT) or ventricular fibrillation (VF); rate of appropriate shocks, defined as shocks for VT/VF; rate of net shocks, defined as appropriate shocks minus inappropriate shocks; and conversion to TV system because of pacing indication. Procedural techniques, including defibrillation testing (DFT), surgical technique, and anesthesia, were left to the operator's discretion. A vector screening was done before s-ICD implantation. Devices were programmed with conditional and shock zones at 200 bpm and 250 bpm. If possible, exercise ECG screening was postoperatively performed.

Statistical analysis

Descriptive statistics are reported using mean \pm SD for continuous variables and frequency and percentage for categorical variables. Continuous variables of subgroups were compared using independent samples t-test or Mann-Whitney U test according to their distribution. We performed multivariable Cox regression analysis, with a backward conditional exclusion of variables at $P=0.2$ for patients experienced appropriate and for patients experienced inappropriate shocks. Age, gender, sensing vector, SMART pass filter, diabetes, body mass index (BMI), presence of atrial fibrillation (AF), primary or secondary prevention of sudden cardiac death, left ventricle ejection fraction (LVEF) and ischemic or non-ischemic cardiomyopathy was entered into the model. Moreover we performed a sub analysis with specific pathology and ECG characteristics and repeated multivariable Cox regression analysis, with a backward conditional exclusion of variables at $P=0.2$ for patients experienced appropriate and for patients experienced inappropriate shocks. Age, gender, sensing vector, SMART pass filter, diabetes,

body mass index (BMI), presence of atrial fibrillation (AF), primary or secondary prevention of sudden cardiac death, left ventricle ejection fraction (LVEF) and ischemic or non-ischemic cardiomyopathy, specific pathology, QRS duration and presence of bundle branch block were entered into the model.

Statistical analyses were performed using SPSS (V24; IBM, Armonk, New York, NY). p values < 0.05 were considered significant.

Results

Clinical data

A total of 218 patients were included in the analyses. Mean follow up was 38 months (3.2 years). The mean age of the study population was 55 ± 25 years and 149 (68%) were male. Baseline characteristics of all patients and for ischemic and non-ischemic cardiomyopathy separately are summarized in Table 1.

The most common indication for s-ICD implantation was ischemic cardiomyopathy ($n = 106$, 49%). Mean LVEF was 41 % (SD ± 12). Other etiologies were dilated cardiomyopathy ($n = 30$, 14%), hypertrophic cardiomyopathy ($n = 26$, 12%), idiopathic ventricular fibrillation or tachycardia ($n = 28$, 13%) and a variety of other less frequent etiologies in 12%. There were significant differences in baseline characteristics between ischemic ($n = 106$, 49%) and non-ischemic cardiomyopathy patients ($n = 112$, 51%). The group of ischemic cardiomyopathy patients were often male (80% vs 57%, $p < 0.001$), elder (60 ± 10 vs 51 ± 33 , $p < 0.01$) and with lower EF compared to non-ischemic cardiomyopathy patients (EF 36% vs 47%, $p < 0.001$). Mean follow-up duration was 38 ± 26 months. A total of 13 patients (6%) died during follow-up. Of these patients, 30% suffered a cardiac death.

Appropriate and inappropriate therapy

A total of 47 appropriate shocks (AS) occurred in 24 patients (11%) during follow-up. Of these 24 patients, 8 patients (33%) experienced 2 or more AS. Appropriate shock rate in patients with an s-ICD was 3.5%/year. VT and VF were respectively in 11 (46%) and 13 (54%) the reason for

AS. Secondary prevention was associated with AS (HR 3.2) during this study (Table 2). Our sub analyses including specific pathology and ECG characteristics showed also an association of QRS duration (HR 1.04) and appropriate shocks. There was no association found between bundle branch block and the presence of appropriate shocks in S-ICD patients. (Table 4)

A total of 30 inappropriate shocks (IAS) occurred in 19 patients (8.7%; 2.7%/year). More than one IAS occurred in 5 patients (26%). The main reasons for IAS were supraventricular tachycardia (n=7, 37%) and T-wave oversensing (n=6, 32%). IAS was associated with atrial fibrillation (HR 3.3), while ischemic heart disease (HR 0.3) was associated with less IAS (Table 3). The sub analysis including specific pathology and ECG characteristics found no association of inappropriate shocks and QRS duration or bundle branch block. (Table 5)

The proportion of appropriate and inappropriate shock rates in patients with different cardiomyopathies shows remarkable variances (Figure 2). Patients with ischemic cardiomyopathy had an appropriate shock rate of 4.1%/year, and a relatively low inappropriate shock rate of 1.7%/year. While patients with non-ischemic cardiomyopathy experienced an appropriate shock rate of 3.1%/year and an inappropriate shock rate of 3.6%/year (Figure 3). There were significant more IAS (3.6%/year vs 1.7%/year, $p=0.048$) in patients with non-ischemic cardiomyopathy versus patients with ischemic cardiomyopathy. There was a trend but not significant more net shocks (AS minus IAS) in patients with ischemic cardiomyopathy versus patients with non-ischemic cardiomyopathy ($p=0.06$). Figure 4 presents the mechanism of inappropriate episode by underlying disease. Although these might be a small amount, we see more frequent cardiac oversensing in non-ischemic cardiomyopathy patients.

Complications

Complication rate needing invasive intervention was 9% (n=21); consisting of infection (n=6, 2.8%), pain (n=6, 2.8%), hematoma (n=4, 1.8%), DFT testing failure (n=4, 1.8%) and T-wave oversensing (n=1, 0.4%) (Table 6). Most of these complications occurred in the first 30 days after implantation 5.5% (n=12). There were no lead problems

reported with a maximum follow-up of 9 years and conversion to a TV system was low, only in 7 patients (3.2%). In 3 cases the need for pacing (including CRT) was the indication for conversion to a TV system. Infection was the reason for another 3 patients and 1 patient due to T-wave oversensing.

Discussion

In this study the proportion of appropriate and inappropriate ICD shock rates in patients with different cardiomyopathies shows remarkable variances with most favorable profile for ischemic cardiomyopathy patients. In general, the group of ischemic cardiomyopathy patients were older and had lower EF compared to non-ischemic cardiomyopathy patients. Our results show less inappropriate therapy in the ischemic cardiomyopathy group compared to the non-ischemic group. This finding is consistent with the EFFORTLESS registry where patients with a prior myocardial infarction (MI) had a lower risk of IAS (HR 0.44 95% CI 0.26-0.75) in the midterm results. (9) However, in the EFFORTLESS registry earlier generation S-ICD's were used with a higher total IAS rate of 3.7%/year compared to our IAS rate of 2.7%/year. There are two important aspects that might contribute to lower rates of IAS. Firstly, the newest version of S-ICD (Emblem) with additional filter settings ('SMART pass') and secondly the increase in experience. (10) The SMART pass filter was available, with no differences between ischemic and non-ischemic patients, in 63% of our total population. Our inappropriate shock rate for the total population is in line with the IAS rate of 2.4% of the recently presented data in the UNTOUCHED study (Gold et al., presented at HRS 2020). The UNTOUCHED study enrolled 1,111 patients and evaluated outcomes with the S-ICD using modern devices and programming settings in a traditional primary prevention population. The 30-day complication of 4.2% is comparable with our 5.5%. Moreover, patients with purely electrical disease were excluded in the UNTOUCHED study. (11) Nonetheless, in this subgroup with younger patients with better LV function, the reported risk of inappropriate shocks was higher than in those with primary prevention heart failure indication. (9,12)

Besides association of underlying etiology, we found furthermore that atrial fibrillation was associated with IAS. This is in line with Olde Nordkamp et al.⁽¹³⁾ History of atrial fibrillation was similar in the ischemic and non-ischemic cardiomyopathy groups. Atrial fibrillation can cause IAS either due to rapidly conducted atrial fibrillation with heart rates falling in the shock zone or because of cardiac oversensing due to intermittent changes in T-wave morphology during paroxysmal atrial fibrillation. Over the 3.2-year average follow-up, 7 (3.2%) patients received a shock for AF or SVT which is relatively high compared the 2.3% (23 out of 985 patients, 3.1-year average follow-up) IAS due to SVT in the EFFORTLESS registry.⁽⁹⁾ IAS on SVT can generally be managed with device reprogramming or medication. Devices were programmed with conditional and shock zones at high rates (200 bpm and 250 bpm). So most likely our management of shocks on supraventricular arrhythmias by medication and/or catheter ablation was not effective enough and underlines the importance to treat the rhythm disturbances appropriate to avoid IAS.

Our present registry is a true real world data sample and possibly very comparable to TV-ICD candidates in many hospitals. The PRAETORIAN trial, a randomized controlled trial with 846 patients with the majority of patients having reduced LV systolic function (mean LVEF 30%), comparing S-ICD to TV-ICD is recently published. After a follow-up of 4 years, Knops et al. reported non-inferiority with respect to IAS. Mortality rates were similar in this study for TV-ICD and S-ICD. In contrast to our study, data regarding type of cardiomyopathy and shock rates were not presented.⁽¹⁴⁾ We participated in this randomized trial by including >10% of patients. Patients that participated in the PRAETORIAN trial were not included in our present study, although the same standard of monitoring was applied in our tertiary, high volume heart center.

We found a trend that the ‘net’ rate of appropriate minus inappropriate shocks in patients with ischemic cardiomyopathy was higher than in patients with non-ischemic cardiomyopathy. Meaning, that in our study patients with non-ischemic cardiomyopathy experience even more inappropriate shocks compared to appropriate shocks (3.6%/year vs 3.1%/year). Patients with ischemic heart disease experienced more

appropriate shocks than inappropriate shocks (4.1%/year vs 1.7%/year). This suggests that the S-ICD may be especially a favorable option for patients with structural heart disease, who form the majority of ICD candidates. On the other hand, younger patients might benefit on the long term from less lead problems. In that context, it is reassuring and promising that no lead related complications were found in our study with a maximum follow up of 9 years. This is consistent with the low lead related complication of 1.4% after 4 years in the PRAETORIAN trial.⁽¹⁴⁾ Furthermore, the conversion to a TV device because of pacing indication was low (n = 3, 1.2%). Only in one patient conversion to a transvenous system was necessary because of unresolved T wave oversensing.

Future innovations in S-ICD systems, with optimal algorithms for arrhythmia detection, advances in implantation techniques and the possibility of ATP application could further change the balance between TV-ICD and S-ICD.

The present study consists of data from a single center, although with high volume and experience. This introduces different kinds of biases. Furthermore, no direct comparison was made with TV-ICD patients, limiting the validity of all comparison with TV-ICD populations. Our prospective registry however, consists of intensive controls and data collection similar to patients that we include in randomized controlled trials.

Conclusion

In this real-world prospective registry, we analyzed S-ICD performance in the more traditional ICD patient. Patients with ischemic cardiomyopathy had significantly less inappropriate therapy compared to patients with non-ischemic cardiomyopathy and appear to be appropriate patients for this type of device.

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Table 1. Baseline Characteristics

	All patients n = 218	ICMP n = 106	Non-ICMP n = 112	Sign
Age at implantation	56 ± 25	60 ± 10	51 ± 33	P < 0.01
Male	149 (68)	85 (80)	64 (57)	P < 0.001
BMI, kg/m ²	27 ± 4	26 ± 4	28 ± 4	NS
Ejection fraction, %	41 ± 14	36 ± 11	46 ± 15	P < 0.001
Primary prevention	129 (59)	65 (61)	64 (57)	NS
Secondary prevention	89 (41)	41 (39)	48 (43)	NS
Comorbidities				
Hypertension	71 (33)	48 (45)	23 (21)	P < 0.001
Hypercholesterolemia	51 (23)	41 (39)	10 (9)	P < 0.001
Diabetes	26 (12)	19 (18)	7 (6)	P < 0.05
Atrium fibrillation	44 (20)	26 (25)	18 (16)	NS
Kidney disease, GFR < 30 ml/min/1.73m ²	15 (7)	9 (8)	6 (8)	NS
Previous cardiac surgery				
CABG	31 (14)	31 (29)	0 (0)	P < 0.001
Transvenous ICD	53 (21)	28 (26)	19 (17)	NS
Primary cardiac disease				
Ischemic cardiomyopathy	106 (49)			
Dilated cardiomyopathy	30 (14)			
Hypertrophic cardiomyopathy	26 (12)			
Idiopathic VT/VF	28 (13)			
Brugada	9 (4)			
Other	19 (9)			
Device and settings				
SMART Pass available A209/A219	138 (63)	70 (66)	68 (61)	NS
Sensing Vector Primary	122 (56)	61 (58)	61 (54)	NS
Sensing Vector Secondary	67 (31)	32 (30)	35 (31)	NS
Sensing Vector Alternate	29 (13)	13 (12)	16 (15)	NS

Values are mean ± SD or numbers with percentages. ICMP, ischemic cardiomyopathy; Non-ICMP; non ischemic cardiomyopathy

Table 2. Multivariable Cox regression analysis, for appropriate shocks in S-ICD patients. Secondary prevention was associated with appropriate shocks during follow-up.

	HR	CI	P-value
Female	0.3	0.7-1.4	0.12
BMI	1.1	1.0-1.1	0.03
Secondary prevention	3.2	1.2-8.6	0.02

Table 3. Multivariable Cox regression analysis, for inappropriate shocks in S-ICD patients. Atrium fibrillation was associated with inappropriate shocks during follow-up. Ischemic cardiomyopathy patients were associated with less inappropriate shocks.

	HR	CI	P-value
Female	0.5	0.2-1.5	0.2
Atrium fibrillation	3.3	1.1-9.4	0.03
Ischemic cardiomyopathy	0.3	0.1-0.8	0.03
Sensing Vector	1.7	0.9-3.0	0.08
BMI	0.9	0.8-1.1	0.3

Table 4. Subanalysis with specific pathology and ECG characteristics multivariable Cox regression analysis, for appropriate shocks in S-ICD patients. Secondary prevention and QRS duration were associated with appropriate shocks during follow-up.

	HR	CI	P-value
Female	0.2	0.8-2.1	0.3
Bundle branch block	1.1	0.8-2.5	0.27
QRS duration	1.04	0.1-6.5	0.01
Secondary prevention	3.2	0.4-6.1	0.01

HR; hazard ratio. CI; confidence interval.

Table 5. Subanalysis with specific pathology and ECG characteristics multivariable Cox regression analysis, for inappropriate shocks in S-ICD patients. Atrium fibrillation was associated with inappropriate shocks during follow-up. Ischemic cardiomyopathy patients were associated with less inappropriate shocks.

	HR	CI	P-value
Female	0.5	0.6-1.3	0.2
Atrium fibrillation	3.7	0.5-5.6	0.02
Ischemic cardiomyopathy	0.3	0.6-3.9	0.04
Sensing Vector	1.7	0.3-3.1	0.08
BMI	0.9	0.1-1.1	0.3
ECG Duration	0.9	0.1-1.4	0.9
Bundle branch block	2.6	0.6-2.5	0.1

HR; hazard ratio. CI; confidence interval.

Table 6. Device-related adverse events requiring invasive intervention occurred in 21 patients (9 %)

Infection	6 (2.8)
Pain	6 (2.8)
DFT fail	4 (1.8)
Hematoma	4 (1.8)
T-wave oversensing	1 (0.5)

Data is presented as number and percentages (%).

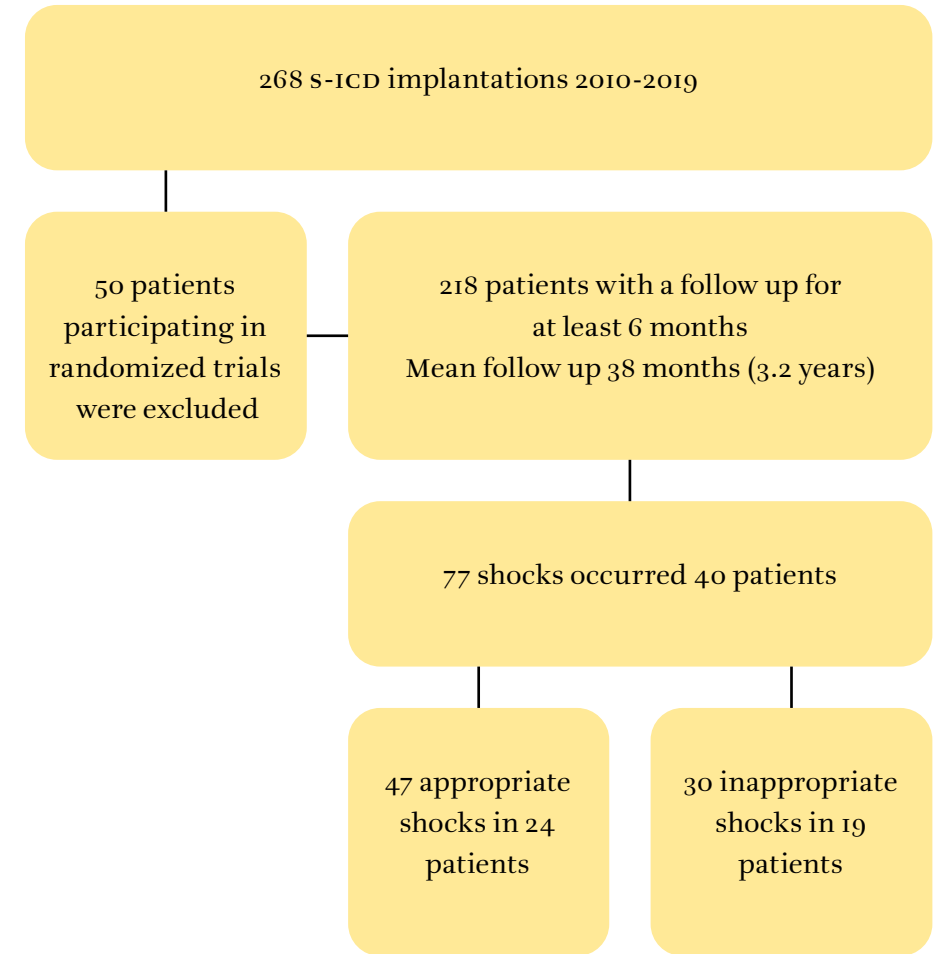
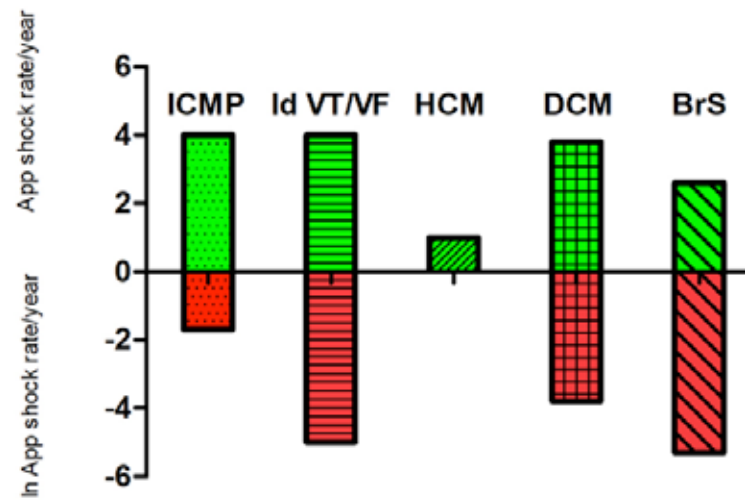


Figure 1. Patient flow chart



Total patients (n)	106	28	26	30	9
Median FU(yrs)	2.8	3.5	3.8	3.5	4.2
Patients with App shocks (n)	12	4	1	4	1
Total App shocks (n)	29	6	1	4	1
Patients with Inapp shocks (n)	5	5	0	4	2
Total Inapp shocks (n)	5	8	0	4	8

Figure 2. Incidence rates of appropriate versus inappropriate shocks per type of heart disease. ICMP indicates ischemic cardiomyopathy; Id VT/VF, idiopathic ventricle tachycardia/fibrillation; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; BrS, Brugada syndrome

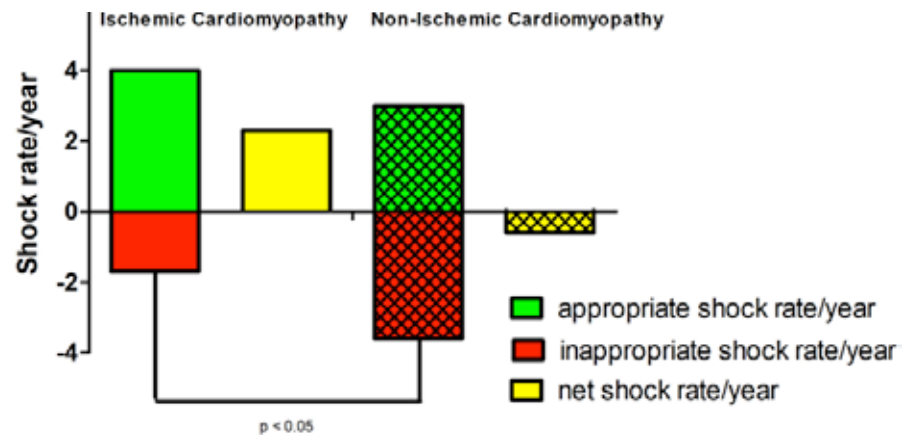


Figure 3. Appropriate, inappropriate and net shock rates for ischemic and non-ischemic cardiomyopathy patients.

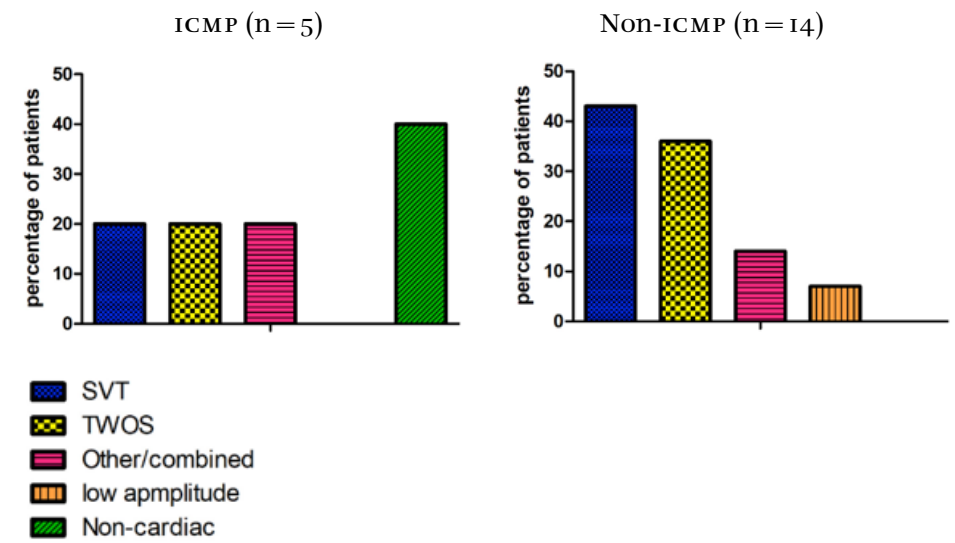


Figure 4. Mechanism of inappropriate shock episode by underlying disease. ICMP indicates ischemic cardiomyopathy; Non-ICMP indicates non-ischemic cardiomyopathy.

Chapter 7

Acute Human Defibrillation Performance of a Subcutaneous Implantable Cardioverter-Defibrillator with an Additional Coil Electrode

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Heart Rhythm 2023 Dec;20(12):1649-1656

Abstract

Background

The subcutaneous implantable cardioverter-defibrillator delivers 80 J shocks from an 8 cm left-parasternal coil (LPC) to a 59-cc left lateral pulse generator (PG). A system that defibrillates with lower energy could significantly reduce PG size. Computer modeling and animal studies suggested a 2nd shock coil either parallel to LPC or transverse from xiphoid to PG pocket would significantly reduce defibrillation threshold (DFT).

Objective

Acutely test defibrillation efficacy of parallel and transverse configurations in patients receiving an s-ICD.

Methods

Testing was performed in patients receiving a conventional s-ICD system (C). A 65 J success with C was required prior to investigational testing. A second electrode was temporarily inserted from the xiphoid incision connected to the PG with an investigational Y-adaptor. Phase 1 (n=11) tested the parallel configuration. Phase 2 (n=21) tested both parallel and transverse configurations in random order.

Results

Thirty-five patients: 76% male, 52±17 years, LVEF 40±15%, BMI 26±4, prior myocardial infarction 50%, congestive heart failure 53%, cardiomyopathy 56%. Compared to C, mean shock impedance decreased for both P (69±15 vs 86±20 ohms, p<.001, n=33) and T (56±14 vs 81±21 ohms, p<.001, n=20). Shock success rates at 20, 30 and 40 J were 55%, 79%, 97% and 25%, 70%, 90% for P and T respectively. DFT testing was well tolerated with no serious adverse events.

Conclusion

Adding a 2nd shock coil, particularly in the parallel configuration, significantly reduced impedance and had a high likelihood of defibrillation success at energies ≤40J. This may enable development of a smaller s-ICD.

Introduction

The Subcutaneous Implantable Cardioverter Defibrillator (s-ICD) system has been shown to be a safe and effective alternative to transvenous ICD systems for patients at risk for sudden cardiac death. (1-3) The key advantage of the s-ICD over the TV-ICD is that it is completely subcutaneous with no leads inserted in the heart chambers or vasculature. The s-ICD system therefore avoids most issues associated with the transvenous ICD and has been shown to reduce long-term lead-related complications. (4,5)

The S-ICD system consists of an electrode and pulse generator (EMBLEM[®] Boston Scientific, Marlborough, MA, USA). The electrode is inserted subcutaneously along the left sternal margin from a ~2 cm incision in the left para-xiphoid region using a tunneling tool and peelable sheath. The pulse generator is placed in a subcutaneous or intramuscular pocket on the postero-lateral aspect of the left thorax from a lateral incision along the 5th or 6th intercostal space. The proximal end of the electrode is tunneled subcutaneously from xiphoid incision to the pulse generator (PG) pocket. The defibrillation shock is delivered between the left parasternal shock coil and the pulse generator. See Figure 1a.

A potential factor limiting s-ICD usage is the size of the pulse generator. Critical mass theory suggests a minimum of 4 V/cm must be achieved across 95% of the heart for successful defibrillation and to accomplish this with an s-ICD system placed outside the rib cage requires more energy than systems with leads inside the heart. (6) The s-ICD delivers 80 J shocks from a 59 cc PG while typical ICD's deliver ~40 J shocks from an ~30 cc PG. New technology will allow some reduction in s-ICD size but significant size reduction will require PG's that deliver less energy. This in turn requires new electrode designs and shock vectors that have lower defibrillation energy requirements compared to current s-ICD systems. Computer modeling studies and an animal study suggested significant reduction in s-ICD energy requirements might be achieved via a simple adaptation employing a 2nd electrode, inserted either parallel to the first, or in transverse direction from the xiphoid towards the PG. Figure 1 b and c. (7,8) The purpose of this acute feasibility study was to assess the defibrillation efficacy of these dual electrode approaches in patients receiving an s-ICD system.

Methods

This study enrolled patients scheduled to receive a conventional s-ICD system (C) for standard indications at four clinical sites experienced in s-ICD implant. Patients believed to be at high risk for complications related to the insertion of a 2nd electrode, additional ventricular fibrillation (VF) conversion testing, stroke or infection were excluded as evidenced by factors including unusual chest anatomy, left ventricular ejection fraction (LVEF) <20%, unstable heart failure (HF)/heart transplant list, BMI >35, hypertrophic cardiomyopathy, atrial fibrillation (AF) or flutter within 4 weeks of the procedure, infection in the past 30 days, dialysis, insulin-dependent diabetes or immunosuppressive therapy. A complete list of inclusion and exclusion criteria may be found here [ClinicalTrials.gov. NCT03802110] The study conformed to the principles of the 2013 Declaration of Helsinki and was approved by the relevant Competent Authority and Ethics Committees.

The procedure began with the implant of the conventional s-ICD system (model 3401 or 3501 EMBLEM Electrode, and EMBLEM model A209 or EMBLEM MRI A219 pulse generators, Boston Scientific) using standard methods. Prior to any investigational testing, successful VF conversion at 65 J with the conventional system was required (a failed 65 J shock was a safety criterion to stop in-procedure acute testing). VF was induced with 50 Hz from the s-ICD pulse generator. If the first shock delivered by the pulse generator at 65 J failed for any reason the patient was excluded from investigational testing since electrode repositioning and/or additional testing may have been needed to assure a safe implant. After verification of successful conversion at 65 J with the conventional system, investigational testing began with temporary insertion of a second electrode (Model 3401 or 3501, Boston Scientific) from the same para-xiphoid incision using the same introducer and sheath tools (Figure 1). For the parallel configuration, the 2nd electrode was inserted just lateral to the first electrode with approximately 1 cm of separation. For the transverse configuration the electrode was inserted from the para-xiphoid incision towards the PG pocket while keeping the shock coil as anterior as possible. Fluoroscopy was used to document electrode locations and assure neither electrode touched

the other or touched the PG. Both electrodes were connected to the pulse generator with an investigational Y-adapter (Model 3598, Boston Scientific) to facilitate VF induction and shock testing. The Investigational Y-adapter was designed to allow both shock coils to be electrically common while limiting sensing to only the first 3401 or 3501 electrode. See Figure 2.

The study was conducted in two phases to gain initial experience and help assure safety. In phase 1 (Figure 3a) only the parallel configuration was tested. Starting energy was 50 J with subsequent tests at 65, 40, 30 and 20 J depending upon shock success or failure. Only one test shock was delivered per VF induction and failed test shocks were followed by either an 80 J shock from the s-ICD or an external shock. This sequence required up to three additional VF inductions for the phase 1 testing. A test shock was considered successful if a return to sinus or a non-shockable rhythm occurred within 5 seconds of the test shock. In phase 2 (Figure 3b) both parallel and transverse configurations were tested in random order. Starting energy was reduced to 30 J with a subsequent test at either 40 J or 20 J. This more efficient testing method (2 VF inductions per shock configuration) enabled testing of both dual-electrode configurations in the same patient.

In addition to the 65 J success requirement for the conventional system prior to the start of investigational testing, the protocol included several other safety precautions that required testing to be stopped if: a) any rescue shock failed; b) time from VF induction to PG shock delivery was >25 s; c) hemodynamic instability; d) excessive bleeding; e) or any other unexpected clinical or system-related event. After testing was completed, the 2nd electrode and investigational Y-adapter were removed, and the conventional s-ICD system implant was completed via standard procedures. A patient's active participation in the study ended at the completion of the acute testing, but the sites were required to report any adverse events within 3 months of the procedure. Either a 3-month visit, or phone call plus chart review, was required to help assure reporting of late-occurring adverse events.

Given the exploratory nature of this study, sample size was not driven statistically. However, it was estimated that a minimum of 20 patients with complete test data (per configuration) would provide

approximately a 10% margin of error for an expected conversion rate of 95% at the highest energy level tested. Parallel configuration test data from phases 1 and 2 were combined. Demographic information for patients beginning the test procedure was expressed as either a percentage of the total of patients or mean \pm standard deviation. Shock impedances were reported as mean \pm standard deviations and compared using a paired Student's t-Test. Conversion success was expressed as percent success (with 95% confidence interval) at each energy test level (i.e., 20, 30 and 40 Joules). While we did not perform a full step-down-to-failure defibrillation threshold tests, we computed a mean \pm standard deviation for the lowest successful energy and compared parallel vs transverse configurations with a Wilcoxon sign-rank test. The duration for experimental testing was calculated from the beginning of insertion of the 2nd electrode to the last VF induction and expressed as mean \pm standard deviation. Fluorographic images were retrospectively analyzed to determine spacings and orientational relationships between first and 2nd electrode.

Results

Forty-two patients at 4 investigational sites in the Netherlands were enrolled between Nov 2018 and Dec 2021. Seven patients were withdrawn prior to S-ICD implant either because they were discovered to not meet I&E criteria, withdrew consent, or the study had been suspended by the sponsor to make protocol changes. Characteristics and medical history of the 35 patients that began implant testing are shown in Table 1. Patients were representative of an S-ICD population although as typical, they were younger, had higher LVEF and fewer comorbidities than a transvenous ICD population. Patient characteristics did not differ between phase 1 and phase 2 except that there were six diabetics in phase 2 vs none in phase 1 and 9 subjects in phase 2 were receiving an aldosterone antagonist vs none in phase 1.

Thirty-three of the 35 patients (94%) who began the procedure had successful VF conversion with the conventional S-ICD system on their first attempt at 65 J and progressed to investigational testing. Phase 1 testing of the parallel configuration began in 11 patients, was complet-

ed in 10 and added 14 ± 3 minutes (range 11-18 minutes) to the implant procedure. Phase 2 testing began in 24 patients, yielded nearly complete data in 23 and was completed in 20. There were three patients that could not reliably be induced into VF in the Transverse configuration, so testing was not completed in these patients. Testing both parallel and transverse configurations in phase 2 added 21 ± 4 minutes (range 17-28 minutes) to the procedure.

Efficacy

The addition of a second electrode in either the parallel or transverse configuration significantly reduced shock impedance compared to the single electrode, conventional S-ICD system (Figure 4). The parallel configuration had a 22% lower mean impedance than conventional ($69 \pm 15 \Omega$ vs $86 \pm 20 \Omega$, $n=33$, $p<0.01$) and, the transverse configuration impedance was 32% lower than conventional ($56 \pm 14 \Omega$ vs $81 \pm 21 \Omega$, $n=20$, $p<0.01$). The shock impedance for the transverse configuration was also 16% lower than the parallel configuration ($56 \pm 14 \Omega$ vs $66 \pm 14 \Omega$, $n=20$, $p=.04$).

Shock success rates ($\pm 95\%$ confidence levels) at 20, 30 and 40 Joules were $55 \pm 17\%$, $79 \pm 14\%$, $97 \pm 6\%$ and $25 \pm 19\%$, $70 \pm 20\%$, $90 \pm 13\%$ for the parallel and transverse configurations, respectively (Figure 5a). The mean lowest successful energy tested were similar for both configurations (parallel: 27.0 ± 8.8 Joules; transverse: 31.5 ± 9.3 Joules). Figure 5b shows the pairs of the lowest successful energies for the 20 patients in phase 2 that completed testing in both configurations. The lowest successful energy was higher for the transverse configuration than parallel configuration in 10 patients (50%), equal in 8 patients (40%), and lower in 2 patients (10%).

Spacing between the two electrodes in the parallel configuration was 11 ± 3 mm overall and decreased from phase 1 (14 ± 3 mm) to phase 2 (10 ± 5 mm) due to learning curve and request by the study sponsor for closer spacing. Spacing did not have a relationship to either shock impedance or shock efficacy. In the transverse configuration, the proximal end of the transverse shock coil was 39 ± 11 mm inferior and 35 ± 20 mm lateral to the proximal end of the left parasternal shock coil. Again, distances between coils did not have a relationship with shock impedance or shock efficacy.

Safety

The investigational testing was well tolerated. Of the two patients that failed initial 65 J testing with the conventional system, one underwent electrode repositioning and subsequent VF conversion success without any issues. The other patient who failed at 65 J proved extremely difficult to convert requiring chest compressions and several external and 80 J S-ICD shocks before conversion but subsequently the patient recovered completely. The S-ICD system was removed and at a later date the patient also failed multiple 40 J shocks during TV-ICD system implant. One additional patient had a single rescue shock that failed during investigational testing, and by protocol the testing was stopped with no clinical consequences. Atrial fibrillation and/or atrial flutter occurred at some point during testing in 4 patients. Two resolved spontaneously and 2 were converted to normal sinus by external cardioversion near the end of the implant procedure. There were no instances of hemodynamic instability, bleeding or other unexpected adverse events.

During three-month follow-up there were a few adverse events that have been previously described and are expected following an S-ICD implant.^(1,4,5) These included: two superficial infections that resolved without surgical intervention, two hematomas that resolved without intervention, two patients reported pocket pain after discharge, one allergic reaction possibly due to antibiotic, one edema during FU treated with diuretics, one paroxysmal AF treated with ablation, and 3 patients with inappropriate shocks. None occurred at a rate higher than expected.

Discussion

Key Findings

This study demonstrates that inclusion of a 2nd shock coil to the S-ICD system yields a high rate of conversion and could therefore enable development of a significantly smaller S-ICD pulse generator. The mechanism of action is likely related to reduction in shock impedance, especially in the parallel configuration. However, impedance is not the

only factor as the transverse configuration had lower impedance but trended towards requiring higher energies. Computer modelling suggests a second electrode in the transverse configuration that extends too far laterally and close to the pulse generator may be less efficacious since too much current flows from the second electrode to PG, thereby missing the heart. (7) Inclusion of a second electrode also helps assure at least one electrode will be deep along the facial plane and/or traverses through less fat, both of which have previously been shown to be associated with improved defibrillation success. (6,9,10,11)

Prior work

The concept for the addition of a 2nd parallel electrode was derived from previous TV-ICD systems that incorporated a subcutaneous array electrode (SQA) that utilized multiple coils tunneled subcutaneously and spaced apart to create a system of electrodes that spanned a large area of the left thorax (sometimes referred to as “phantom area”). Clinical studies showed that the SQA reduced shock impedance and significantly reduced DFT.⁽¹²⁾ The concept for the transverse design was derived from the desire for a simpler implant whereby both shock coils could be included on a single electrode body, similar to dual-coil TV-ICD leads. Clinical studies have also shown dual-coil TV-ICD leads provide a lower DFT's than single-coil leads.⁽¹³⁾ Both parallel and transverse configurations were assessed in a computer model of human defibrillation that suggested DFT's could be approximately 50% lower for either the parallel or transverse configurations compared to the conventional, single left parasternal electrode system.⁽⁷⁾ The parallel configuration was also assessed in-vivo in a swine model that suggested a more moderate reduction in DFT of ~15-20%.⁽⁸⁾ However, swine anatomy is considerably different than humans, so this human feasibility study was necessary to assess true defibrillation performance. Given the feasibility nature of this study, direct comparison of single vs dual coil systems was not the objective and true DFT's were not obtained (i.e., no tests <20 J or >40 J in phase 2). Therefore, it is not possible to estimate how much energy reduction from single to dual coil systems was obtained, but some comparisons to prior studies may be informative. Bardy et al. reported means DFT's of 32.5 ± 17.0 and

36.6±19.8 Joules for two series of 78 and 49 patients, respectively. (14) In the present study, using the lowest energy that converted VF yielded means of 27.0±8.8 and 31.5±9.3 Joules for the parallel and transverse systems, respectively. The lowest successful energy tested in the present study likely overestimates DFT due to the fairly large number of successes at 20 J and lack of testing at lower energies.

Biffi et al reported on a series of 308 patients implanted at 28 sites that were uniformly tested for conversion success at an energy of 40 J. (15) Overall conversion success with 40 Joules was 84%. The 97% and 90% success at 40 Joule (parallel and transverse, respectively) seen in this study suggest better efficacy, but the numbers of patients tested were small and was not a true all-comers population. Data from Quast et al suggest that when implanting an s-ICD following specific implant criteria, that high success rates at low energies can be achieved even with the conventional single shock coil system. (16) Thus, one might envision future s-ICD implants starting with single coil and only adding a second coil in a smaller subset of patients in specific situations.

Clinical Relevance

The data from this study support the development of a smaller, lower energy s-ICD system; however, the clinical acceptance of such a system depends upon several factors. The first factor is size of the s-ICD pulse generator. The size/volume of the high voltage capacitors used to deliver the shock are directly proportional to the maximum energy the pulse generator must deliver. Energy and charge time also affect the size and voltage required for the device's battery. Current s-ICD systems are 59 cc and deliver 80 J at ~1350 V peak, in a charge time of ~8 s using a 9 V battery system. For comparison, ICD's are typically ~32 cc and deliver an ~40 J shock at ~700 V, in a charge time of ~8 s using a 3 V battery. The present study, showing very high success at 40 J, suggests a device with a maximum energy of ~50 J may be feasible and while not as small as a transvenous ICD, it would be significantly smaller than current s-ICD's, perhaps ≤40 cc.

A second factor influencing clinical acceptance is how a dual shock coil s-ICD system is implemented. Providing a Y-adaptor similar to that used in this study is an obvious, but perhaps least favorable option. A

more favorable approach might be to create a pulse generator with two ports in the header to allow for the optional use of a second electrode. This would provide flexibility to allow the implanter to determine what is best for an individual patient. A new electrode with two shock coils on the same body might be the most attractive option for many.

Finally, one must also consider the implant workflow and need for VF conversion testing. In today's clinical practice, transvenous ICD's are most often implanted without a VF conversion test due to the results of the SIMPLE study. (17) s-ICD implants typically include a VF conversion test but the need for such testing is currently under study in the PRAETORIAN-DFT study and favorable results would be expected to significantly reduce VF testing during s-ICD implants. (18) However, VF conversion testing might still be prudent for a lower energy s-ICD system as is also the case for recently introduced extravascular systems. Future clinical preferences – particularly choice of small, lower energy PG with VF testing vs conventional s-ICD with no VF testing – are unclear and could significantly affect the viability of new s-ICD systems.

Limitations

The results of this study must be considered with respect to some potential limitations. The sample size was relatively small and the investigators at the four sites were highly experienced in s-ICD implant. Per the protocol design, patients thought to be at higher risk were prospectively excluded and testing was discontinued in two patients that failed conversion at 65 J with the conventional single electrode system. Performance of a dual shock coil system would have been very interesting to assess in these two patients, but the study was designed conservatively for safety and to fit within established implant workflow. Another limitation is that we did not assess possible risks associated with lead-lead interactions and the possible implications of shorting between the 2 coils or between transverse coil and pulse generator. This possible risk was mitigated using fluoroscopy to assure the coils did not touch each or the pulse generator. Future product designs would need to assess this interaction and mitigate risks accordingly. Finally, we did not directly compare the defibrillation efficacy of

conventional single coil to dual coil systems in this study. Two subjects that failed initial testing at 65 J did not contribute dual-coil data and true step-down to failure DFR's were not obtained so there is potential for bias in both directions and it is difficult to compare our results to prior studies.

Conclusions

Adding a 2nd shock coil to the conventional s-ICD system significantly reduced impedance and had a high likelihood of defibrillation success at energies ≤ 40 J, particularly in the parallel configuration. This may enable development of a smaller, lower energy s-ICD pulse generator, however clinical viability is also dependent upon parameters other than defibrillation efficacy like implant workflow and the need for VF conversion testing.

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Table 1 Patient characteristics for the 35 patients that began testing in this study.

Characteristic	Result
Age at Enrollment (years, mean±sd)	51 ± 17
Gender (male / female)	80% / 20%
Height (cm, mean±sd)	180 ± 9
Weight (kg, mean±sd)	84 ± 15
Left Ventricular Ejection Fraction (% ,mean±sd)	40 ± 15
Cardiovascular Disease History	
Any Cardiovascular Disease	32 (91%)
Hypertension	13 (37%)
Coronary Artery Disease	11 (31%)
Myocardial Infarction	16 (46%)
Congestive Heart Failure	17 (49%)
NYHA Class I	2 (6%)
NYHA Class II	15 (43%)
Cardiomyopathy	22 (63%)
Genetic Heart Disease	4 (11%)
Valvular Heart Disease	4 (11%)
Hyperlipidemia	14 (40%)
Non-Cardiovascular Disease History	
Any Non-Cardiovascular Disease	10 (29%)
Diabetic	6 (17%)
COPD	1 (3%)
Stroke	1 (3%)
TIA	1 (3%)
GI Bleed	1 (3%)
Cardiac Surgery History	
Any Cardiac Surgery	14 (40%)
Angioplasty	12 (34%)
Stent	10 (29%)
CABG	6 (17%)
Valve Surgery	1 (3%)

Table 1 continued

Characteristic	Result
Arrhythmia History	
Atrial Flutter/Atrial Fibrillation	2 (6%)
NSVT	6 (17%)
Ventricular Fibrillation	9 (26%)
Medications at time of enrollment	
ACE/ARB	21 (60%)
b-blocker	25 (71%)
Anti-arrhythmic	0 (0%)
Aldosterone antagonist	9 (25%)

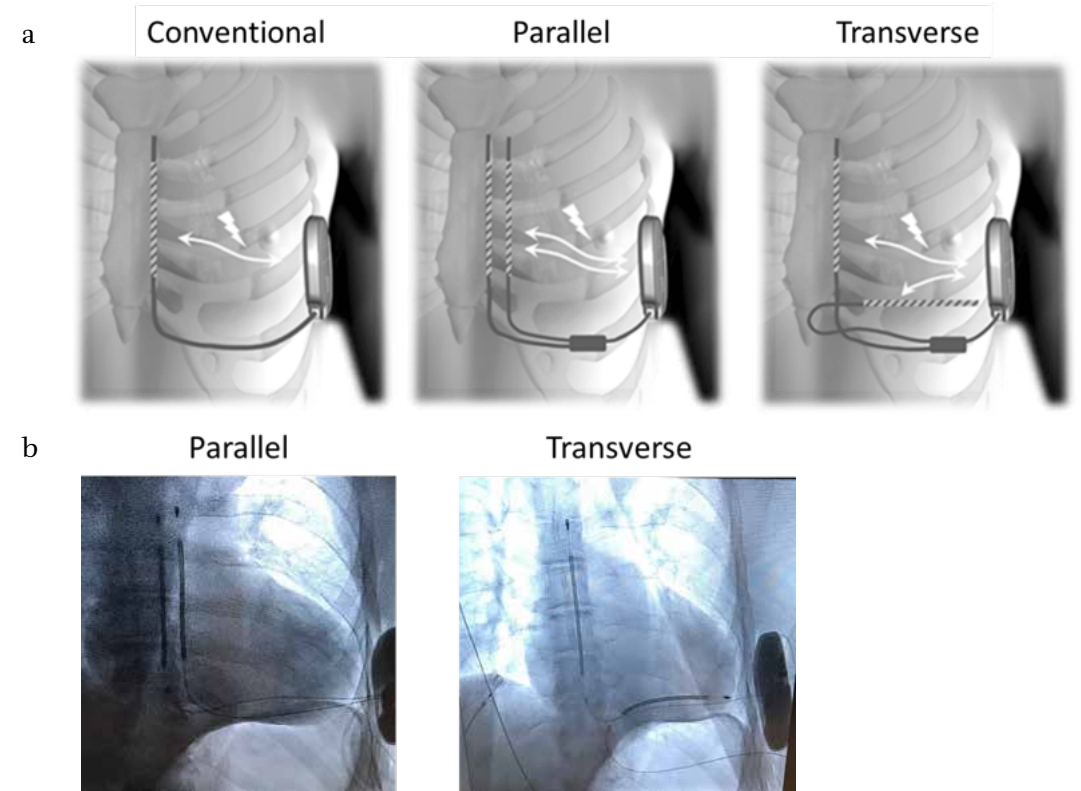


Figure 1 a) S-ICD Shock configurations. The conventional configuration was a single left parasternal electrode and S-ICD pulse generator, as used for all current S-ICD system implant. Parallel and transverse configurations added a second coil electrode for testing of new dual electrode configurations in this study. b) Fluorographic images of one tested patient showing parallel and transverse electrode locations.



Figure 2 Photo illustrating how the dual electrode configurations tested in the study were realized using an EMBLEM S-ICD, an investigational Y-adaptor, and two S-ICD electrodes.

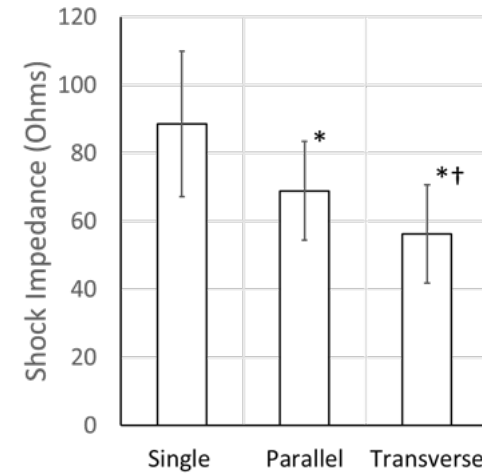


Figure 4 Shock impedance results displayed as mean±SD. * indicates $p < .01$ vs conventional and † indicates $p < .05$ vs parallel.

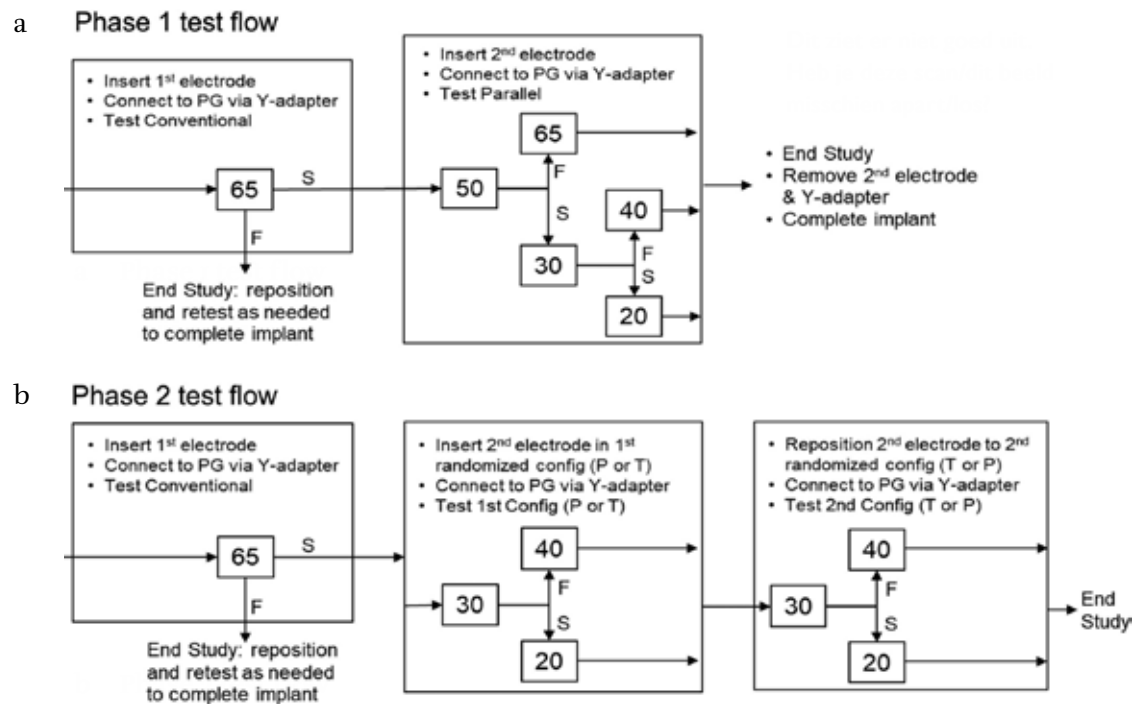


Figure 3 Flow charts illustrating the sequence of testing used in the study: a) phase 1 testing in the first 11 patients, and b) phase 2 testing in the subsequent 24 patients.

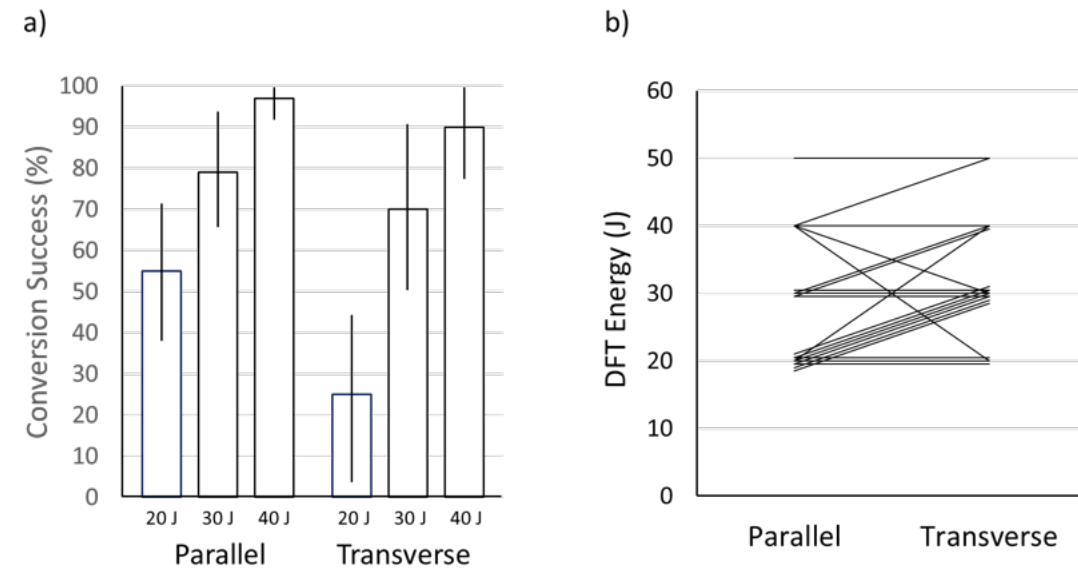


Figure 5 Defibrillation results. a) percent defibrillation success ($\pm 95\%$ confidence interval) at 20 J, 30 J and 40 J, for both parallel configuration ($n=33$ patients), and transverse configuration ($n=20$ patients).



Illustration: Björn de Vries

Part III

Chapter 8

Thesis summary and future perspectives

Thesis Summary

This thesis focuses on innovation and post-market surveillance of cardiac electronic devices for the treatment of slow and fast heart rhythms in patients. The case at the emergency room, in which a patient received multiple inappropriate shocks, demonstrates the need for improvement of cardiac implantable electronic devices (CIED's) therapy.

Cardiology is a field characterized by continuous innovation, which has led to increased life expectancy and improved quality of life for patients with cardiovascular diseases. (1) In particular, percutaneous coronary interventions/angioplasty (PCI) have made a significant contribution. (2) Due to improved treatments, more patients survive after a myocardial infarction, but they often develop heart failure. The prevalence of heart failure is, beside improved survival after myocardial infarction, also increasing due to the ageing of the population. (3) Heart failure is often the cause rhythm disturbances. This has led to an increasing need for effective treatments for rhythm disturbances with a crucial role for cardiac electronic devices. (4)

The pacemaker was a groundbreaking innovation in 1959. (5) The development of the implantable cardiac defibrillator (ICD) followed later, with Dr. Michel Mirowski implanting the first ICD in a patient in 1980. (6) Since then, the technology has improved significantly resulting in the current devices. (7) A remaining hurdle in cardiac device technology is the reliability of the leads, often referred to as the "Achilles heel" of the technology. This vulnerability has led to the development of leadless pacemakers and ICD's with leads outside the chest wall, which offer promising options for future treatments.

Part I describes the use of the first leadless pacemakers in the Netherlands. In Chapter 2 the experiences of the Isala hospital are presented with the first leadless pacemaker, the Nanostim. A serious issue with the Nanostim was that the battery had a chance of premature failure. The company that produces the Nanostim issued a so-called Field Safety Notification (FSN) in response, stating that there is a 0.5% chance of failure. However, longer observation showed a considerably higher

failure rate, namely 37%. In addition, the article discusses practical tools for dealing with sudden battery failure. Chapter 3 describes the battery performance of the second leadless pacemaker in the Netherlands, the Micra. Extensive analysis shows that, in contrast to the Nanostim, the Micra battery performs excellently with a long lifespan. The results of 153 patients in two centers show that up to 7 years after implantation the manufacturer's predicted average battery lifespan of 12 years still seems to apply. Long-term safety largely depends on the lifespan of the battery, since an empty battery is the main reason for replacement. Chapter 4 describes the results of a five-year observation period of the first leadless pacemakers in 179 patients in the Netherlands. Apart from the battery problem with the Nanostim, the introduction of the leadless pacemaker went effortlessly. The study showed a low incidence of complications requiring reinterventions, namely 4%. These results are consistent with industry-driven studies (8) and are even more favorable than with pacemakers with a lead. (9)

Part II describes the experiences with transvenous and subcutaneous ICD's in patients in the Netherlands. In Chapter 5, the experiences with 3,993 Linux leads in four large centers in the Netherlands are described. Our study shows that a significant number of patients (10.6%) experienced lead defects, which can have important negative consequences. In particular, detection of 'noise' which could incorrectly interpret as a high heart rate, can have serious consequences for patients resulting in inappropriate shocks. Previous studies with shorter observation periods were already available, but our study followed a larger patient group for a longer period. Our data show an increase in defective leads after approximately eight years, with younger patients in particular having an increased risk of defects. The access method also appears to have an effect; leads inserted via the subclavian vein have a greater chance of defects probably due to the so-called 'subclavian crush' phenomenon. Our results diverge significantly from the outcomes of industry-driven studies. Since 2009, there has been an alternative to a transvenous ICD: the subcutaneous ICD. (10) Chapter 6 discusses the use of the subcutaneous ICD in the Isala hospital. Initially, this therapy was mainly used in younger patients with fast cardiac

arrhythmias, with the aim of preventing long-term problems with ICD leads. However, our study shows that older patients with ischemic heart disease also have favorable outcomes with relatively many appropriate shocks and a low incidence of inappropriate shocks. This indicates that a subcutaneous device may also be a suitable alternative for this patient group. Chapter 7 discusses the potential of adding an additional lead to correct an arrhythmia with less energy. An additional advantage would be the possibility of connecting a smaller device, which could improve patient comfort. The study shows that adding an additional lead reduces shock impedance. However, further research is needed to further support the development of a more compact device.

Future perspectives

The importance of physician driven studies

Ideally in the future a real-world physician driven data monitoring system would provide continuous insight in CIED's functioning, revealing shortcomings on a short notice. Current industry driven post-marketing registries has some shortcomings. Industry post-marketing registries have a sample size requirement driven by the performance goal of 92.5% freedom from complications at 5 years follow-up. Enrollment and patient follow-up do have challenges, with reduced power when patients are lost to follow-up. And finally, they are underpowered for some important endpoints. This limits the ability to address post market questions before next-generation devices are available. (11-13) Chapter 2 and 5 illustrated the remarkable and striking differences between physician driven data and industry driven data.

Both patients and clinicians would benefit from better access to more actual real-time information about the CIED's. To support this post-marketing surveillance of lead performance, there should be a more joint responsibility. Currently, in daily practice, device cardiologists and technicians have to rely on devices companies for quality surveillance. On the other hand, for manufacturers, the accessibility to accurate long term performance data is also a challenge. Non-profit organizations, like the Netherlands Heart Registration (NHR), that

facilitates physician-driven quality registries, can play an important role. (14) The recently initiated Netherlands Extravascular Device Registry (NL-EVDR) is a good example of a promising high-quality registry. (15) Unbiased data from non-industry-related studies of good scientific quality is crucial. Medical professionals have the best insight into CIED's performance and their impact for their patients in case of malfunction. (16,17) These types of studies should have an essential role for a robust post-market surveillance system. Besides, proof of concept studies are crucial to introduce new concepts and solutions in improving device technology.

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Chapter 9

Nederlandse samenvatting

Naar aanleiding van een casus op de Eerste Hart Hulp, waarbij een patiënt meerdere onterechte shocks kreeg, richt dit proefschrift zich op innovatie en post-market surveillance van cardiale elektronische hulpmiddelen voor de behandeling van trage en snelle hartritmes bij patiënten. Cardiologie is een vakgebied dat zich kenmerkt door voortdurende innovatie, wat heeft geleid tot een verhoogde levensverwachting en verbeterde kwaliteit van leven voor patiënten met hart- en vaatziekten. (1) Met name de percutane coronaire interventies/ dotterprocedures (PCI) hebben een aanzienlijke bijdrage geleverd aan de cardiologie. (2) Door verbeterde behandelingen overleven meer patiënten na een hartinfarct, maar ontwikkelen zij vaak hartfalen. Daarnaast is het ouder worden van de populatie een oorzaak van een toename van hartfalen. (3) Hartfalen gaat vaak gepaard met verstoringen van het hartritme. Hierdoor is er een toenemende behoefte aan effectieve behandelingen voor trage en snelle hartritmes, waarbij cardiale elektronische hulpmiddelen een cruciale rol spelen. (4)

De pacemaker, waarvan de geschiedenis teruggaat tot 1959, was een baanbrekende innovatie op dit gebied. (5) De ontwikkeling van de implanteerbare cardiale defibrillator (ICD) volgde later; in 1980 implanteerde Dr. Michel Mirowski de eerste ICD bij een patiënt. (6) Sindsdien is de technologie aanzienlijk verbeterd, resulterend in de apparaten zoals we die vandaag de dag kennen. (7) Een huidige uitdaging binnen de cardiale device-technologie is de betrouwbaarheid van de draden, ook wel de ‘achilleshiel’ van de technologie genoemd. Deze kwetsbaarheid heeft geleid tot de ontwikkeling van draadloze pacemakers en ICD’s met draden buiten de thoraxwand, wat een veelbelovende richting biedt voor toekomstige behandelingen.

Deel I beschrijft het gebruik van de eerste draadloze pacemakers in Nederland. In Hoofdstuk 2 worden de ervaringen van het Isala ziekenhuis gepresenteerd met de eerste draadloze pacemaker, de Nanostim. Het lastige aan de Nanostim bleek dat de batterij kans had op vroegde uitval. Het bedrijf dat de Nanostim produceert heeft hierop een zogenaamde Field Safety Notification (FSN) uitgevaardigd waarin ze aangeven dat er een kans van 0.5% is op uitval. Langere observatie toonde echter een aanzienlijk hogere uitval, namelijk 37%. Daarnaast worden in het artikel praktische handvatten besproken hoe om te gaan

met plotselinge batterij-uitval. Hoofdstuk 3 beschrijft de batterijprestaties van de tweede draadloze pacemaker in Nederland, de Micra. Uitvoerige analyse toont aan dat, in tegenstelling tot de Nanostim, de Micra-batterij uitstekend presteert met een lange levensduur. De resultaten bij 153 patiënten in twee centra tonen dat tot 7 jaar na implantatie de door de fabrikant voorspelde gemiddelde levensduur van de batterij van 12 jaar nog lijkt te gelden. De veiligheid op lange termijn hangt grotendeels af van de levensduur van de batterij, aangezien een lege batterij de belangrijkste reden is voor vervanging. Hoofdstuk 4 beschrijft de resultaten van een observatieduur van vijf jaar van de eerste draadloze pacemakers bij 179 patiënten in Nederland. Naast het batterijprobleem bij de Nanostim is de introductie van de draadloze pacemaker verder soepel verlopen. De studie toonde een lage incidentie van complicaties waarvoor heringrepen nodig waren, namelijk 4%. Deze resultaten komen overeen met industrieel gedreven studies (8) en zijn zelfs gunstiger dan bij pacemakers met een draad. (9)

Deel II beschrijft de ervaringen met transveneuze en subcutane ICD’s bij patiënten in Nederland. In Hoofdstuk 5 worden de ervaringen met 3.993 Linx-leads in vier grote centra in Nederland beschreven. Ons onderzoek toont aan dat een aanzienlijk aantal patiënten (10,6%) met dit type lead last krijgt van slijtage, wat negatieve gevolgen kan hebben. Met name het onterecht afgaan van het apparaat door ‘ruis’, dat ten onrechte als een hoge hartslag wordt geïnterpreteerd, kan voor patiënten ernstige gevolgen hebben. Eerdere studies met kortere observatieduren waren al beschikbaar, maar ons onderzoek volgde een grotere patiëntengroep gedurende langere tijd. Uit onze gegevens blijkt een toename in defecte leads na ongeveer acht jaar, waarbij vooral jongere patiënten een verhoogd risico hebben op defecten. Ook de toegangsmethode blijkt van invloed; leads die via de vena subclavia zijn ingebracht, hebben een grotere kans op slijtage door het zogenaamde ‘subclavian crush’-fenomeen. Onze resultaten wijken significant af van de uitkomsten van industrieel gedreven studies. Sinds 2009 bestaat er een alternatief voor een transveneuze ICD: de subcutane ICD. (10) In Hoofdstuk 6 wordt het gebruik van de subcutane ICD in het Isala ziekenhuis besproken. Aanvankelijk werd deze therapie voornamelijk toegepast bij jongere patiënten met snelle hartritmestoornis-

sen, met het doel om op de lange termijn problemen met ICD-leads te voorkomen. Uit onze studie blijkt echter dat ook oudere patiënten met ischemisch hartlijden gunstige uitkomsten hebben met relatief veel terechte shocks en een lage incidentie van onterechte shocks. Dit geeft aan dat een subcutaan device ook voor deze patiëntengroep mogelijk een geschikt alternatief is. Hoofdstuk 7 gaat in op het potentieel van het toevoegen van een extra lead, waarmee met minder energie een hartritmestoornis kan worden hersteld. Een bijkomend voordeel zou de mogelijkheid zijn om een kleiner apparaat te koppelen, wat het draagcomfort voor de patiënt zou kunnen verbeteren. Uit de studie blijkt dat door het toevoegen van een extra lead de shock-impedantie wordt verlaagd. Vervolgonderzoek is echter nodig om de ontwikkeling van een compacter apparaat verder te ondersteunen.

Toekomstperspectieven

Het belang van dokters geïnitieerde studies

Idealiter krijgen dokters geïnitieerde studies een centralere rol in het post-market surveillance systeem voor CIED's. Industrie gedreven post-marketing registraties kennen namelijk belangrijke tekortkomingen. Deze registraties hebben een inclusie aantal die gericht is op een uitkomstmaat van 92,5 % zonder complicaties na 5 jaar follow-up. Het volgen van de patiënten kent uitdagingen met vaak uitval. Vaak zijn de studies door uitval van patiënten dan ook underpowered op belangrijke uitkomstmaten. Hierdoor kunnen belangrijke vragen soms niet beantwoord worden voordat het nieuwe device of lead al klaarstaat voor introductie. (11-13) In dit proefschrift zien we dat terug in de hoofdstukken 2 en 5 waarin onze resultaten opmerkelijk verschillen tonen ten opzichte van de data van de industrie.

Zowel patiënten als dokters hebben behoefte aan adequate real-time informatie over de cardiale hulp apparatuur. Om de post-market supervaillance te verbeteren zou er meer samenwerking moeten zijn met meer gezamenlijke verantwoordelijkheid. In de huidige situatie zijn de cardioloog en de pacemaker technicus voor kwaliteitscontrole te afhankelijk van de fabrikant. En aan de andere kant is het

voor de fabrikant ook heel lastig om betrouwbare informatie te krijgen van de patiënten met hun apparatuur. Non-profit organisaties zoals de Nederlandse Hart Registratie (NHR) kunnen hier een belangrijke rol inspelen (14). Het starten van Nederlandse Extravasculaire Device Registratie (NL-EVDR) is hier een goed voorbeeld van. (13) Kwalitatieve goede studies die onafhankelijk zijn van de industrie zijn cruciaal. Dokters hebben het beste inzicht in de klinische consequenties bij falen van de apparatuur. (16,17)

In dit proefschrift zijn zowel de initiële innovatieve studies opgenomen waarin een nieuw device of subtype voor het eerst bij patiënten wordt toegepast alsmede de zogenoemde 'post-market' registraties. De combinatie van beide type wetenschappelijk onderzoek draagt bij aan een duurzame en betrouwbare inzet van pacemakers en ICD's. In de huidige situatie is er bij post market surveillance nog geen belangrijke plek voor dokters gedreven registries. Dit proefschrift toont het potentieel om juist deze data te gebruiken voor het verder verbeteren van de zorg met cardiale devices.

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List of publications

Included in this thesis

- 1 Oosterwerff E, Adiyaman A, Elvan A, Ghani A, Hoek L, Breeman K, Smit JJ, Ramdat Misier A and Delnoy PP. Significantly less inappropriate shocks in ischemic patients compared to non-ischemic patients. The s-ICD experience of a high volume single-center. *Pacing Clin Electrophysiol.* 2021 Nov;44(11):1918-1924
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Not included in this thesis

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PhD portfolio

Name PhD student: F.J. (Erik) Oosterwerff
 PhD period: 2018-2025
 Names of PhD supervisor(s): prof. dr. A. Wilde
 prof dr. R. Knops
 co-supervisor(s): dr. L. van Erven
 dr. A. Elvan

Presentations

Oral presentation

NVVC	2018	I
NVVC	2019	I
NVVC	2022	I

Moderated poster presentation

EHRA	2021	I
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Poster presentation

EHRA	2021	0.5
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PhD training

Year	ECTS
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Courses

European Heart Rhythm Association (EHRA) Cardiac Pacing and Implantable Cardioverter Defibrillators Certification Level 1 and 2	2020	10
Masterclass Hartfalen	2022	10

Conferences

Nederlandse vereniging voor cardiologie (NVVC)	2018	1.0
EHRA congres, Lissabon	2019	1.5
European Society of Cardiology (ESC), Parijs	2019	1.5
NVVC	2019	1.0
ESC, online congress	2020	1.5
ESC, online congress	2021	1.5
EHRA online congress	2021	1.5
NVVC	2022	1.0
EHRA congress, Barcelona	2023	1.5
ESC congress, Amsterdam	2023	1.5
Heart Failure congress, Lissabon	2024	1.5

Awards

s-ICD experience in a common ICD population with predominantly patients with ischemic cardiomyopathy winner best presentation at NVVC 2018

The PhD program was combined with a fellowship cardiac devices and heart failure at Isala Hospital

List of abbreviations

AF	atrial fibrillation
AS	appropriate shocks
ATP	anti tachy pacing
BMI	body mass index
BRS	Brugada syndrome
CIED's	cardiac implantable electronic devices
DCM	dilated cardiomyopathy;
DFT	defibrillation testing
HCM	hypertrophic cardiomyopathy
HF	heart failure
ICD	implantable cardioverter- defibrillators
IAS	inappropriate shocks
ICMP	ischemic cardiomyopathy
LP	leadless pacemaker
LPC	left-parasternal coil
LVEF	left ventricle ejection fraction
MI	myocardial infarction
Non-ICMP	non ischemic cardiomyopathy
PG's	pulse generators
S-ICD	subcutaneous ICD system
SVT	supra ventricular tachycardia
SQA	subcutaneous array electrode
TV-ICD	transvenous implantable cardioverter defibrillators
VF	ventricular fibrillation
VT	ventricular tachycardia

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Curriculum Vitae

Frederik Jacob (Erik) Oosterwerff werd geboren op 17 augustus 1982 in Grou. Hij groeide op in Friesland en behaalde in 2000 zijn vwo-diploma aan het Comenius College te Leeuwarden. Hierna begon hij aan de studie Bewegingswetenschappen aan de Vrije Universiteit in Amsterdam. Hij behaalde zijn Bachelor en begon aan de studie Geneeskunde. Tijdens zijn studie Geneeskunde verdiepte hij zich reeds in de cardiologie. In 2006 volgde hij in Boedapest een summer school aan de Semmelweis University om kennis te maken met de elektrofysiologie. Drie jaar later ging hij naar Vancouver om meer te weten te komen over de invasieve cardiologie. Hier kreeg hij inspiratie voor de hartkatheterisatie kamer (HCK). In 2010 behaalde hij zijn artsdiploma. Hij volgde daarna zijn opleiding tot cardioloog, met als opleiders dr. G.A. Sommen, drs. T. Slagboom en dr. J.P.R. Herrman, in het Onze Lieve Vrouw Gasthuis (OLVG) in Amsterdam. Na het afronden van deze opleiding in 2018 begon hij aan een gecombineerd onderzoekstraject en fellowship 'cardiale devices and hartfalen' in het Isala ziekenhuis in Zwolle. Dit leidde tot het promotietraject onder supervisie van prof.dr. A.A.M. Wilde, prof dr. R.E. Knops, dr. A. Elvan en dr. L van Erven. Inmiddels werkt hij als (device) cardioloog in Gelre ziekenhuizen (Apeldoorn en Zutphen) en het St. Antonius in Nieuwegein. In 2014 is Erik getrouwd met Berber. Samen hebben zij twee kinderen, Milou (2015) en Silke (2018).

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Mijn copromotor dr. A. Elvan, beste Arif. Dank voor jouw wetenschappelijk bijdrage en dank voor het overbrengen van jouw elektrofysiologische kennis.

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