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Experience from a Danish nationwide cohort

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DOI (link to publication from Publisher):
10.5278/vbn.phd.med.00025

Publication date:
2015

Document Version
Publisher's PDF, also known as Version of record

THE ST. JUDE MEDICAL RIATA DEFIBRILLATOR LEAD ADVISORY – EXPERIENCE FROM A DANISH NATIONWIDE COHORT

BY
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DISSERTATION SUBMITTED 2015

AALBORG UNIVERSITY
DENMARK

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DENMARK

Ph.D. thesis

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The Faculty of Medicine, Aalborg University, Denmark has approved this PhD dissertation for public defense. The public lecture and defense will take place January 23, 2015 at 13.00 in the Auditorium in the House of Research, Aalborg University Hospital

Preface

The studies for this thesis were made during my time as a PhD student at the Department of Cardiology, Aalborg University Hospital, from 2011 to 2014. The project was completed in collaboration with the Working Group on Arrhythmias and Device Therapy under the Danish Society of Cardiology, with data from five Danish ICD implanting centers in Aalborg, Aarhus, Odense, Gentofte, and Copenhagen. There are so many people to whom I owe my gratitude for their helpfulness, making this project possible: numerous research secretaries, ICD technicians, nurses, physicians, statisticians, and industry technicians all over the country. I have been welcomed with open arms and have learned a great deal about this fascinating field of cardiology. With an honest heart I can say that our Danish national electrophysiological and device community indeed is a fantastic place to work bursting with smart, friendly, curious, innovative, and caring persons. Thank you all for your help.

I have been fortunate to have five clinical electrophysiologists as my academic advisors: Sam Riahi (main supervisor, Aalborg), Søren Pilkjær Hjortshøj (Aalborg), Anna Margrethe Thøgersen (Aalborg), Jens Cosedis Nielsen (Aarhus), and Jens Brock Johansen (Odense). It has been a blast working together with you on this project and getting to know you on a personal level. You have always given me sincere, honest, and constructive criticism and guidance on the project, but also left a room for my own ways: the ideal framework for a PhD study. I look forward to the continued collaboration across centers in the coming years.

In Aalborg, I would like to thank Consultant Ole Eschen and biostatisticians Søren Lundbye-Christensen, Martin Berg Johansen, and Karen Margrethe Due for valuable input to the project and statistical supervision; all the nurses in our ICD clinic for their valuable help with getting the project going; Professor Erik Berg Schmidt for letting me into his PhD student office and for input on scientific and practical questions despite my work being from an entirely different field within cardiology; all the researchers in our office for making a vibrant scientific environment and lots of fun in the last three years: Thomas, Michael, Jakob, Henrik, Vibeke, Stine, Anders, Steen, Christian, Line, Martin, and Anette; Research Secretary Hanne Madsen for helping with so many things during my time as a PhD student.

Outside Aalborg, I would like to thank consultants Jens Haarbo (Gentofte), Regitze Videbæk (Rigshospitalet), and Helen Høgh Petersen (Rigshospitalet) for data collection and critical input to the studies; Data Manager Ole Dan Jørgensen and Nurse Lisbeth Skov Nielsen from the Danish Pacemaker and ICD Register (Odense) for help with data extraction; Cardiology Fellow Rikke Kirkfelt Esbjerg (Aarhus) for sharing her experience working with device registry data; Associate Professor Dominic Theuns (the Netherlands) for valuable expert help in our first fluoroscopic screening; Professor Susanne Schmidt Pedersen (Odense) for introducing me to the important work of cardiac psychology using multi-item questionnaires.

The PhD project has only been possible due to financial support from the Danish Heart Foundation, the Danish Pacemaker and ICD Register, and the Department of Cardiology, Aalborg University Hospital.

Finally, I would like to thank my wonderful wife Sanne for her support and understanding and for taking care of our fantastic twins William and Sofia, often with a helping hand from our parents, when I have been away from home.

Jacob Moesgaard Larsen
August 2014

Table of Contents

List of Papers

This thesis is based on the following three papers.

Study I

Larsen JM, Riahi S, Nielsen JC, Videbaek R, Haarbo J, Due KM, Theuns DA, Johansen JB. Nationwide fluoroscopic screening of recalled Riata defibrillator leads in Denmark. *Heart Rhythm* 2013; 10: 821-827.

Study II

Larsen JM, Nielsen JC, Johansen JB, Haarbo J, Petersen HH, Thøgersen AM, Hjortshøj SP. Nationwide Fluoroscopic and Electrical Longitudinal Follow-up of Recalled Riata Defibrillator Leads in Denmark. *Heart Rhythm* 2014; 11: 2141-2147.

Study III

Larsen JM, Riahi S, Johansen J, Nielsen JC, Petersen HH, Haarbo J, Pedersen SS. The patient perspective on the Riata defibrillator lead advisory: a Danish nationwide study. *Heart Rhythm* 2014; 11: 2148-2155.

Abbreviations

CI	confidence interval
EC	externalized conductor
F	French gauge (1 F = 1/3 millimeter)
FDA	American Food and Drug Administration
FPAS-12	Florida Patient Acceptance Survey (12-item version)
GAD-7	Generalized Anxiety Disorder questionnaire (7-item version)
ICD	implantable cardioverter defibrillator
ICDC-8	ICD patient Concerns questionnaire (8-item version)
MAUDE	Manufacturers and User Facility Device Experience
PHQ-9	Patient Health Questionnaire (9-item version)
VAS	visual analog scale

Introduction

The implantable cardioverter defibrillator (ICD) is the treatment of choice for the prevention of sudden cardiac death in high-risk patients.[1, 2] As with any technology, the ICD has been associated with unexpected problems with several advisory notifications, also known as recalls, typically issued by the manufacturers according to the rules from the American Food and Drug Administration (FDA). The St. Jude Medical Riata defibrillator lead advisory was issued in November 2011 due to an increased risk of insulation defects including fluoroscopically visible externalized conductors (ECs) outside the protective silicone lead body.[3] Initially, not much was known about the Riata lead failure mechanisms, and no clear association was seen between ECs and electrical function as most active leads were appearing to be well-functioning despite fluoroscopic status. These potentially failing Riata leads posed a major challenge to the worldwide device community with much uncertainty, reviving unpleasant memories from the struggles with the preceding Medtronic Sprint Fidelis defibrillator lead advisory.[4]

Worldwide, at the time of the Riata advisory, 227,000 patients had received a recalled lead, and in the United States of America 79,000 out of 141,000 leads were still active.[3] In Denmark, 299 patients had active Riata leads with an urgent need for management. Our Riata investigations were started to help fill this knowledge gap by contributing with high quality data to enable the device community to provide the best care for our patients. This was managed on a national level in Denmark, and as recommended by the American Institute of Medicine, not only the technical characteristics of the advisory were investigated, but also patient-centered aspects by including patient-reported outcomes (PROs) on general well-being and psychological function.[5] The results of this joint national effort are presented in the studies in this thesis.

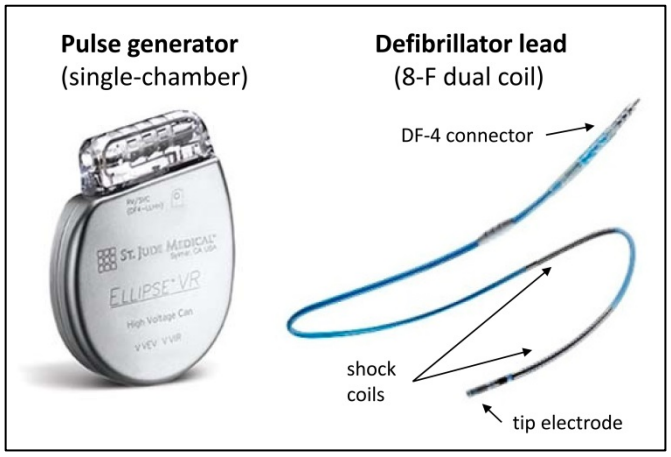
Background

The implantable cardioverter defibrillator

Ventricular arrhythmia is the number one reason for out-of-hospital cardiac arrest.[6, 7] Out-of-hospital cardiac arrest has a poor prognosis and is a major cause of death.[8] The concept of preventing sudden cardiac death using an implantable cardioverter defibrillator (ICD) was developed in the 1970s. In 1980, Mirowski *et al* performed the first human ICD implant.[9] In the first years, the ICD technology was characterized by bulky simple devices (>200 g; >100 cc) with a low battery longevity <2 years requiring abdominal implant and thoracic surgery with epicardial patches to deliver sufficient defibrillation energy.[10] Implants were associated with a high rate of complications and were only offered as secondary prevention in case of symptomatic ventricular arrhythmias. Mortality reduction compared with medical antiarrhythmic therapy was demonstrated in the pioneering randomized AVID, CIDS, and CASH studies.[11-13] In a meta-analysis of these studies, the patients randomized to ICD treatment had a relative risk of death of 72%, with an absolute risk reduction of 6.0% (mean follow-up 1.5 to 4.5 years) giving a number needed to treat of 17.[1] The benefit was less in patients with left ventricular ejection fraction >35%.

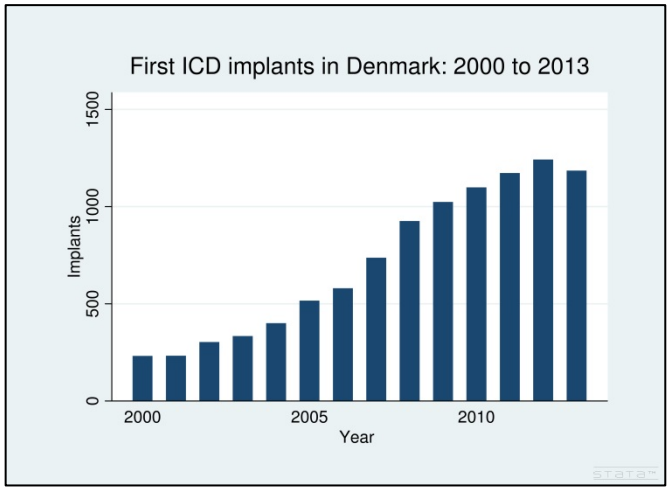
The ICD technology has been vastly improved, now featuring much smaller programmable devices (≈70 g; ≈35 cc) with longer battery longevity >6 years, higher energy output, more efficient biphasic shock waveform, active generator can, anti-tachycardia-pacing, advanced brady-pacing capabilities, and intravascular leads with complete capability of sensing, pacing, and shock delivery.[10] An example of a modern transvenous ICD is depicted in Figure 1. The technical advances have simplified ICD implantation, making it similar to a standard pacemaker implant with pulse generator placement subcutaneously in the left pectoral area connected via a lead to the endocardial surface of the right ventricle through the central venous vasculature. ICD indications have expanded. Now, the majority of implants are primary prevention in patients with a high risk of sudden cardiac death, with demonstrated mortality reduction in several randomized trials, including MADIT, MUSTT, MADIT II, and ScD-HeFT.[14-17] In a meta-analysis of 10 primary prevention trials, the patients randomized to ICD treatment had a relative risk of death of 75% and an absolute risk reduction of 7.9% (mean follow-up 1.3 to 4.0 years) giving a number needed to treat of 13.[2] Recently, an entirely subcutaneous ICD without intravascular leads has been introduced for patients not dependent on pacing or cardiac synchronization therapy with promising preliminary outcomes.[18, 19]

Figure 1



Modern transvenous implantable cardioverter defibrillator**.** ***Left****:* A pulse generator in a titanium box (66 x 51 x 12 mm; 67 g; 30 cc). ***Right****:* A dual coil defibrillator lead with active fixation (8-F = 2.7 mm diameter and length 52-65 cm). The pulse generator is placed subcutaneously in the left pectoral area and connected via the intravascular lead to the right ventricle. Courtesy of St. Jude Medical.

Figure 2



First implants of implantable cardioverter defibrillators (ICD) in Denmark from 2000 to 2013. Data reproduced with permission from the Danish ICD Register, June 2014.

ICD implantation in Denmark and the Danish Pacemaker and ICD Register

In Denmark, the first ICD implantation was performed in 1989 in Aarhus. The implant rate has increased, especially since 2007, with the introduction of primary prevention mainly in patients with symptomatic heart failure and concomitant ischemic heart disease (Figure 2). In 2013, the rate of first ICD implants was 212 per million inhabitants and seems to have reached a plateau. All Danish ICD implants have been performed at five university hospitals, and from 2013 also one non-university hospital.

Since 1982, the Danish Pacemaker and ICD Register has collected data from all cardiac implantable electronic device implants and subsequent surgical system interventions.[20] The implanting physicians report hardware specifications, procedure-related data, and selected clinical characteristics. After discharge, the patients are followed in outpatient clinics with regular visits and, if possible, supplementary remote monitoring. The number of variables reported increased in 2007. Data on ICD therapy, complications, and anti-arrhythmic medical therapy are reported by the technicians in the outpatient clinics.

Defibrillator lead design

The evolution of defibrillator leads is a success story with a steady development toward smaller and more reliable leads, but with a few backward steps along the way. The early intra-vascular defibrillator lead designs were coaxial with an inner central conductor surrounded by a tubular insulation, a tubular conducting shield, and an outer protecting jacket with large diameters of up to 14-F (F = French gauge = 1/3 mm → 14-F = 4.7 mm). Modern defibrillator leads have very complex multi-lumen designs with diameters <9-F, consisting of more than 40 separate parts of various materials. The low and high voltage conductors are protected by layers of insulation consisting of a mixture of materials with different strengths and limitations: silicone (biocompatible, biostable, flexible but soft), polyurethane (biocompatible and stiff but prone to stress fracture and metal ion oxidation), and fluoropolymers (very biocompatible and stiff but prone to micro insulation failures).[10] Shock coils in the newest lead generations are coated with expanded fluoropolymers or backfilling with medical adhesive and flat-wire design to reduce tissue in-growth, which eases lead extraction, for example in case of infection or lead dysfunction. Due to common industry standards, defibrillator leads from one manufacturer can be used with pulse generators from competing manufacturers using either the classic DF-1/IS-1 connectors (pace-sense cables and defibrillation cables from each shock coil are connected separately) or the newer DF-4 connector (all cables combined in one single connection).

Defibrillator lead failure

The defibrillator lead is the Achilles heel of the ICD system. Even modern lead designs have relatively high rates of electrical failure, most often due to insulation defects with estimated overall 5-year and 10-year failure-free survival of <85-90% and <60-75%, respectively.[21, 22] However, if death as a competing risk is accounted for, the cumulative incidence of lead failure at 5 years has been reported to be only 2.5% of the implanted leads.[23] Failure rates in different studies are not easily compared as criteria for failure usually vary.[24] The key problem is that the current monitoring of lead integrity is limited as stable measurements of, for example, pacing impedance can be within normal limits despite clinically important insulation failures or conductor fractures.[25] Therefore, clinical expert evaluations are often needed to diagnose lead failure, and this judgment will vary depending on experience and aggressiveness in resorting to lead replacement in case of subtle electrical changes. The clinical presentation of defibrillator lead failure is variable from subclinical changes in electrical measurements (pacing threshold, R-wave sensing, and impedances) to clinical therapy failure or painful inappropriate shock therapy due to noise. The risk of ICD malfunctions has decreased with hardware improvements, but is still a significant but accepted drawback of ICD treatment due to the high mortality reduction with low numbers needed to treat in primary and secondary prevention.[1, 2]

Class I advisory notifications – unexpected serious hardware malfunctions

ICD hardware malfunctions that emerge after market introduction are communicated by the manufacturers in accordance with the rules from the FDA.[26, 27] These communications of device problems have for several years been recommended by the American Heart Rhythm Society to be called “advisory notifications” or “safety warnings”. These terms are more neutral than “device recall” which may mislead the physicians and patients to believe that the communication is synonymous to an unavoidable need for device removal. However, the FDA and most researchers still use these terms interchangeably. The most serious communication is a class I advisory issued in case of a reasonable probability that the use of the product will cause serious adverse health consequences or death. In the last decade, two major class I advisories concerning small-diameter defibrillator leads have been issued, i.e. the Medtronic Sprint Fidelis lead family due to conductor fractures and the St. Jude Medical Riata lead family due to insulation failures.[3, 4] These recalled lead families are clearly outperformed by larger-diameter benchmark leads such as Sprint Quattro (Medtronic) and Endotak Reliance (Boston Scientific).[28] They were approved for clinical use via the fast FDA 510k-pathway without any demands for clinical testing, as they were considered improved updates of existing leads. Worldwide, both lead families reached more than 200,000 implants before the advisory notifications were issued. The fast 510k-pathway for approval has been demonstrated to be significantly overrepresented compared with the more comprehensive and slower pre-market approval-pathway in recalled cardiac implantable electronic devices.[29]

The impact of advisory notifications on health-related quality of life, including psychological functioning, is unsettled. It has been investigated in relation to the Sprint Fidelis lead advisory with conflicting results, but these studies are limited by the fact that they were performed a long time (9-24 months) after the patients were exposed to the advisory.[30-33] Research on the patient-centered aspects of advisory notifications is needed as pointed out in a recent scientific statement endorsed by the Heart Rhythm Society.[34]

Extraction of non-functional or potentially failing leads

When a defibrillator lead fails, it has to be replaced, preferably before inappropriate shock therapy or therapy failure. The timing in management of the non-functional or potentially failing recalled lead is challenging, and the choice between abandonment, extraction, or adding a supplementary pace-sense or shock-lead is not always easy. The decision should be based on an individual risk-benefit evaluation. Extraction of non-functional or recalled leads without concurrent infection and no immediate threat to the patient is a class IIa or IIb recommendation depending on the perceived threat of the lead to the patient with level of evidence C (expert opinion).[35]

In a recent review of the hastily increasing extraction literature, most studies show high procedural success rates >95% with a low mean rate of major complications of 1.8% and mortality of 0.4%.[36]

Defibrillator leads can usually be explanted by simple traction within the first 12 months after implant, but thereafter it is often a much more complicated procedure due to fibrous adhesions to other leads, endocardial structures, and venous vasculature with need for mechanical or laser-powered large diameter sheaths, with outcomes highly dependent on operator experience. The typical minor complication is pocket hematoma, and the most feared major complications are perforation of the heart and central vasculature with tamponade or hemothorax with a high risk of fatal outcome despite acute thoracotomy.[37, 38] Dual coil leads are more difficult and dangerous to remove due to the position of the proximal shock coil at the vulnerable level of the superior vena cava, especially if the shock coils are not backfilled or coated with expanded fluoropolymers.[39] A European survey highlights a concerning fact that despite the known importance of operator experience for outcomes, most extractions in real life are performed in centers with high implant rates but low extraction rates with variable backup from thoracic surgeons.[40] The outcomes of lead extraction under these real life circumstances outside the large high-volume extraction centers are not known. However, in two small single center studies the proportions of major complications were as high as 4.2% and 7.6%, respectively.[41, 42]

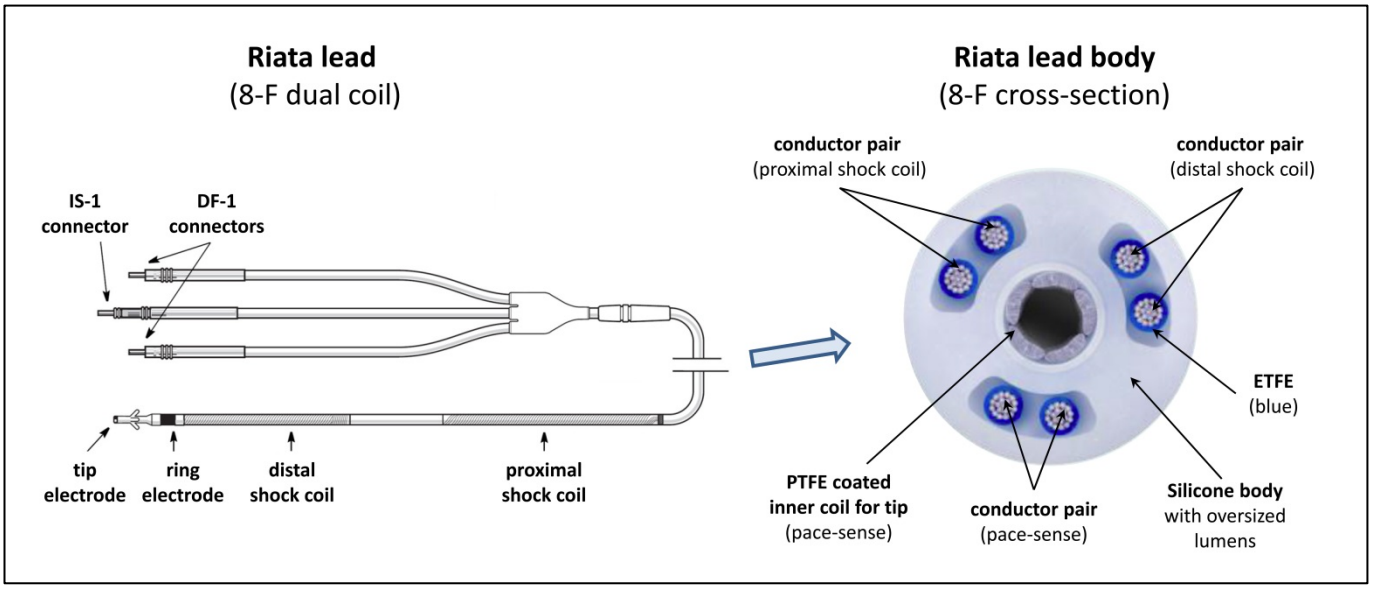
The recalled St. Jude Medical Riata leads investigated in the present thesis

The Riata 8-F leads introduced to the market in 2002 and their successors, the Riata ST 7-F leads released in 2005, were recalled in November 2011 due to a high rate of insulation defects, including inside-out movement of conductor cables outside the protective silicone body known as externalization or externalized conductors (ECs).[43] Externalization can increase the risk of erosion of the ethylene-tetrafluroethylene insulation of the conductor cables, but most leads in the first systematic fluoroscopic screening from Northern Ireland appeared to have normal electrical function despite fluoroscopically visible ECs.[43] A total of 20 sub-models were recalled (8-F models: 1560, 1561, 1562, 1570, 1571, 1572, 1580, 1581, 1582, 1590, 1591, and 1592; 7-F models: 7000, 7001, 7002, 7010, 7011, 7040, 7041, and 7042). The Riata ST Optim leads introduced in 2006 have not been recalled due to the addition of an outer protective jacket of a durable silicone-polyurethane copolymer (Optim), which is 50 times stronger than silicone and thereby significantly reduces the risk of inside-out and outside-in insulation defects.

The recalled Riata leads are good examples of modern multilumen defibrillator lead designs (Figure 3). The lead body is composed of silicone with a polytetrafluoroethylene covered pace-sense coil to the lead tip electrode in the center surrounded by two (in single coil lead) or three (in dual coil lead) oversized lumens with separate pairs of ethylene-tetrafluoroethylene covered low-voltage or high-voltage conductor cables to distal ring, distal shock coil, and proximal shock coil, respectively. In ten of the recalled sub-models with integrated bipolar sensing (no ring electrode), identical but passive pairs of filler conductor cables are placed in the lumen to keep a balanced design.[44] These passive filler cables are only attached distally by silicone adhesive instead of mechanical crimps as for active cables. Comparing the 7-F lead with the 8-F predecessor, the main differences are smaller lead diameter with conductor cables closer to the lead center, reducing the shear stress of lead bending exerted by the constant movement of the myocardium and improved shock coil design with flat-wire and silicone backfilling.

The development of ECs has been suggested to be caused by the combination of a flexible silicone lead body fixed to the central venous vasculature by fibrosis and the free moving much stiffer internal conductors in the oversized lumens, which enables differential lead component pulling by movement of the myocardium and skeletal muscles, so that the conductor cables can saw their way inside-out through the soft silicone.[45]

Figure 3



Schematic outline of main design element in an 8-F recalled Riata lead with dual coil and passive fixation. ***Left***: Truncated view of the lead from connector to tip. ***Right***: Cross-section of lead body proximal to the superior vena cava shock coil. ETFE = Ethylene-tetrafluoroethylene; PTFE = polytetetrafluoroethylene. Courtesy of St. Jude Medical.

Aims and hypotheses

The overall aim of the studies in this thesis was to provide data to support an evidence-based clinical management of ICD patients living under the Riata defibrillator lead class I advisory. The specific aims and hypotheses addressed in the three studies are presented below.

Study I

Aims: To determine the prevalence of ECs in a nationwide screening of active recalled Riata leads, and secondarily to examine time dependence and location of ECs, association with electrical abnormalities, fluoroscopic diagnostic performance, and potential predictors of ECs.

Primary hypothesis: The prevalence of ECs in a nationwide screening is relatively high but may be lower than reported in singlecenter studies due to minimal patient selection.

Secondary hypotheses: (1) The degree of externalization is associated with lead dwell time. ***(2)*** The most common location of ECs is intracardiac due to a high level of mechanical stress. ***(3)*** ECs are associated to electrical abnormalities. ***(4)*** The clinical diagnostic properties of fluoroscopy for detection of ECs are acceptable. ***(5)*** The rate of ECs is dependent on lead diameter and number of shock coils (exploratory analysis).

Study II

Aims: To describe the longitudinal dynamic nature of ECs and to investigate the clinical impact of ECs on electrical function and lead extraction outcomes.

Primary hypothesis: The evolution of ECs is dynamic with progression in size and new incident events over time.

Secondary hypotheses: (1) The incidence rate of electrical abnormalities in recalled Riata leads is relatively high, especially in patients with baseline ECs. ***(2)*** Lead extraction outcomes are good with a high rate of success and a low rate of complications. Lead extraction as compared with abandonment will be more frequent in younger patients in case of lead replacement. **(*3)*** The typical location of new ECs is in the intracardiac location and more frequently near the distal coil in dual-coil models.

Study III

Aims: To describe the acute impact of the Riata advisory on patients' well-being and psychological functioning and changes over time.

Primary hypothesis: In the early phase of the advisory, patients with recalled Riata leads will report poorer psychological functioning, especially seen in disease-specific measures of device-acceptance and device-related concerns compared with non-advisory controls.

Secondary hypotheses: (1) Patients with recalled Riata leads are expected to adapt to the advisory notification during 1-year follow-up, with improvements seen especially in disease-specific measures of device-acceptance and device-related concerns. ***(2)*** *Y*ounger age, female sex, baseline ECs, and Type D personality are expected to be predictors of an acute high impact of the advisory on general well-being.

Methods

Detailed descriptions of methods are given in each paper. Here is a shorter description with additional information on methodological considerations including explanations for differences in measures in Study I and Study II as a result of the hastily increasing knowledge on the Riata lead advisory over time.

Data from the Danish Pacemaker and ICD Register

In 2013, I made an unpublished internal audit by means of chart review of a random sample of 200 first-time ICD implants from 2007 to 2012 including all ICD centers. This audit showed acceptable positive predictive values for defibrillator lead model (95.3%), pulse generator model (96.5%), and implant diagnosis (91.6%).

The Riata study cohort and design of the three studies

From 2003 to 2010, a total of 486 patients had an implant with a recalled 8-F or 7-F Riata defibrillator lead at five university hospitals in Denmark. In March 2012, a survivor cohort of all living 299 Danish patients with active recalled Riata leads were identified in the Danish Pacemaker and ICD Register. The patients underwent a 2012 baseline fluoroscopic and electrical screening with one year of follow-up including a second similar 2013 screening. In connection with these screenings, sets of questionnaires with PROs were completed by the patients tapping into their well-being and psychological functioning.

Study I *(n = 298):* was a prospective cross-sectional study on the Riata cohort reporting on the baseline fluoroscopic and electrical screening. Primary endpoint was prevalent ECs. Secondary endpoints were location of ECs, degree of externalization, and prevalent electrical abnormalities.

Study II *(n = 295):* was a prospective longitudinal study on the Riata cohort reporting on fluoroscopic and electrical follow-up from baseline to the second screening. Primary endpoint was incident ECs. Secondary endpoints were incident electrical abnormalities, change in length of ECs, location of incident ECs, extraction outcomes, and prevalent ECs and electrical abnormalities in active leads at the second screening.

Study III *(n = 256 x 2 = 512):* was a prospective longitudinal study on the Riata cohort reporting on PROs at baseline and at follow-up, with a cross-sectional baseline comparison with a contemporary sample of non-advisory controls matched 1:1 by random on age (5-year groups), sex, and implant indication (primary vs. secondary). Non-advisory patients enrolled in the DEFIB-WOMEN Study with response to a set of questionnaires 12 months after ICD implant were eligible for matching. The DEFIB-WOMEN Study is an ongoing Danish prospective observational study on consecutive patients with a first-time ICD implant designed to evaluate gender differences in PROs and clinical outcomes. Primary endpoints in Study III were measures of device acceptance and device-related concerns. Secondary endpoints were generic measures of symptoms of depression and anxiety, and a purpose-designed question on the impact of the advisory on general well-being.

Fluoroscopy and definitions of ECs (Study I & II)

At the two fluoroscopic screenings, the Riata leads were examined in full length with cine-loops in three projections at a recommended frame rate of 15 per second: posterior-anterior, left anterior oblique 45° or best possible, and right anterior oblique 45° or best possible. Fluoroscopy was repeated in case of lead discontinuation before the second screening.

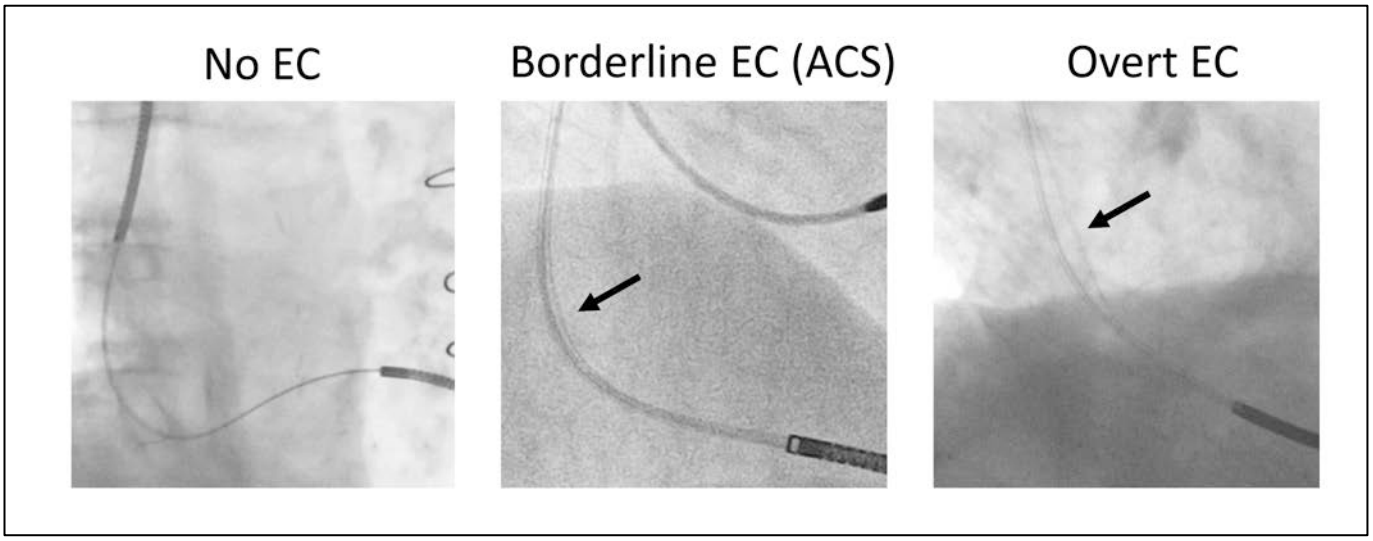
When the baseline screening was started early 2012, no guidelines for evaluation of ECs were available, and therefore we adjudicated the presence and extent of ECs in collaboration with Dr. Theuns from the Erasmus Medical Center in the Netherlands, who, at that time, was finishing the largest fluoroscopic screening study to date with more than 1000 Riata leads.[46] From the Dutch cohort, we adapted the use of the following criteria in the evaluation of ECs: the main criterion for ECs was a distance perpendicular across the conductors larger than the width of the lead body. Additional signs were a different radius of curvature of the conductors and an independent pattern of movement during the cine-loops of the conductors compared with the rest of the lead body.

In ***Study I***, we conservatively considered only leads with a clear separation of the conductors from the lead body as having ECs. Leads with visible localized abnormal spacing between conductors just at the limit of the lead body width and a slightly abnormal radius of curvature of the conductors compared with the rest of the lead body were categorized as “abnormal conductor spacing”. In ***Study II***, we included the leads previously classified as “abnormal conductor spacing” in the definition of ECs and named it “borderline EC”. This change to analyze all leads with abnormal fluoroscopies as a common entity seemed appropriate as in the meantime, St. Jude Medical had issued guidelines on the evaluation of ECs that included a different radius of curvature of the suspected EC as a valid criterion for EC despite no visible separation of conductors from the lead body.[47] Figure 4 shows examples of leads with (i) no EC, (ii) abnormal conductor spacing / borderline EC, and (iii) overt EC. In both studies, the fluoroscopic diagnosis of ECs was adjudicated using centralized re-evaluation of all fluoroscopies involving multiple investigators.

EC location was categorized into three zones: distal, intermediate, and proximal (Figure 5).

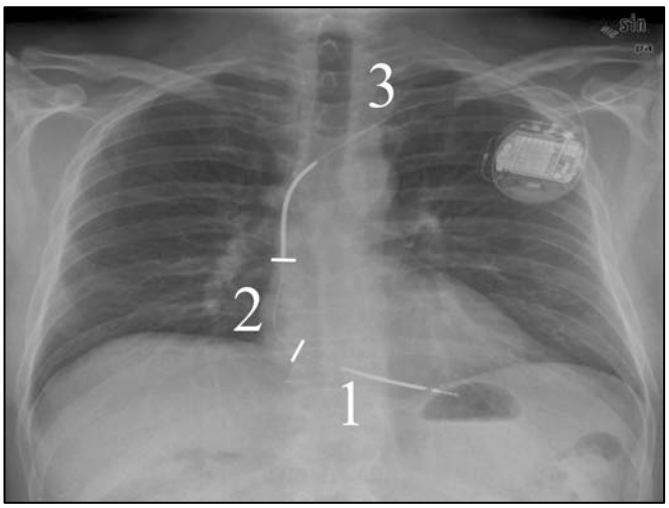
In ***Study I***, the size of ECs was described by four degrees: (1) localized abnormal conductor spacing without overt externalization; (2) externalization <1 cm length; (3) externalization >1 cm length in one zone; and (4) externalization >1 cm length crossing adjacent zones. As mentioned, localized abnormal conductor spacing was not considered an EC but was included in the scale as it was considered to precede the development of overt EC. In ***Study II***, a more refined evaluation of EC size was performed by measurement on fluoroscopic still pictures of the maximal linear length of the conductors from lead body exit to entry. The diameter of the distal coil was used as scale to adjust for magnification (Figure 6)

Figure 4



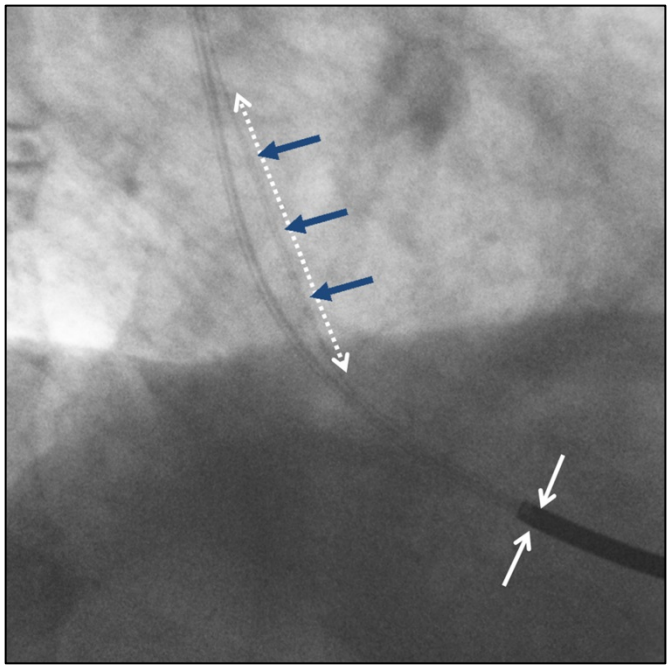
Examples of fluoroscopic still pictures of recalled Riata leads. ***Left:*** Normal lead without any signs of externalized conductors; ***Middle:*** Abnormal conductor spacing (Study I) or borderline externalized conductors (Study II) with no clear separation of the suspected conductor from the silicone lead body. There is, however, an abnormal localized conductor spacing (arrow), which is most evident during cine-loops rather than still pictures with a slight difference in the radius of curvature between conductors. **Right:** Large defect with overt externalized conductors (arrow). Abnormal conductor spacing (ACS) is equivalent to borderline externalized conductor (EC).

Figure 5



Location of externalization divided into three zones (1) Distal - below tricuspid valve annulus; (2) Intermediate - from tricuspid valve annulus up to superior vena cava (single coil leads) or proximal coil (dual coil leads); (3) Proximal - superior vena cava (single coil leads) or proximal coil (dual coil leads) and above.

Figure 6



Single coil Riata lead with overt externalization (marked by blue arrows). The length of the externalized conductors outside the lead body was measured (dotted white arrow), and distal coil was used as scale to adjust for differences in magnification (solid white arrows).

Device interrogation and definitions of electrical abnormalities (Study I & II)

Device interrogation was performed with standard clinical programmers from several manufacturers with measurements of pacing threshold, R-wave sensing, pacing impedance, and inspection of electrograms for non-physiological noise. High voltage lead impedance testing was only encouraged if painless integrity check was available, as this test seemed to be of limited value to predict high voltage short circuits. Prior to our Study I, Dr. Theuns had experienced a case at his Dutch hospital with a Riata lead short circuit at high voltage shock testing despite normal values at low voltage testing of the shock impedance.

In *Study I*, *prevalent* electrical abnormalities were defined by absolute limits and relative changes since latest follow-up: pacing threshold >5V or >100% increase; R-wave sensing <3.0mV or >50% reduction; pacing impedance outside the interval 200-2000 Ω or >100% increase or >50% decrease; high voltage lead impedance outside the interval 20-200 Ω or >100% increase or >50% decrease; electrogram with non-physiological noise; and previous lead failure with implant of supplementary leads. This definition was based on a mutual agreement between the investigators from the Danish centers inspired by the definitions used in the early Riata studies without fluoroscopies and the ongoing fluoroscopic Riata study in the Netherlands run by Dr. Theuns.[46, 48-50]

In *Study II*, *incident* electrical abnormalities were evaluated in patients with normal electrical function at the baseline screening. Due to the longitudinal design, incident electrical abnormalities were defined as a composite of three: (1) lead discontinuation due to a new electrical abnormality adjudicated by a panel of three electrophysiologists with access to data on electrical function from baseline to discontinuation but blinded from fluoroscopic status, (2) death due to a new electrical abnormality evaluated by reviewing available data in medical records; and (3) new electrical abnormalities at device interrogation at the second screening with values outside absolute limits or relative changes since the baseline screening (criteria as at baseline).

Questionnaires for evaluation of PROs (Study III)

In connection with the nationwide screenings, a set of standardized and validated multi-item questionnaires and purpose-designed questions were completed to measure PROs. The Type D personality measure was included to strengthen adjustment for potential confounding in statistical analyses. The matched non-advisory controls did not complete the generic questionnaire on general anxiety.

Device acceptance: was evaluated using the 12-item Florida Patient Acceptance Survey (FPAS-12). Two separate studies with Danish and Dutch ICD patients indicate that the FPAS might be better used as a 12-item version than the original 18-item version.[51, 52] Examples of items are *"Thinking about the device makes me depressed"* and *"The positive benefits of this device outweigh the negatives"*. All items are rated on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree). The total score was calculated and linearly converted into a score from 0 to 100, with a higher score indicating better device acceptance. The internal consistency was good with Cronbach's alpha of 0.79 and similar to that found in a previous study of 0.82.[52] A high Chronbach's alpha represents a high mean inter-correlation between the items in a questionnaire and therefore indirectly describes the degree to which a set of items measures a single latent construct, i.e. a complex psychological variable such as device acceptance.[53] A well-accepted guideline for acceptable values of Chronbach's alpha is 0.70 to 0.90.

Device-related concerns: were evaluated using the 8-item ICD patient Concerns questionnaire (ICDC-8).[54] Example of an item is "*I am worried about my ICD firing"*. All items are rated on a 5-point Likert scale from 0 (not at all) to 4 (very much so). The total score ranges from 0 to 32, with a higher score indicating increased device-related concerns. The internal consistency was excellent, with Cronbach's alpha of 0.93 and equivalent to that previously described of 0.91.[54]

Symptoms of depression: were evaluated using the 9-item Patient Health Questionnaire (PHQ-9).[55] Patients are asked to rate items according to how often symptoms have bothered them in the last 2 weeks on a 4-point Likert scale: 0 (not at all), 1 (several days), 2 (more than half of the days), and 3 (nearly every day). The total score ranges from 0 to 27, with a higher score indicating more depressive symptoms. The internal consistency was good with Cronbach's alpha of 0.83 equivalent to that previously described of 0.86-0.89.[55]

Symptoms of anxiety (Riata cohort only): were evaluated using the 7-item Generalized Anxiety Disorder questionnaire (GAD-7).[55] All items are rated as described above for the PHQ-9. The total score ranges from 0 to 21, with a higher score indicating more symptoms of anxiety. The internal consistency was excellent with Cronbach's alpha of 0.91 in accordance with a previously described value of 0.92.[55]

The distressed (Type D) personality: was measured with the 14-item Type D Scale.[56] Type D personality is defined as a high score on negative affectivity (7 items, e.g. *"I often feel unhappy"*) and social inhibition (7 items; e.g. *"I am a closed kind of person"*). All items are rated on a 5-point Likert scale from 0 (false) to 4 (true). The total score for each subscale ranges from 0 to 28. Only patients scoring ≥ 10 on both subscales have a Type D personality. The internal consistency was good for both subscales with Cronbach's alpha 0.93 and 0.85 in accordance with that previously described of 0.88 and 0.86, respectively.[56]

Impact on general well-being (Riata cohort only): was evaluated using a purpose-designed question: *"What is the impact of the information about possible problems with your ICD lead on your general well-being"*. This was answered using a visual analog scale (VAS) with a vertical 20 cm line from zero (marked no impact) to 10 (marked most thinkable impact). The line had major ticks at integers and minor ticks at decimals. A high impact was defined a priori as VAS >5.

Statistical considerations

The analyses for the three studies were performed with Stata versions 11.2 and 13.1 (StataCorp, College Station, TX, USA). Two-sided p-value <0.05 was considered statistically significant. All confidence intervals (CIs) were calculated with 95% limits. The choice of statistical tests including regression models depended on the distribution of the outcome variable and whether data were paired or unpaired.

Multivariable regression analyses were performed according to the commonly accepted rule of 10 events (binary outcome) or 20 patients (continuous outcome) for each model parameter to ensure an appropriate model complexity.[57] Covariates were selected

from predefined prioritized lists of potential confounders and predictors based on the literature and discussions with fellow researchers to reduce the risk of type 1 errors with rejection of false null hypotheses due to multiple testing. Bonferroni correction for multiple testing was not applied. This methodology is too conservative with a very high risk of type 2 errors with acceptance of false null hypotheses missing important associations, as it wrongly assumes the most likely reason for low p-values to be chance rather than the alternative hypothesis of a true association between tested groups.[58] This is not the case if hypotheses are predefined and theoretically sound.

No power calculations were performed as this would not have had any impact on the execution of the three descriptive observational studies with the maximum number of participants given beforehand, limited by the size of the Riata survivor cohort in Denmark. Therefore, the interpretation of neutral findings was done with caution and guided by a combination of the point estimates and especially the width of CIs. A very wide CI indicates a reduced statistical power for a given analysis with an increased risk of type 2 errors.

Study I: The prevalence of ECs was calculated with CI. The association between lead dwell time and degree of externalization was analyzed by Spearman's correlation. The fluoroscopic diagnostic performance was evaluated by calculation of Cohen's Kappa, sensitivity, specificity, and positive and negative predictive values, with the adjudicated findings as gold standard. Changes in electrical measurements from implant to fluoroscopic screening were analyzed using paired t-tests and adjusted for lead dwell time at baseline screening using multivariable linear regression. Potential predictors of ECs were analyzed in a multivariable additive hazards regression assuming the data on ECs to be extremely interval censored between time of implant and fluoroscopic screening, also known as current status data.[59] This was necessary as the silent nature of most ECs makes the exact time of development of a visible EC unknown. Due to few events only two potential predictors were included: lead diameter and number of shock coils.

Study II: The incidence rate of ECs was calculated with CI using time-at-risk from baseline to latest fluoroscopy in patients with normal baseline fluoroscopy. Comparative analyses for incident ECs were made only by estimating crude incidence rate ratios due to low event count. The incidence rate of electrical abnormalities was calculated using time-at-risk from baseline to lead discontinuation, death, or the second screening in patients with no baseline electrical abnormalities. Comparative analyses for electrical abnormalities were made by estimating crude incidence rate ratios and a simple adjusted multivariable analysis by Poisson regression with EC and lead diameter as covariates.

Study III: Baseline data in matched groups and within-patients over time were analyzed using logistic and linear regressions for paired data. Baseline data within the Riata cohort were analyzed using logistic and linear regressions for unpaired data. Covariates for the adjusted analyses between Riata patients and controls were: age, ischemic heart disease, cardiac resynchronization therapy, self-reported other chronic diseases, shock therapy within one year (appropriate and inappropriate), high school, higher education, Type D personality and ICD center. Covariates for analysis of independent predictors of a high impact of the advisory notification were: age, female sex, ECs, and Type D personality. Covariates for the adjusted analyses of changes over time were new events since baseline screening believed to be of importance for changes in PROs: shock therapy, loss of spouse/partner, and new self-reported chronic disease. Cohen's effect size index *d* was used to determine the clinical relevance of estimated adjusted mean differences (0.20 = small, 0.50 = moderate, ≥0.80 = large).[60] Missing values were imputed using multiple imputation for covariates to be used in the adjusted regression analyses and for single items in multi-item questionnaires with acceptable data quality with >70% of items reported. Questionnaires with <70% items reported were excluded from analyses for that given PRO. Imputed missing values accounted for ≤ 2.5% for each covariate and also ≤ 2.5% of items for each questionnaire.

Results

Detailed descriptions of the results are given in each paper. Here are the main results.

Study I

Study population

All 299 living patients with recalled Riata leads attended the baseline screening, but one patient did not undergo fluoroscopy due to severe disability and was excluded from data analyses. No significant differences were seen in characteristics at time of lead implant between patients with and those without ECs (Table 1).

Table 1 Characteristics of patients and ICD systems in the Riata survivor cohort

	EC (n = 32)	No EC (n = 266)	p-value
Time of Riata implant			
Age, years	61.3±12.5	62.6±11.8	0.56
Sex, men	78%	82%	0.60
Primary prophylaxis	13% [2]	26% [17]	0.18
IHD	63% [8]	71% [19]	0.39
LVEF, %	29±16 [18]	33±14 [96]	0.39
Time of screening			
Age, years	66.9±12.6	67.7±12.0	0.73
Height, cm	174±9 [3]	175±9 [14]	0.72
Weight, kg	82±17 [2]	83±18 [16]	0.68
Pacing dependence	9%	5%	0.21
Appropriate shock therapy	28%	26%	0.83
Inappropriate shock therapy	0%	9%	0.15
Total lead count	2 (1;3)	1 (1;3)	0.25
Lead dwell time (Riata), years	5.6±1.0	5.1±1.1	0.01
Lead diameter 8-F (Riata)	66%	29%	<0.001
Single coil (Riata)	59%	47%	0.17
Septal position (Riata)	19%	24% [2]	0.52
Generator dwell time, years	4.8 (0.7;6.8)	4.5 (1.1;6.2)	0.65
Biventricular (generator)	34%	26%	0.31
Non-left pectoral (generator)	20%	11%	0.26

Data are presented as mean ± SD, median (10^{th} percentile; 90^{th} percentile), and percentage. Missing values are reported in squared brackets. EC = externalized conductor; F = French; ICD = implantable cardioverter defibrillator; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction.

Baseline fluoroscopy

The prevalence of ECs was 11% CI (7%; 15%) at a mean lead dwell time of 5.1 ± 1.1 years (Table 2). ECs were more common in 8-F than 7-F leads (21% vs. 6%, p < 0.001), but the 8-F leads also had a longer dwell time than 7-F leads (6.4 ± 0.8 vs. 4.5 ± 0.6 years, p < 0.001).

The degree of externalization was significantly correlated to lead dwell time (Figure 7). All but one ECs were localized in the distal and intermediate intracardiac zones. ECs more often included the distal zone 1 below the tricuspid valve annulus in dual coil leads than in single coil leads (69% vs. 16%; p = 0.004). No difference in location was seen between 8-F and 7-F leads, p = 0.17.

The agreement between the fluoroscopic evaluation of ECs by the attending electrophysiologists and the adjudicated fluoroscopic findings was excellent with a Kappa value of 0.88 CI (0.79; 0.97). The clinical diagnostic properties were: sensitivity 90% CI (74%; 98%), specificity 99% CI (96%; 100%), positive predictive value 88% CI (71%; 97%), and negative predictive value 99% CI (97%; 100%). No single projection was 100% sensitive for the detection of ECs.

Lead diameter and number of shock coils were not independent predictors of the hazard of ECs in interval-censored time-to-event analysis, with an adjusted additive hazard for 8-F vs. 7-F = 2% CI (-8%; 11%), and for single vs. dual coil = 0.1% CI (-4.7%; 4.9%).

Table 2 Prevalence of ECs in 13 recalled Riata lead models

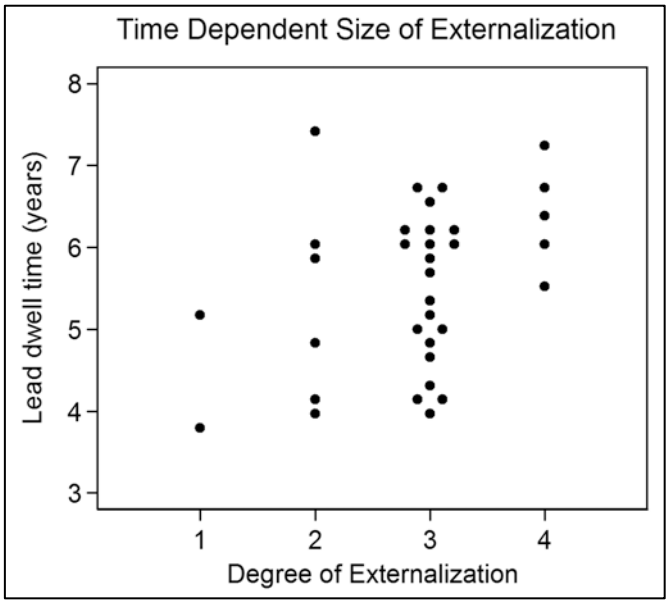
Lead model	Shock coils	N	Dwell time Years	EC (95% CI)
8-F Riata		98	6.4±0.8	21% (14%; 31%)
1570	Dual	11	6.3±0.6	27%
1572	Single	12	7.0±1.1	16%
1580	Dual	25	6.1±0.7	16%
1581	Dual	1	8.1	0%
1582	Single	43	6.3±0.6	28%
1590*	Dual	1	6.9	0%
1591*	Dual	3	6.8±0.0	0%
1592	Single	2	6.8±0.1	0%
7-F Riata ST		200	4.5±0.6	6% (3%; 10%)
7000	Dual	74	4.5±0.6	5%
7001	Dual	38	4.1±0.5	5%
7002*	Single	77	4.7±0.5	4%
7040	Dual	2	4.7±0.3	0%
7042	Single	9	4.6±0.2	22%
All leads		298	5.1±1.1	11% (7%; 15%)

Data are presented as mean ± SD and percentage with 95% confidence interval if appropriate. *Three integrated bipolar lead models with a pair of inactive filler cables to keep design balanced. CI = confidence interval; EC = externalized conductor; F = French; N = number of implanted leads.

Electrical measurements

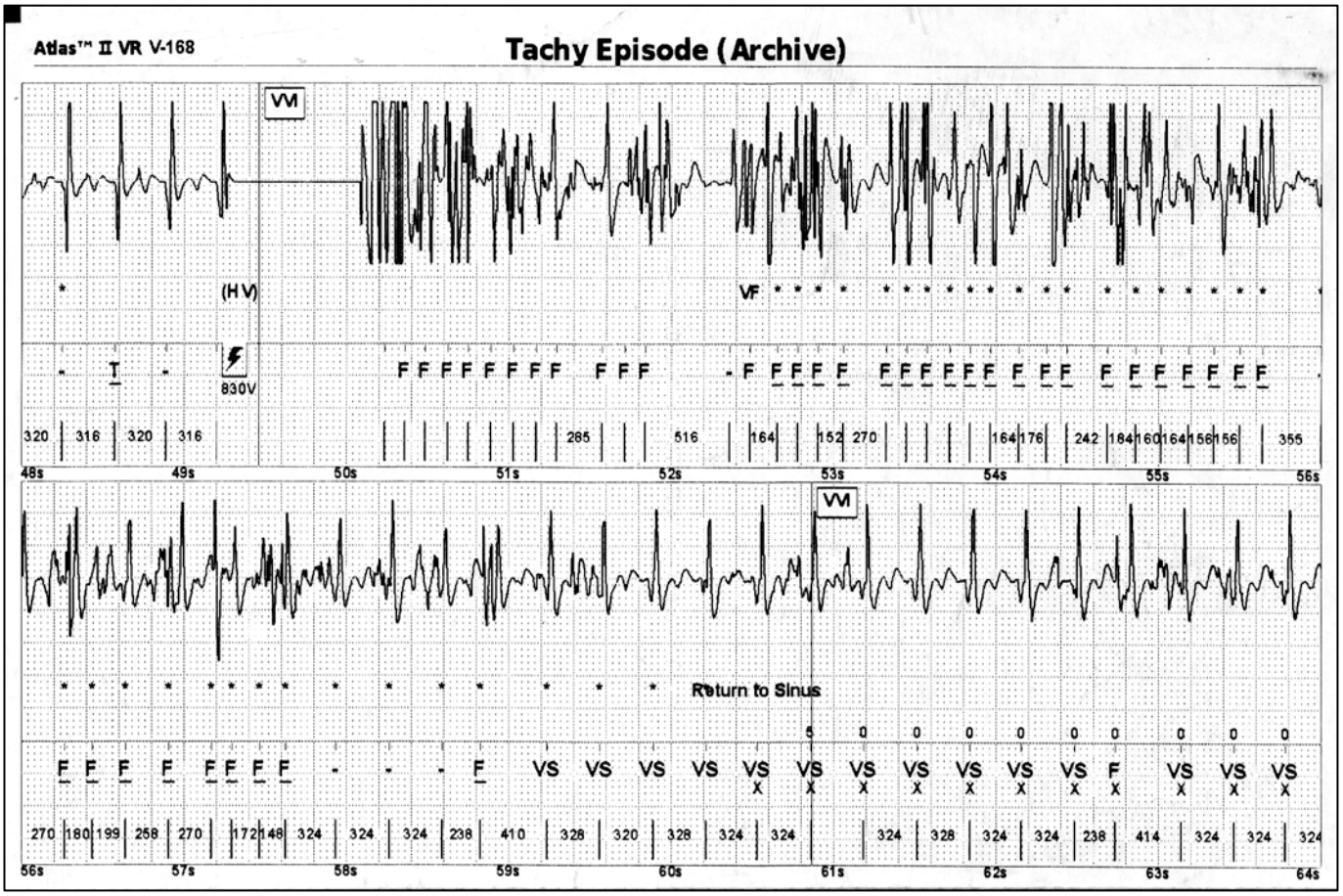
The prevalence of electrical abnormalities was 6% in both patients with and those without ECs. Two patients with ECs had a supplementary lead for pacing and sensing, but no new electrical abnormalities were observed. Three patients without ECs had supplementary leads for pacing and sensing, and 14 patients had one or more new abnormalities at device interrogation in pacing threshold (n = 1), R-wave sensing (n = 7), pacing impedance (n = 4), and non-physiological noise (n = 3). Figure 8 illustrates an example of post-shock noise in an electrogram from a patient with a Riata lead. High voltage lead impedance check was normal in all 117 tested patients, and previous shock impedance was normal in all 88 patients with a history of shock therapy. The only significant electrical difference between patients with and those without ECs was the pacing impedance at implant (568±142 vs. 512±118 Ω, p = 0.02).

Figure 7



Dot plot demonstrating an association between the externalization degree and lead dwell time (n = 34). (1) = localized abnormal conductor spacing without overt EC; (2) = EC <1 cm length; (3) = EC >1 cm length limited to one zone of location; and (4) = EC >1 cm length crossing adjacent zones of location. Spearman's rho = 0.37, *P* = 0.03. EC = externalized conductor.

Figure 8



Near-field electrogram from a patient with a dysfunctional Riata lead demonstrating non-physiological noise revealed seconds after an appropriate shock therapy. The fluoroscopy was without externalization, and device interrogation and electrical measurements were otherwise normal.

Study II

Study population

Four Riata patients were not included in the follow-up study due to severe stroke, terminal illness, emigration, or refusal to participate. The remaining 295 patients constituted the follow-up study cohort. At baseline in 2012, the thirty-four patients with ECs (incl. two borderline ECs) had significantly higher lead dwell time since implant (5.5±1.0 vs. 5.1±1.1, p = 0.02) and higher proportion of 8-F leads (61.8% vs. 29.1%, p < 0.001) compared with patients without ECs. At the time of the second screening in 2013, 25 patients were dead, 23 leads had been abandoned, 15 leads had been extracted, and 232 leads were still active.

Fluoroscopic follow-up

In 239 patients with normal baseline fluoroscopy and repeated fluoroscopy after 1.1 ± 0.2 years, 10 new cases of incident ECs (2 borderline and 8 overt) were confirmed at adjudication resulting in an incidence rate of 3.7 CI (2.0-6.9) per 100 person-years (Table 3), with no significant differences for lead diameter (p = 0.89), number of shock coils (p = 0.33), or dwell time since implant (p = 0.76).

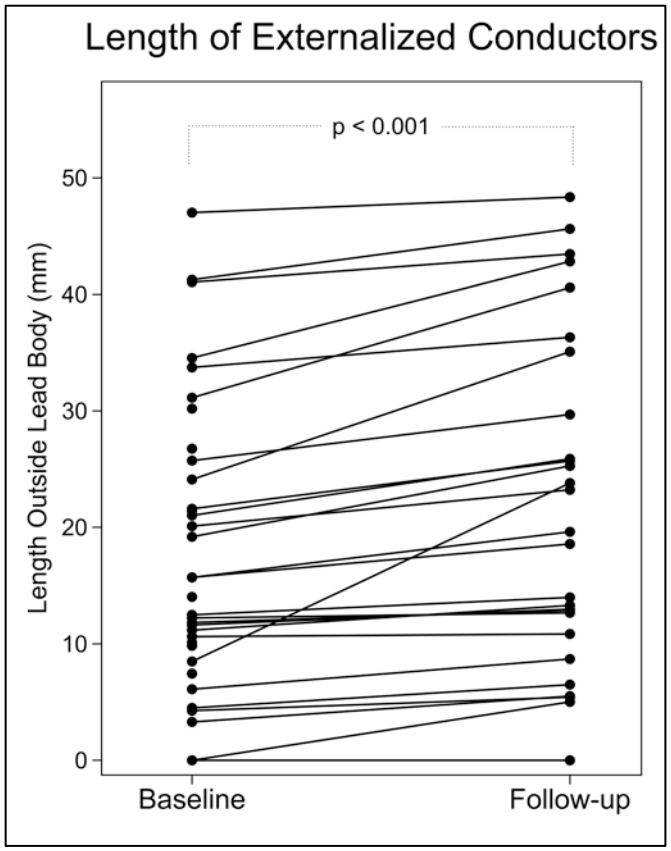
The new ECs were detected in the intracardiac distal (n = 2) and intermediate (n = 8) zones with no differences between single and dual coil leads (p = 1.00). The eight overt ECs had a mean length of 11 ± 3 mm (total range 5-14 mm). Valid measurement of EC length was not possible at follow-up in seven patients with baseline ECs, but the mean length of ECs in the remaining 27 patients with ECs at baseline increased by 4 ± 1 mm (*P* < 0.001) during a mean follow-up of 1.1 ± 0.3 years (Figure 9). An example of changes over time with development of a new EC from baseline to follow-up is depicted in Figure 10.

Table 3 Incidence of ECs in 13 recalled Riata lead models

Lead model	N	Risk time Years	Incident cases	Incidence rate per 100 PY (95% CI)
8-F Riata	67	1.1±0.2	3	4.0 (1.3-12.3)
1570	7	1.2±0.2	0	-
1572	9	1.0±0.4	0	-
1580	18	1.1±0.1	1	-
1581	1	1.2	1	-
1582	27	1.1±0.2	1	-
1590*	1	1.1	0	-
1591*	3	1.2±0.3	0	-
1592	1	1.1	0	-
7-F Riata ST	172	1.1±0.2	7	3.6 (1.7-7.5)
7000	64	1.2±0.3	3	-
7001	33	1.1±0.2	2	-
7002*	67	1.1±0.2	2	-
7040	1	1.0	0	-
7042	7	1.0±0.1	0	-
All	239	1.1±0.2	10	3.7 (2.0-6.9)

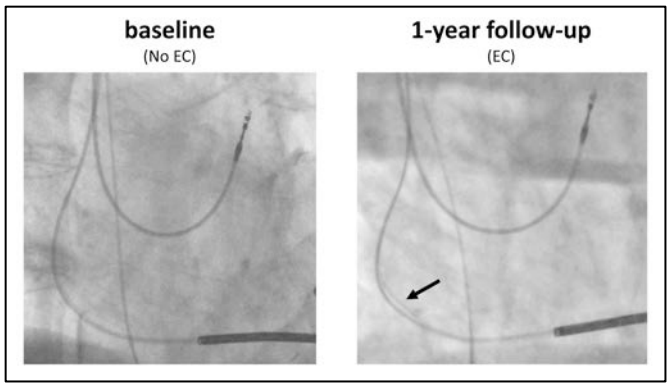
Risk time is presented as mean ± SD. The incidence rate ratio between 8-F vs. 7-F leads was 1.10 CI (0.28-4.24), p = 0.89. *Three integrated bipolar lead models with a pair of inactive filler cables to keep design balanced. CI = confidence interval; EC = externalized conductor; N = number of leads; PY = person-years.

Figure 9



Line and scatter plot illustrating the length outside the lead body of externalized conductors evaluated by fluoroscopy at baseline and follow-up (n = 34). The mean length increased by 4 ± 1 mm during a mean follow-up of 1.1 ± 0.3 years.

Figure 10



Development of a new externalization in a patient with a single coil Riata lead from baseline to follow-up one year later. EC = externalized conductor.

Electrical follow-up

In total, 20 incident electrical abnormalities were found (12 at lead discontinuations, 0 at death, and 8 at final interrogation) among 276 patients with normal baseline electrical function followed for 1.0 ± 0.3 years, resulting in an incidence rate of 7.1 CI (4.6; 11.0) per 100 person-years. This rate was higher with baseline EC, giving an incidence rate ratio of 4.4 CI (1.7; 11.5), p = 0.002, adjusted for differences in lead diameter (Table 4). Noise and impedance abnormalities were most common findings (Figure 11).

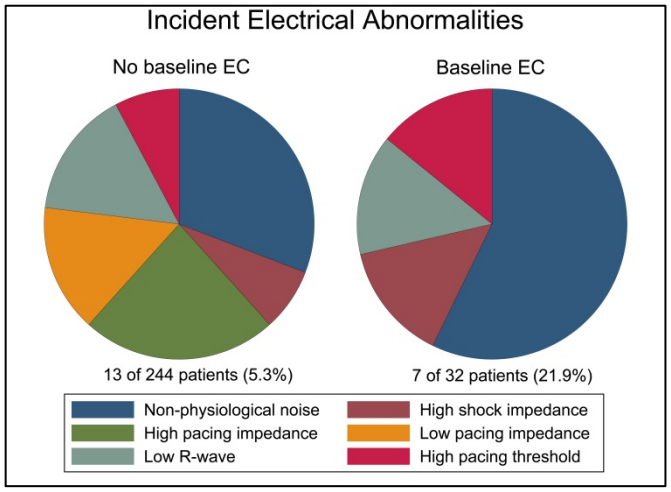
Lead extraction outcomes

Thirty-eight leads were discontinued with 15 extractions and 23 abandonments. Reasons for discontinuation were electrical abnormality at baseline (n = 6), incident electrical abnormality during follow-up (n = 12), and prophylactic replacements (n = 20) of which 12 were performed at elective generator replacement. Lead extraction compared with lead abandonment was more frequent in younger patients (57.6 ± 14.5 vs 69 ± 7.5 years, p = 0.01). All leads were removed in toto with powered tools with one minor complication (a large pocket hematoma postponing discharge) and two major complications (a stroke due to paradoxical thromboembolism, and a right ventricular wall tear with cardiac tamponade with successful thoracotomy but post-operative death nine days later due to respiratory failure).

Prevalent findings in active leads at the 2013 screening

The prevalence of ECs in the 232 active leads was 11.2% CI (7.5-16.0) at a lead dwell time of 6.2 ± 1.0 years. The prevalence of ECs was higher in 8-F leads (18.6% vs 8.0%, p = 0.02) with longer dwell time (7.5 ± 0.7 years vs 5.7 ± 0.6 years, p < 0.001). The prevalence of electrical abnormalities was 6.5% CI (3.7-10.4). Prevalent electrical abnormalities were more common with prevalent ECs (19.2% vs 4.9%, p = 0.02), mainly driven by a higher proportion of supplementary pace-sense leads implanted in patients with ECs due to electrical abnormalities before the lead advisory.

Figure 11



Pie charts with incident electrical abnormalities during follow-up in patients with and those without baseline externalized conductors (n = 276). In case of several abnormalities in a patient, only the first on a prioritized list was depicted: lead noise, shock impedance abnormality, pacing impedance abnormality, poor R-wave sensing, and elevated pacing threshold. EC = externalized conductor.

Table 4 Predictors of incident electrical abnormalities

	Univariable					**Multivariable**	
	Yes IR/100 PY (95% CI)	**No** IR/100 PY (95% CI)	**IRR** (95% CI)	**p-value**		**Adjusted IRR** (95% CI)	**p-value**
EC	27.4 (13.1-57.5)	5.1 (2.9-8.7)	5.4 (2.2-13.6)	<0.001		4.4 (1.7-11.5)	0.002
8-F lead	12.1 (6.7-21.8)	4.7 (2.5-9.1)	2.6 (1.1-6.2)	0.04		1.9 (0.8-4.8)	0.16
Dwell time ≥ 6 years	9.9 (4.4-22.0)	6.3 (3.7-10.7)	1.6 (0.6-4.0)	0.36		-	-
Dual coil	8.5 (5.0-14.7)	5.4 (2.6-11.3)	1.6 (0.6-4.0)	0.33		-	-

Potential covariates for the multivariable analysis were pre-specified in a prioritized list, but due to few events, the association between externalized conductors and electrical abnormalities was only adjusted for lead diameter. Lead dwell time from implant to baseline was strongly correlated with lead diameter, spearman's rho 0.79 ($P < 0.001$). EC = externalized conductor; IR= incidence rate; IRR = incidence rate ratio; PY = person-years. N = 276.

Study III

Study populations

Riata patients were excluded from analyses if they had a previous class I lead advisory, no matched controls, no response to baseline questionnaires, or insufficient data quality (<70% reported items in all questionnaires). PROs were completed in 86% (256/299) of the patients at baseline and 70% (210/299) at follow-up. Most patients were screened within three months from identification in the Registry. Included Riata patients were not significantly different in terms of age, sex, ICD indication, and ischemic heart disease compared with the non-included Riata patients, and follow-up responders were not significantly different from the surviving non-responders in terms of age, sex, ICD indication, ischemic heart disease, and all baseline PROs.

At baseline, the included Riata patients were slightly older (67.8±10.9 vs 67.5±10.9 years, p = 0.04) despite age-group matching, had an ICD implanted for a longer period of time (5.7±2.2 vs. 1.0±0.1 years, p < 0.001), and were less likely to have Type D personality (9.3% vs. 18.2%, p < 0.001) as compared with the controls.

Acute impact of the Riata advisory on PROs

Baseline PROs are presented in Table 5. The mean scores for device acceptance (FPAS-12) were relatively high and for device-related concerns (ICDC-8) relatively low in both groups. However, Riata patients had significantly impaired crude and adjusted estimates for device acceptance and device-related concerns compared with non-advisory controls, although adjusted Cohen's effect sizes were small. No differences were seen for depressive symptoms (PHQ-9). There were no significant differences in PROs between ICD centers. The 27 Riata patients with baseline ECs reported worse crude mean scores for all PROs except for depressive symptoms compared with the 229 Riata patients with normal fluoroscopy, but none of these differences were statistically significant (Figure 12).

Female sex was the only significant univariable and multivariable predictor of a high impact of the advisory notification on general well-being with an unadjusted odds ratio = 2.34 CI (1.12; 4.89) and adjusted odds ratio = 2.23 (1.05; 4.74), p = 0.04.

Our study design introduced a difference in time since first ICD implant with no group overlap, but a sensitivity analysis within the Riata cohort revealed no significant associations between time since implant and device acceptance (β = 0.05, p = 0.91), device-related concerns (β = -0.25, p = 0.17), and depressive symptoms (β = 0.09, p = 0.49).

Changes over time in PROs within the Riata cohort

Changes in PROs from baseline to 1-year follow-up are presented in Table 6. Only very small significant improvements were seen in crude and adjusted mean device-related concerns. The estimated Cohen's effect sizes for mean changes over time for other measures were close to zero.

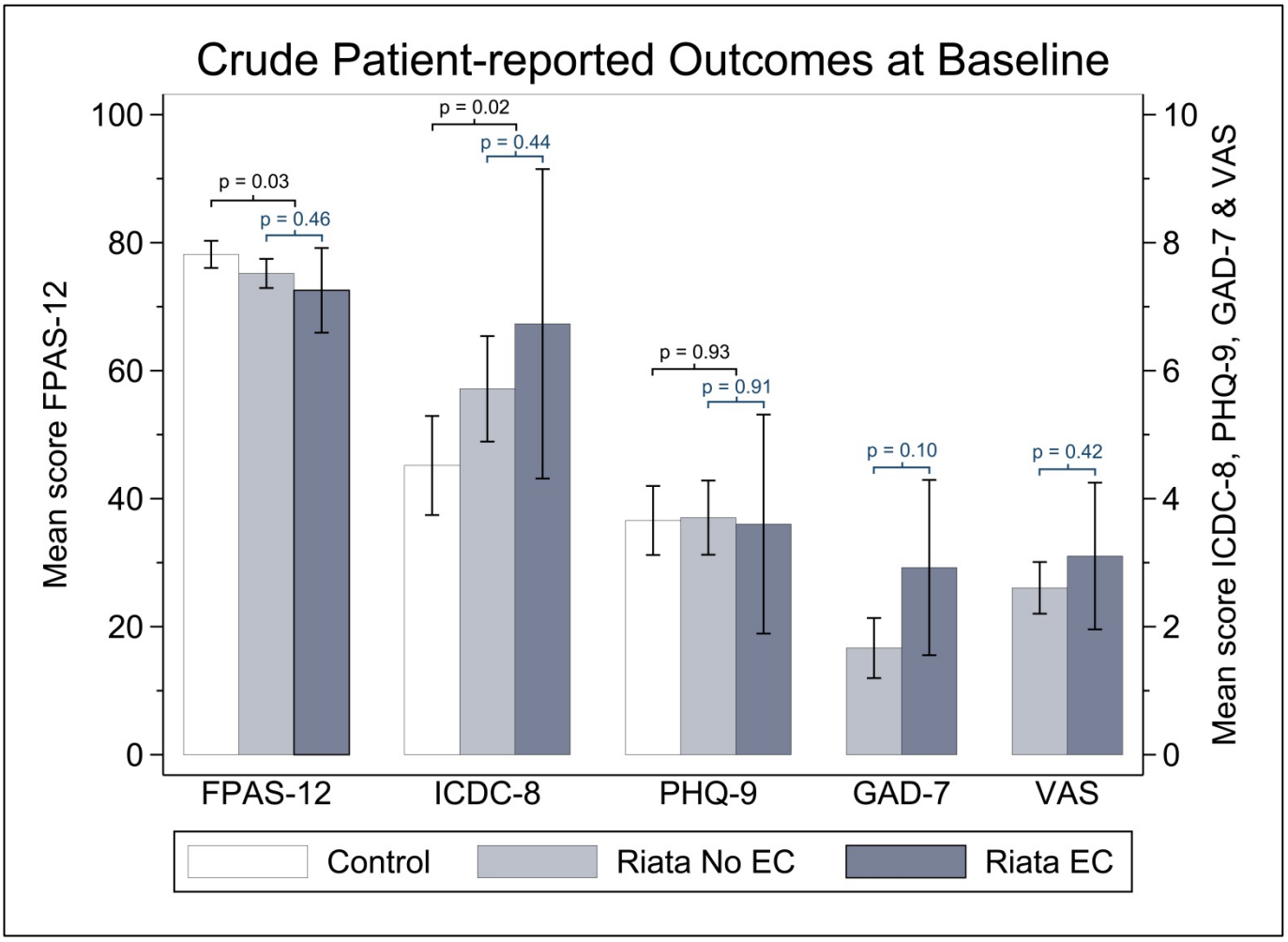
Twenty-eight patients underwent lead replacement with only 19 responders completing follow-up questionnaires. They were heterogeneous with 11 abandonments and 8 extractions, and reasons were 8 electrical failures and 11 prophylactic indications. At follow-up, patients who had underwent lead replacement reported borderline significantly lower symptoms of anxiety (adjusted GAD-7 change = -1.2, Cohen's *d* = -0.26, p = 0.05). No significant differences were seen for the other PROs.

Table 5 Baseline patient-reported outcomes in Riata patients versus matched controls

	N	Crude estimates				Adjusted estimates*		
		Riata advisory (95% CI)	**Matched controls** (95% CI)	**Difference** (95% CI)		**Difference** (95% CI)	**Cohen's *d***	**p-value**
Device acceptance (FPAS-12)	498	74.9 (72.8; 77.1)	78.2 (76.1; 80.3)	-3.3 (-6.2; -0.3)		-4.8 (-7.6; -2.0)	-0.28	0.001
Device-related concerns (ICDC-8)	504	5.8 (5.0; 6.6)	4.5 (3.7; 5.3)	1.3 (0.2; 2.4)		2.0 (1.0; 3.0)	0.29	<0.001
Depressive symptoms (PHQ-9)	494	3.7 (3.1; 4.2)	3.7 (3.1; 4.2)	0.0 (-0.7; 0.8)		0.6 (-0.2; 1.3)	0.13	0.13
Anxiety symptoms (GAD-7)	248	1.8 (1.4; 2.3)	-	-		-	-	-
Impact on well-being (VAS)	245	2.7 (2.3; 3.0)	-	-		-	-	-

Estimates are displayed as means with 95% confidence intervals. *The estimates are adjusted for age, ischemic heart disease, cardiac resynchronization therapy, self-reported other chronic diseases, shock therapy within one year (appropriate and inappropriate), high school, higher education, Type D personality, and ICD center. CI = confidence interval; GAD-7 = Generalized Anxiety Disorder questionnaire; FPAS-12 = Florida Patient Acceptance Survey; ICDC-8 = ICD patient Concerns questionnaire; PHQ-9 = Patient Health Questionnaire; VAS = Visual Analog Scale (impact of lead advisory on general well-being).

Figure 12



Bar chart representing crude mean-scores with error bars indicating 95% confidence intervals for the five patient-reported outcomes on patients' well-being and psychological functioning. The left y-axis refers to Florida Patient Acceptance Survey (FPAS-12), and the right y-axis refers to ICD patient Concerns questionnaire (ICDC-8), Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder questionnaire (GAD-7), and impact on general well-being on a visual analog scale from 0 to 10 (VAS).

Table 6 Changes in patient-reported outcomes in Riata patients after 1-year follow-up

	N	Crude estimates				Adjusted estimates*		
		Baseline (95% CI)	**Follow-up** (95% CI)	**Difference** (95% CI)		**Difference** (95% CI)	**Cohen's *d***	**p-value**
Device acceptance (FPAS-12)	197	75.9 (73.6; 78.3)	75.3 (72.9; 77.6)	-0.7 (-3.0; 1.6)		0.1 (-2.3; 2.6)	0.01	0.91
Device-related concerns (ICDC-8)	205	5.9 (5.0; 6.8)	5.2 (4.3; 6.1)	-0.7 (-1.3; 0.0)		-1.1 (-1.8; -0.4)	-0.17	0.002
Depressive symptoms (PHQ-9)	198	3.3 (2.7; 3.9)	3.6 (3.0; 4.2)	0.3 (-0.1; 0.7)		-0.05 (-0.5; 0.4)	-0.01	0.83
Anxiety symptoms (GAD-7)	206	1.9 (1.4; 2.4)	2.0 (1.6; 2.5)	0.1 (-0.2; 0.5)		0.1 (-0.4; 0.5)	0.01	0.79
Impact on well-being (VAS)	196	2.6 (2.2; 3.1)	2.7 (2.3; 3.1)	0.1 (-0.3; 0.5)		-0.1 (-0.5; 0.4)	-0.01	0.76

Discussion

In 2011, St. Jude Medical issued a class I advisory notification for the Riata defibrillator lead family due to an unexpected high rate of insulation failures including inside-out ECs seen by fluoroscopy.[3] Initially, not much was known about the failure mechanism of Riata leads. In the past 2½ years, the device-community has risen to the challenge with a high research activity, trying to uncover the natural history of these recalled troublesome leads. Much has been learned with contribution from the studies in this thesis, but many questions remain unanswered.

The main findings of the three studies were as follows: In the cross-sectional screening in ***Study I***, the prevalence of ECs was 11% and significantly higher in 8-F compared with 7-F leads, but 8-F leads also had a significantly longer dwell time since implant, and no significant difference was seen in the hazard of ECs when accounting for this time difference; the location of ECs was mainly intracardiac and differed significantly between single coil leads and dual coil leads; lead dwell time was significantly correlated to the degree of externalization; no association was observed between ECs and electrical abnormalities; and the fluoroscopic diagnostic performance for ECs was good. In the longitudinal follow-up in ***Study II***, the nature of ECs was dynamic with development of new ECs and progression in size of existing ECs over time; the overall incidence rate of electrical abnormalities was high and 4.4-fold higher in leads with baseline ECs. In the cross-sectional comparison and longitudinal follow-up in ***Study III*****,** patients in the Riata cohort reported a statistically significantly lower level of device acceptance (FPAS-12) and a higher level of device-related concerns (ICDC-8) as compared with matched non-advisory controls, although the effect sizes were small; female sex was a significant independent predictor of an acute high impact of the advisory on general well-being; and there was only a minimal but significant reduction in device-related concerns over time.

Prevalence, incidence rate, and risk of survivor bias

The occurrence of a condition can be described using prevalence and incidence rate. The prevalence is a cross-sectional picture of the proportion of the condition at a specific point in time. It is therefore influenced by the incidence rate and duration of the condition.[61] The prevalence of a condition in two groups can therefore be the same despite very different incidence rates and durations. In lead failure, patients with the most severe outcome would either die or have their lead changed before enrollment for a cross-sectional screening. Analyzing associations with lead failure using prevalence as outcome should therefore always be interpreted with extreme caution due to the risk of selection bias, in this case also called incidence-prevalence bias or survivor bias. Longitudinal prospective designs are not prone to this special kind of selection bias and are therefore always preferred in the analysis of associations of covariates with a given condition. This very important difference between prevalence and incidence should be kept in mind when interpreting differences in the findings of Study I and II.

Prevalence, incidence, and dynamic nature of ECs (Study I & II)

In 2008, the first case report with ECs was described by Duray *et al* in an 8-F lead with noise oversensing and inappropriate shock therapy.[62] Several case reports followed with ECs detected by fluoroscopy due to concurrent electrical abnormalities.[63-66] The first two retrospective lead performance studies without systematic fluoroscopy identified a prevalence of insulation damage of 0.2% (mean follow-up 18 months)[67] and prevalence of ECs of 1.6% (mean follow-up 42 months),[48] respectively. In December 2010, St. Jude Medical made their first "Dear Doctor letter" about the Riata leads.[68] In this letter, they stressed that the 8-F and 7-F Riata silicone leads were prone to outside-in abrasion failures, and about 10% of reported insulation abrasions were unique inside-out with visible ECs. The company's response to the observed insulation failures was that they stopped selling these leads with effect from 31 December 2010, and they recommended follow-up according to standard best practice. The reason for not intensifying monitoring was that outside-in abrasions were mainly observed in the early life of the defibrillator leads within 27 months from implant, and about 90% of the leads in clinical practice had been implanted for more than 27 months. The data from the first prospective systematic fluoroscopic screening in Northern Ireland were presented by Kodoth *et al* at the European Society of Cardiology conference in fall 2011, showing an alarmingly high 15% prevalence of ECs with a mean dwell time of 48 months, and most leads had normal electrical function despite the fluoroscopic lead status.[43] In November 2011, more than three years after the first case report, the class I Riata lead advisory notification was voluntarily issued by St. Jude Medical with a second "Dear Doctor letter", in which they referred to the high 15% prevalence of ECs in the Northern Irish study but stressed that ECs were only seen in 0.1% of leads undergoing returned product analysis.[3] The low occurrence of ECs in the early studies without systematic fluoroscopic screenings is readily explained by short-term follow-up and by the electrically silent nature of most ECs. The underreporting compared with the systematic fluoroscopic screening highlights the limitation of the insensitive current post-marketing surveillance mainly based on voluntary return product analysis and voluntary reporting to the FDA's Manufacturer and User Facility Device Experience (MAUDE) registry, which was also pointed out by Dr. Hauser in an editorial published shortly after the advisory notification.[69]

The largest multicenter study to date with systematic screening of 1029 Riata leads from the Netherlands reported a 14.3% EC prevalence at a median dwell time of 63 months.[46] This is very close to the finding in Study I that provided an EC prevalence of 11% with a median dwell time of 59 months (Table 2). In other prospective studies, the reported baseline EC prevalence varies from 11.5% to 27% in systematic fluoroscopic or x-ray screenings, generally with a higher prevalence in 8-F leads that also have a longer dwell time due to an earlier market introduction.[70-78] Some of the differences between these cross-sectional studies may be explained by difference in study participation rate, lead dwell time,

use of supplementary leads in case of electrical abnormalities, implanting technique, included lead sub-models, and statistical uncertainty. The prevalence of ECs in the five largest multicenter studies including Study I was 11-22% and 21-33% for 7-F and 8-F leads, respectively.[46, 70, 73, 75] The reason that our baseline prevalence of ECs was in the lower end of the reported range may be a high proportion of 7-F leads and the unselected properties of the nationwide cohort. The difference between 8-F leads and 7-F leads has been suggested to be explained by design improvements in 7-F leads by which the conductors are closer to the lead center and therefore less exposed to shear stress,[75] but longer dwell time in 8-F leads may also play an important part. For further discussion see section on predictors of ECs below.

The dynamics in the evolution of ECs are difficult to examine in cross-sectional designs, as most ECs are electrically silent, making the time of development of a visible EC extremely interval censored between implant and screening, typically more than 5 years later. The aforementioned cross-sectional studies with systematic screenings therefore cannot be used to determine whether an EC is a stationary or a dynamic finding beyond the first couple of years after implant. However, observations of higher EC prevalence[46, 73, 79] and larger EC size[79] with increasing lead dwell time in these studies do render a dynamic nature of ECs probable as we observed in Study I (Figure 7). The longitudinal data of Study II confirm this plausible dynamic progressive nature of ECs by showing that the size of existing ECs increased over time (Figure 9), and that new incident ECs developed despite long dwell time since implant with an incidence rate of 3.7 per 100 person-years (Table 3). The longitudinal data from the study with repeated fluoroscopy by Demirel *et al* demonstrated a higher incidence rate of 6.7 per 100 person years,[78] but this difference can readily be explained by statistical uncertainty. They also found a mean progression in the size of baseline ECs of 4 mm at their 1-year follow-up, similar to our findings.

Location of ECs (Study I & II)

In the advisory notification letter, the location of ECs was described to occur most commonly at the intracardiac level of the leads.[3] This has been confirmed in several studies, including Study I and II. We found one EC at the level of the superior vena cava and the remaining in the intracardiac location. In Study I, we observed that ECs were significantly more common in the most distal part of dual coil compared with single coil leads. This was not a prespecified hypothesis, and the finding was not confirmed by the longitudinal data in Study II. However, this should be interpreted with caution due to few incident ECs with limited statistical power. A possible explanation for the observed difference between single and dual coil leads could be a stabilizing effect at the level of the superior vena cava or right atrium in dual coil leads of the proximal coil.

Predictors of the development of ECs (Study I & II)

Predictors of ECs have been examined in several studies. Suggested multivariable independent predictors using either logistic or Cox regressions are longer time since implant,[72, 76] multiple leads,[72, 77] non-ischemic cardiomyopathy,[77, 78] 8-F lead diameter,[76] female sex,[78] lower left ventricular ejection fraction[78], higher left ventricular ejection fraction,[80] and decrease in R-wave sensing since implant.[80] However, these analyses have several limitations: (i) use of data-driven selection of variables for the multivariable analyses; (ii) they rely on cross-sectional data with prevalent ECs with inherent risk of survivor bias; (iii) they assume the time of development of ECs to be at the fluoroscopic screening despite the true extreme interval censored nature between implant and screening; and (iv) some, but not all, studies used unstable multivariable models with too many covariates included, resulting in unreliable estimates with extremely wide CIs. The use of data-driven variable selection may be a key explanation to differences in identified independent predictors between studies as chance rather than theoretical plausibility drives the selection of covariates. The limitation of data-driven variable selection is clearly demonstrated by its tendency to identify significant predictors even in completely random computer-generated data.[57]

In Study I, we tried to address some of these challenges by an explorative analysis including only the two first potential predictors on a prespecified prioritized list using an interval censored additive hazard regression. This showed that neither lead diameter nor number of shock coils were significant predictors of ECs, but with very wide confidence intervals for the estimated additive hazards. This indicated that the present data set did not hold sufficient information to answer the tested null hypothesis with acceptable certainty due to a combination of extreme interval censoring, few events and only a small overlap in the ranges of dwell times since implant between 8-F and 7-F leads. Another approach to deal with the extreme interval censoring is simple stratification on lead dwell time as done in the Multicenter Riata Lead Evaluation Study, initiated by St. Jude Medical, by Hayes *et al* including 776 patients with almost five times as many events as in our Study I.[75] They demonstrated a relatively strong univariable association between 8-F and ECs in the lower stratum with dwell time ≤6 years, and the groups did not differ significantly on other non-specified covariates. In Study II, 8-F was not a significant univariable predictor of incident ECs, but this neutral finding should be interpreted with caution due to low event count with limited statistical power. Thus, the association between 8-F and ECs still remains to be confirmed in a prospective longitudinal follow-up, but this may be very difficult as the mere suspicion that 8-F lead design may be a risk factor for ECs may result in selection bias due to differential loss to follow-up as a result of prophylactic lead replacement. A more active attitude toward lead replacement may also radically reduce the number of leads with new incident ECs as uncertain borderline subtle visible fluoroscopic abnormalities may result in replacement before true ECs develop. Given the current evidence, considering 8-F *per se* as high risk leads to guide follow-up and lead management, as suggested in the 2012 German guidelines for Riata lead management, may be inappropriate. [81]

Electrical abnormalities and association with ECs in cross-sectional and longitudinal studies (Study I & II)

The defibrillator lead is the weakest link in the ICD system, and insulation defects are the most common reason for failure.[21] The definition of lead failure is used with little consensus in the general literature on defibrillator lead performance, which makes comparisons between studies challenging.[24] In studies on Riata lead electrical performance, including Study I and II, the applied definitions of lead failure vary, but most include non-physiological noise, impedance abnormalities, and high pacing threshold, and some also poor

R-wave sensing. However, exact criteria for electrical abnormalities in the studies differ. This contributes to the overall between-study differences in reported prevalence and incidence rate. However, the reported relative differences between sub-groups, such as patients with and those without ECs, should be affected to a less extent by differences in criteria for electrical abnormalities as long as the same objective criteria apply to the tested subgroups within the studies.

The electrical performance of recalled Riata leads has been described in several longitudinal studies. Early studies with short mean lead dwell times of less than two years show relatively low incidence rates of electrical lead failure <0.5% per year.[67, 82, 83] More recent studies with longer dwell times of between 3 and 5 years demonstrate higher electrical failure rates ranging from 0.5% to 2.7% per year.[48-50, 84-91] In one study, an acceleration over time in lead failure rate was described and was predicted past 4 years to be 5.2% per year.[90] This is very close to the overall incidence rate of electrical abnormalities of 7.1 per 100 person-years described in Study II, with only a weak trend for 8-F diameter being an independent predictor (adjusted incidence rate ratio 1.9, p = 0.16). Several of the studies have found a higher failure rate in 8-F leads,[48, 50, 87, 90, 91] whereas others show higher failure rate in 7-F leads,[49, 78] and one is neutral[88]. Compared with well performing benchmark leads, the recalled Riata leads have higher electrical failure rates.[49, 50, 84, 86, 89, 90] Compared with recalled Sprint Fidelis leads, the results are less clear: some demonstrate higher failure rates in Sprint Fidelis leads,[49, 86] and others are neutral.[50, 84, 88]

The clinical impact of ECs on the electrical lead function is not straightforward as most leads with ECs appear to be electrically well functioning. Studies with return product analysis of selected electrically failed leads have demonstrated a causal failure mechanism of ECs with erosion of the ethylene-tetrafluoroethylene insulation outside the protective silicone body.[90, 92] Erosion due to a similar inside-out movement of conductors can also occur beneath shock coils not visible by fluoroscopy, but insulation failure is also seen due to outside-in abrasion, especially in the low-cycle high-stress milieu of the shoulder-near pocket area.[92] The cross-sectional design has been used in several studies to investigate the association between ECs and electrical abnormalities. This is, as mentioned, a weak design to detect valid associations with dynamic events like incident electrical abnormalities, as patients with events tend to be treated for their problem and lost before enrollment (survivor bias). This was the reason for our cautious interpretation of the observed neutral association between ECs and electrical abnormalities in the baseline screening in Study I. We considered the significant finding of an unexplained 56 Ω higher pacing impedance in patients with ECs at implant a possible random finding (type 1 error) due to multiple testing. In retrospect, an alternative plausible explanation could be that leads with ECs have been implanted in a way that increases intracardiac shear stress on the conductor cables. This will also stress the lead-endocardial interphase, which is known to increase pacing impedance.[93] Significant associations between prevalent ECs and electrical abnormalities have been reported in other studies: a higher proportion of prevalent electrical abnormalities (10.9% vs 3.5%, p < 0.001);[46] a larger decrease in R-wave amplitude from implant to screening;[73, 80] and marginally higher pacing thresholds.[76] Several retrospective studies with selective fluoroscopies and x-rays have suggested a possible association between ECs and electrical function.[79, 89, 90]

The longitudinal prospective design in Study II is a more powerful tool to investigate the possible association between ECs and electrical abnormalities, as it is less prone to selection bias if only few patients are lost to follow-up. Our findings of a strong association therefore support a potentially true connection between ECs and electrical abnormality, with an adjusted incidence rate ratio of 4.4 (Table 4). However, the confidence interval was relatively wide, from 1.7 to 11.5. Furthermore, we do not have return product analysis from the leads with electrical abnormalities as most leads were not extracted, and we therefore cannot verify causality between ECs and the observed electrical abnormalities. Perhaps ECs may only be a marker for a potentially failing "stressed" lead in accordance with the above described higher pacing impedance at implant. The other longitudinal prospective study to investigate this association is the Multicenter Riata Lead Evaluation Study.[75] They report on their preliminary results with only 10 electrical failures in 776 patients within a mean follow-up of about 10 months, with no significant difference between patients with and those without ECs (2.0% vs 1.1%, p = 0.4). Analysis of data that have more events from longer follow-up including information on reasons for loss to follow-up in this large cohort is awaited. Their reported overall cumulated incidence of electrical abnormalities was much lower than in Study II and the majority of longitudinal studies with shorter lead dwell times as mentioned above. A small longitudinal study with externalized Riata leads showed an incidence rate of electrical abnormalities of 6.4 per 100 person-years, but this estimate is very uncertain as the study only included two events in 52 patients.[94] Additional explanations for the higher rate in Study II may be the unselected nationwide cohort, few patients lost to follow-up, differences in the applied definitions of electrical abnormalities/failures, but also possible differences in lead sub-models. In Study II, only three patients with ECs had a lead model with integrated bipolar sensing with a pair of passive filler cables, so the chance that the observed externalized cables were electrically active was above 95%. In most other studies, including the Multicenter Riata Lead Evaluation Study, sub-models are not reported, and we therefore do not know the exact chance of a visible EC to be electrically active.

The loss to follow-up or censoring in time-to-event analyses is extremely important when analyzing the association between ECs and electrical abnormalities. Knowledge on fluoroscopic status of the leads may result in bias toward the null hypothesis if differential lead replacements are performed more often in leads with ECs before subtle sub-clinical electrical abnormalities are classified as true abnormalities. In the longitudinal fluoroscopic study by Demirel *et al*, 96% (25/26) with ECs and only 18% (26/144) without ECs had their leads replaced prophylactically within the first year of follow-up.[78] Thus, they wisely refrained from making any longitudinal time-to-event analysis on electrical abnormalities as this would certainly have been invalid. Only time will tell if the findings in Study II will be confirmed in other studies with a similar low loss to follow-up, low degree of censoring, and relatively low rate of differential prophylactical lead replacements. It is notoriously difficult to investigate the true natural history of a lead malfunction as soon as the advisory has been notified. This has recently been demonstrated by Liu *et al* for recalled Sprint Fidelis leads with a decrease in failure rate over time, with a plateauing of the electrical event-free survival curves due to prophylactical replacement in the first years after the advisory notification.[28]

The observed electrical abnormalities in Study II are typical for structural lead failure with non-physiological noise and impedance abnormalities dominating in numbers both for patients with and those without ECs (Figure 11). Similarly, non-physiological noise was described as the most common electrical abnormality seen in one of the largest studies with follow-up of Riata leads without known fluoroscopic status.[49] However, looking through the Riata literature, it is striking that pace-sense abnormalities are much more common than high voltage abnormalities, as from a design point of view, the low-voltage and high-voltage conductors should carry a more even risk in case of insulation defects. The most obvious explanation is that we do not have the right monitoring tools to validly detect small, but important insulation failures in the high voltage circuits. The first presentation of high voltage lead failures can be fatal or near fatal due to short circuits as described in reports from the MAUDE registry.[92, 95] Several case reports have demonstrated that low-voltage testing of shock impedance can be completely normal despite insulation failures in Riata leads with and without ECs only detected by failed high voltage shocks due to short circuits.[96-98] In Study I, one patient demonstrated electrical abnormality with non-physiological noise only in relation to a high voltage shock, with all other measurements normal at the following interrogation (Figure 8). In Study I and II, no patients underwent high voltage shock testing, and only about half the patients had a low-voltage test of shock impedance of limited value. Systematic high voltage testing in patients with Riata leads has been performed in one study, in collaboration with St. Jude Medical, presented only as an abstract at the Heart Rhythm Society Congress in 2013.[99] Out of 289 patients with 36 cases of ECs, only 115 patients underwent high voltage max output testing, and one patient with ECs had a failed shock due to low shock impedance <10 Ω. However, the number of tested patients with ECs was not reported, so we do not know the prevalence of high voltage failures in patients with ECs from this study. Even a normal high voltage test may not be enough as a case with shock testing in a Riata patient demonstrated three successful shocks, but the fourth failed due to short circuit with low shock impedance.[100] In Study II, we only found a detailed description of reasons for death in medical records for about half the patients, and no systematic postmortem device-interrogation had been performed. We can only speculate if a number of fatal electrical failures are hiding among these unknowns. An independent study with systematic, synchronized high voltage shock testing without induction of ventricular arrhythmias is warranted. This should include Riata leads with and without ECs, but also other lead models from other manufacturers as the knowledge on high voltage performance of defibrillator leads implanted for more than 5 years is sparse. To make such a study feasible, it could be performed in relation to elective generator replacement.

Lead replacement in patients living under the Riata lead advisory (Study II)

Two high-volume singlecenter studies have demonstrated high extraction success rates for recalled Riata leads with relatively short dwell times.[101, 102] In one of these studies, no difference in complication rate was observed compared with extractions of the recalled Medtronic Sprint Fidelis leads (10.6% vs 5.5%),[102] but this neutral finding is limited by a low statistical power. The possibly more difficult extractions in Riata leads may be explained by no coating of the shock coils in the older 8-F leads and the disintegration of the lead body with ECs that can be worsened by pulling forces during extraction with snowplowing at the tip of the extraction catheter. In high volume extraction centers, the recalled Sprint Fidelis leads have very good extraction outcomes with 100% success and low risk of complications, probably because these leads are all with coated shock coils and without disintegration of the lead body.[103] A recent multicenter study showed 1.4% major complications in 295 patients with Riata lead extraction, and in patients with ECs, laser sheaths were employed significantly more often.[104] We do not know whether these relatively favorable results from high volume centers apply to smaller centers, and as ECs can make the procedure more complex, it may be wise to leave the extraction of these leads to experienced extractors. In Study II, the observed one minor and two major complications in only fifteen leads could be due to chance but should be a used as a reminder that lead extraction is not without risk. One of these complications was a stroke with paradoxical thromboembolism through a persistent oval foramen,[105] which may be directly linked to ECs, as it is suspected to be a predilection site of thrombus formation.[106] However, lead-related thrombi can be seen in all types of intravascular leads.[107] If the hypothesis of ECs being thrombogenic should be substantiated, a systematic controlled study is needed with transesophageal or intracardiac echocardiography in Riata patients with and without ECs. This could be done in patients undergoing elective lead replacement.

The progressive nature of ECs with increasing size over time and a strong association with new electrical abnormalities in Study II emphasizes that lead replacement should be considered in high-risk patients and patients with long life expectancy, especially if a golden moment of opportunity arises as in elective generator replacement due to battery depletion or system up-grade. This was the strategy employed in the Danish Riata cohort. In 2012, we made a Danish national guideline for the management of the Riata leads based on the data from our own and other studies (Appendix IV). The risk associated with lead extraction is not zero, and an individualized approach weighing risk and benefits should guide the decision, always in respect of the wishes of a thoroughly informed patient.[35] We have to remember the lesson learned from the Teletronics Accufix atrial lead advisory, in which the risk at lead extraction was higher than the risk posed by the recalled lead failure itself.[108] However, since then, extraction tools and experience have vastly improved. The American Heart Rhythm Society and the European Heart Rhythm Association have published position papers on transveneous lead extraction emphasizing the need for well-equipped and well-trained high-volume lead extraction teams with immediate access to thoracic surgeon assistance to avoid unnecessary risks for the patients.[35, 109]

ECs in non-recalled leads - new “icebergs” on the move?

The design of the recalled 8-F and 7-F Riata leads has been improved in its two St. Jude Medical successors, the 7-F Riata ST Optim and the 7-F Durata leads, most importantly by adding a resilient extra outer jacket of Optim, a copolymer of silicone and polyurethane 50 times stronger than silicone. Only a single case of EC has been reported in a Riata Optim lead just above the proximal coil where the lead, in contrast to the Durata design, is not covered by Optim insulation.[110] No ECs have been detected in systematic[111]

or selective[112] screenings of the Optim coated leads. The design improvements with Optim will theoretically reduce the risk and rate of development of ECs, which is also supported by bench testing, demonstrating that differential pulling in the lead components will be reduced due to the increased stiffness of the outer Optim co-polymer.[45] As most ICD patients have relatively restricted expected life times, ECs therefore are less likely to become a clinical issue for these leads. However, Riata ST Optim and Durata leads are not protected by inside-out movement beneath the shock coils, so electrical failure due to erosion of the inner ethylene-tetrafluoroethylene coating of the conductors can develop and may become a clinical problem with time. Several reports on this have already been registered in the MAUDE registry or presented in case reports.[113, 114] However, the early reports on the electrical performance of Durata leads seem to be favorable,[91, 111, 112] but these are limited by the fact that fatal high voltage shock failure due to short circuits will most likely not be detected. This has raised concerns in the device community about the true long-term performance of these leads and about the lack of sensitive tools to monitor and identify patients at risk just as for the Riata patients.[100] Currently, the brand new successor to the Durata lead has just been launched to the market (Optisure) with an increased thickness of the outer Optim jacket with increased recommended introducer size from 7-F to 8-F and also Optim insulation beneath the shock coils to avoid internal short circuits. It seems as if the manufacturers' race to make constantly smaller diameter leads has been halted…at least temporarily. In the spring of 2014, there have also been reports of findings of ECs in defibrillator leads from Biotronik,[115, 116] but at the current time we have no scope of the size of this only potential problem.

The patient perspective on the Riata lead advisory (Study III)

Physicians may be challenged by the Riata advisory, but what about patients? What is the impact of the Riata advisory notification on their well-being and psychological functioning? The FDA does not recommend routine replacement of Riata leads with normal electrical function.[117] Many patients therefore live with an active Riata lead under advisory with a potential negative influence on their health-related quality of life. To our knowledge, Study III is the first in the world to have addressed this.

The elusive complex Riata failure mechanism with no reliable means for monitoring may contribute to the observed negative impact on device acceptance and device-related concerns in the early advisory phase as presented in Table 5 and Figure 12. The ICDC-8 is mainly measuring device-related concerns for shock therapy, and our data therefore suggest that the advisory notification may induce acute anticipatory shock anxiety with some improvement over time, possibly due to adaptation, despite no information delivered to patients on increased risk for inappropriate shock therapy. A maintained loss of confidence and negative attitude toward ICD technology may be a key explanation for the observed preserved reduction in device acceptance.[118] Nevertheless, despite a statistically significant impact, effect sizes were small questioning whether the impact on patients' health-related quality of life can be considered clinically relevant. The observed small effect sizes might be due to no media exposure in the early advisory phase in Denmark, where all patients learned about the advisory from their physician.[119] Patients with ECs might be particularly vulnerable, as we observed the lowest mean score for device acceptance and the highest mean scores for device-related concerns, symptoms of anxiety, and impact on general well-being in this subset of patients, although this was not statistically significant, possibly due to our limited sample size (Figure 12). The borderline significant small improvement in symptoms of anxiety in Riata patients undergoing lead replacement seems plausible but should be interpreted with caution as this was not a pre-specified hypothesis.

Previous studies on the patient perspective on advisory notifications are conflicting. The Sprint Fidelis advisory is the one most comparable with the Riata lead advisory, but the failure mechanism in Sprint Fidelis leads is more transparent and mainly includes low-voltage failures due to conductor fracture, and in contrast to the Riata leads, impeding lead failure can be monitored successfully, reducing but not eliminating the risk of inappropriate shocks.[120] Conform to our findings, Heatherly *et al* observed a significantly higher level of device-related concerns in 158 Sprint Fidelis patients compared with non-advisory controls with the majority examined within 18 months from the advisory notification.[30] Two earlier smaller follow-up studies also indicate a higher level of general anxiety after generator advisory notifications.[121, 122] Conflicting with our findings, the studies by Keren *et al* (n = 273 advisory patients), Pedersen *et al* (n = 207 advisory patients), and D'Antono *et al* (n = 114 advisory patients) did not find any significant impairment in the psychological functioning of Sprint Fidelis advisory patients compared with non-advisory controls.[31-33] These three studies were not performed in the early advisory phase, but after 9-24 months. The timing for assessment of the impact of the device advisory may be a key factor in explaining the inconsistent results so far, which is in line with our observed minimal, but significant reduction in device-related concerns over time (Table 6). The neutral findings by Keren *et al* may also be explained by a very well-established advisory management program inviting patients and relatives in for a 1-hour lecture and individual discussions with their physician.[31]

Female sex was an independent predictor of an acute high impact on general well-being in Study III. In a small follow-up study, an analog higher "worry-score" was seen in women in the early generator advisory phase.[123] Selected studies examining gender disparities in ICD patients have also reported higher levels of psychological distress in women,[124] but sufficiently powered studies designed a priori to evaluate gender differences on PROs are warranted to determine whether women truly comprise a more vulnerable group than men.[125]

The results of Study III suggest that Riata advisory patients have a significant impairment in general well-being and psychological functioning even in a setting without early media exposure. The awareness of possible negative psychological consequences of advisories is important to provide the best patient-centered care. Patients should be provided with access to health care professionals with expertise in device management, education and counseling to ensure awareness and anxiety are addressed in the context of an advisory. The inclusion of PROs in national registries with repeated assessments as part of standard practice would enhance our knowledge of the impact of device advisories on patients. Generally, larger studies have to be set up after advisory notifications are released, which is currently occurring ad hoc and in most cases a long time after the notifications have been released. This is not optimal from a design point-of-view, and is unlikely to provide

the knowledge needed to improve the care of patients with hardware under advisories.

Limitations

The three studies in this thesis have differences in designs, but all are observational, based on a survivor cohort with data from several sources, including the Danish ICD Register, clinical outpatient visits with fluoroscopy and device interrogation, and questionnaires completed by patients. Hence, results can be subject to selection bias and information bias, and tested associations between sub-groups can be subject to confounding due to lack of randomization.

Selection bias is an error in estimates due to systematic differences in characteristics between those selected for a given analysis and those not selected.[61] In the prospective cross-sectional Study I, estimating the occurrence of ECs and electrical abnormalities using prevalence can underestimate the true problem due to a kind of selection bias called survivor bias as described above. However, the cross-sectional design is most often the only possibility in an early phase of describing an acute clinical problem to give some sort of estimate of the size of problem, but it should always be interpreted with caution. Study I included a near to complete nationwide cohort leaving no risk for further selection bias, resulting in a valid point-in-time picture. In the prospective longitudinal Study II, the risk of selection bias was quite small as we only lost three patients to overall follow-up, but further 25 patients died before follow-up fluoroscopy, and if these patients differed substantially from the survivors in risk of developing ECs, a small bias cannot be excluded. In Study III, the risk of selection bias in the Riata cohort was small due to high baseline study participation, low loss to follow-up, and no significant difference in characteristics between responders and non-responders at baseline and follow-up. The matched non-advisory controls were selected by random from a large nationwide cohort of consecutive patients who survived and responded to questionnaires one year after first-time ICD implant. The matching was on age group, sex, and ICD indication, and potential selection bias cannot be ruled out in these patients as demonstrated by a higher proportion of type D personality compared with the Riata cohort, but this was controlled for in analyses by supplementary use of multivariable regression. Comorbidity was adjusted for by proxy variables such as age and ICD indication but not functional status. However, the applied adjustments enlarged estimated differences (suppressor effect), which indicates slightly more comorbidity in the controls. Residual confounding is therefore less likely as an explanation for the impaired baseline PROs in the Riata cohort. Time since first ICD implant was different by design in the Riata cohort and non-advisory controls with no group overlap, which could therefore not be controlled for statistically. But within the Riata cohort, no signs were seen of a worsening in PROs over time, and the estimates for the primary endpoints pointed in the opposite direction. It is therefore less likely that the differences we observed in PROs between Riata patients and controls could be explained by time-related confounding. This is also in line with the fact that PROs tapping into psychological functioning are relatively stable beyond 3-6 months after implant.[126] The use of multiple imputation in case of missing values also contributed to less risk for selection bias as the alternative would have been excluding patients with non-complete questionnaires or using more primitive imputation methods, such as simple mean imputation, that tend to inflate the statistical power of the collected data.

Information bias is an error in estimates due to systematic inaccuracy of measurement/classification of exposures, covariates, and outcomes.[61] Data on hardware and clinical variable registered in the Danish ICD Register were validated in a random sample of 200 patients with high positive predictive values >90%, but we cannot with certainty rule out that a few patients in Denmark with Riata leads have not been identified due to misclassification. In Study I and II, the definition of ECs was adjudicated using multiple investigators, but the use of expert fluoroscopic consensus as gold standard may introduce minor misclassification of leads with small ECs in some areas with less lead movement and in the busy pocket area. A case report has demonstrated that fluoroscopy may be insensitive to small ECs when compared with findings from extractions,[127] but extraction forces in this case report may just have accentuated a latent EC. Lead extraction followed by return product analysis was not feasible in our nationwide observational studies. Electrical abnormalities were defined using absolute limits, relative changes over time, and expert panel evaluation blinded from fluoroscopic status, reducing the risk of misclassification. However, we cannot account for possible underestimation of high voltage abnormalities as reliable tools for this purpose are limited, and only about half the patients underwent high voltage integrity check. However, we tested the relative differences between groups of patients, and these associations should be valid assuming no differential misclassification between groups. In Study III, we used standardized and validated multi-item questionnaires on PROs, reducing the risk of misclassification. A purpose-designed single-item VAS seemed appropriate to evaluate overall impact on general well-being as a single global quality of life VAS has previously been demonstrated to have good validity, reproducibility, and responsiveness over time.[128]

Estimated associations can be subject to ***confounding*** by a given variable if it (i) is a risk factor for the outcome, (ii) is associated to the exposure of interest, and (iii) is not part of the causal pathway between the exposure and outcome.[129] We managed the risk of confounding in all three studies using multivariable regression analysis with prespecified potential risk factors for the outcome as covariates, and in Study III we also used matching. However, the relatively small sample size and low number of events in the studies limited our possibilities of making rich regression models, increasing the risk of residual confounding. Furthermore, we can only adjust for known measurable confounders, and this is why associations tested in observational data should always be interpreted with caution, with only very careful claims of possible causality in case of strong associations in prospective longitudinal data.

The moderate sample size of the Riata cohort and relatively few events seen from a statistically point of view resulted in a relatively low statistical power for comparative analysis. Therefore, neutral findings should be considered tentative as the risk of ***type 2 errors*** with acceptance of false null hypotheses is generally elevated. Multiple testing for PROs in Study III without Bonferroni correction increased the risk of ***type 1 errors*** with rejection of true null hypothesis, but this risk was acceptably reduced by interpretation of the findings in relation to prespecified prioritized hypotheses.

Main conclusions

Study I

The prevalence of ECs in a complete nationwide screening of active recalled Riata leads is at the same level as reported in previous studies with similar lead dwell times. The degree of externalization is time dependent, and location seems to differ between single and dual coil leads. Long-term lead performance and the association between ECs and electrical failure need further clarification. Fluoroscopy has a good diagnostic performance for ECs in clinical practice.

Study II

The development of ECs is a dynamic and progressive process despite long lead dwell time. ECs are associated with a higher risk of electrical abnormalities. Therefore, lead replacement should be considered, especially in patients with long life expectancy.

Study III

The Riata advisory is associated with a persistent small reduction in device acceptance and a small increase in device-related concerns with minimal improvement over time. Female sex is a predictor of a high negative advisory impact on general well-being. A need for counseling may arise in vulnerable subsets of patients.

Overall conclusion of the thesis

The prevalence of ECs in a complete nationwide screening of active recalled Riata leads is at the same level as reported in previous studies with similar lead dwell times. The development of ECs is a dynamic process with a relatively high incidence rate and progression in size over time. ECs are associated with a higher risk of incident electrical abnormalities. The current tools for monitoring insulation failures seem to be inadequate, and prophylactic Riata lead replacement should be considered on an individual level, especially in patients with long life expectancy. The Riata advisory is associated with a persistent small reduction in device acceptance and a small increase in device-related concerns with minimal improvement over time. Female sex is a predictor of a high negative advisory impact on general well-being. A need for counseling may arise in vulnerable subsets of patients.

Perspectives

The studies in this thesis have contributed with results to increase our understanding of the complexity of the major Riata defibrillator lead class I advisory, seen from the perspective of both physicians and patients. We have so far learned important lessons from this advisory. It has been highlighted that our current methods for monitoring the integrity of the high voltage circuits of ICD systems are not reliable. This has to be improved as high voltage failure is the ultimate most critical and often fatal failure of an ICD system, but it will often not be recognized in clinical practice outside the hospitals. This is, in my opinion, the most import single issue to be further explored in new studies on the Riata advisory.

It is striking that more than three years passed from publication of the first case report with ECs in 2008 until the advisory notification was issued in 2011, and even at that time, the proportion of ECs, based on return product analysis, was only 1% of what was observed in later systematic fluoroscopic screenings. This emphasizes that the combination of a fast 510k-approval without clinical testing and poor demands for systematic post-marketing monitoring of cardiac implantable electronic devices is a dangerous cocktail. Mandatory and independent hardware registries as the Danish Pacemaker and ICD Register can act as a role model for registries to enable a better monitoring, but to increase the sensitivity to timely detect potentially problematic devices and leads, we should strive to improve the international collaboration between registries. In retrospect, it would probably have been wise if two or three large and sufficiently powered studies, independent of the industry, were launched at the time of an advisory notification to answer the key questions important for lead management in the interest of patients, physicians, and industry. The many interested parties in the highly competitive device industry with high economical stakes make advisory notifications complex with intensified intricacy via media exposure. Declaring new “icebergs” every time we see a small drift of snow should therefore be avoided. The losers are the patients. Generally, physicians and industry should make every effort to collaborate as soon as technical hardware or software problems arise and work on the problems instead of making things worse by guessing. This has been the applied model for good collaboration between implanting hospitals and industry for years in Denmark including the management of the Riata advisory. History has shown that advisory notifications are a natural part of rapidly evolving disruptive technologies, and we should continually learn from our mistakes and be even better prepared for the next advisory notification….it will come. This will get us closer to our common goal: to provide the best care for our patients.

Summary

Introduction: Implantable cardioverter defibrillator (ICD) therapy is well established for prophylaxis of sudden cardiac death. The weakest link of the ICD is the defibrillator lead connecting the pulse generator to the heart. In three studies, the present thesis describes the nature of the class I advisory concerning malfunction of the St. Jude Medical Riata defibrillator lead family, which was recalled in 2011 due to increased risk of insulation failures, including fluoroscopically visible inside-out externalized conductors (ECs). The overall aim of the studies was to provide data to support an evidence-based clinical management of the patients living under the Riata lead advisory.

Methods: In March 2012, a Danish nationwide cohort of 298 patients with active recalled Riata leads was established. In ***Study I***, a cross-sectional screening was performed with fluoroscopy in three projections and device interrogation at five ICD implanting hospitals. In ***Study II***, the patients were followed for 1 year until a similar final second screening. In ***Study III***, the patients' perspective on the advisory was examined using patient-reported outcomes (PROs) measured by standardized and validated questionnaires tapping into their well-being and psychological functioning. The PROs were evaluated at the baseline and follow-up screenings for the Riata patients. Baseline PROs in Riata patients were compared with matched non-advisory controls. Clinical relevance of mean adjusted differences in PROs was evaluated using Cohen's effect size *d* (0.20 = small; 0.50 = moderate; ≥0.80 = large).

Main results: In ***Study I***, the prevalence of ECs was 11% and significantly higher in 8-F (21%) compared with 7-F (6%) leads, but 8-F leads also had a longer dwell time since implant; the location of ECs was mainly intracardiac and more often included the lead segment below the tricuspid annulus in dual coil leads as compared with single coil leads; lead dwell time was significantly correlated to the degree of externalization; no association was observed between ECs and electrical abnormalities; and the fluoroscopic diagnostic performance for ECs was good. In ***Study II***, the nature of ECs was dynamic with development of new ECs with an incidence rate of 3.7 per 100 person-years and significant progression in size over time of 4 ± 1 mm of existing ECs; the overall rate of electrical abnormalities was 7.1 per 100 person-years with an adjusted incidence rate ratio for patients with baseline ECs of 4.4 ($p = 0.002$). In ***Study III***, there were a significant lower level of device acceptance ($d = -0.28$, $p = 0.001$) and a higher level of device-related concerns ($d = 0.29$, $p < 0.001$) in the Riata cohort as compared with non-advisory controls, although the effect sizes were small; no significant difference was seen for symptoms of depression; female sex was a significant independent predictor of an acute high impact of the advisory on general well-being; and there was only a minimal reduction in device-related concerns ($d = -0.17$, $p=0.002$) over time and no changes were seen in the other PROs.

Main conclusions of the thesis: The prevalence of ECs in a complete nationwide screening of active recalled Riata leads is at the same level as reported in previous studies with similar lead dwell times. The development of ECs is a dynamic process with a relatively high incidence rate and progression in size over time. ECs are associated with a higher risk of incident electrical abnormalities. The current tools for monitoring insulation failures seem to be inadequate, and prophylactic Riata lead replacement should be considered on an individual level, especially in patients with long life expectancy. The Riata advisory is associated with a persistent small reduction in device acceptance and a small increase in device-related concerns with minimal improvement over time. Female sex is a predictor of a high negative advisory impact on general well-being. A need for counseling may arise in vulnerable subsets of patients.

Dansk resumé

Introduktion: En implanterbar cardioverter-defibrillator (ICD) er effektiv som profylakse mod pludselig hjertedød. Det svageste led i ICD-systemet er ledningen, der forbinder pulsgeneratoren med hjertet. Denne ph.d.-afhandling beskriver i tre studier forskellige aspekter af tilbagekaldelsen af Riata ICD-ledninger fra firmaet St. Jude Medical. Tilbagekaldelsen blev foretaget i 2011 på grund af uventet høj forekomst af isoleringsdefekter, inklusiv eksternalisering (EC), hvor de elektriske kabler i ledningen bevæger sig uden for den beskyttende ydre silikoneisolering. Det overordnede formål med studierne var at indhente viden til at understøtte en evidensbaseret klinisk håndtering af patienterne med tilbagekaldte Riata-ledninger.

Metoder: I marts 2012 blev der identificeret en national dansk kohorte med 298 patienter med aktive Riata-elektroder. I ***studie I*** blev der udført en tværsnitsscreening med røntgengennemlysning af ledningen i tre projektioner og kontrol af ICD'ens elektriske funktion på fem ICD-implanterende hospitaler. I ***studie II*** blev patienter fulgt 1 år frem til en tilsvarende screening. I ***studie III*** blev patienternes perspektiv på tilbagekaldelsen af ledningerne undersøgt med validerede spørgeskemaer ved de to screeninger omhandlende indflydelse på det almene velbefindende og psykologisk status. Resultater fra baseline-screeningen blev sammenlignet med resultater fra en matchet kontrolgruppe uden en tilbagekaldt ledning. Den kliniske relevans af justrede middelforskelle i resultater fra spørgeskemaerne blev vurderet med Cohen's effektstørrelse *d* (0.20 = lille; 0.50 = moderat; ≥0.80 = stor).

Hovedresultater: I ***studie I*** var prævalensen af EC 11% og signifikant højere ved 8-F (21%) sammenlignet med de lidt tyndere 7-F (6%) ledninger, men 8-F ledninger havde været implanteret i signifikant længere tid; EC blev primært set intrakardielt og hyppigere distalt for tricuspidalklappen ved dobbelt coil ledninger; tid siden implantation var signifikant korreleret med graden af EC; Ingen association blev set mellem EC og elektriske abnormiteter; og de kliniske diagnostiske egenskaber af gennemlysninger for EC var gode. I ***studie II*** var EC dynamisk med udvikling af EC med incidensrate 3.7 per 100 personår og progression i størrelsen af eksisterende EC over tid på 4 ± 1 mm; den overordnede incidensrate af elektriske abnormiteter var 7.1 per 100 personår, med en justeret incidensrateratio for patienter med baseline EC på 4.4 (p = 0.002). I ***studie III*** havde Riata-patienterne en signifikant dårligere accept af at leve med ICD'en (*d* = -0.28, p=0.001) og en højere grad af ICD-relaterede bekymringer (*d* = 0.29, p<0.001) sammenlignet med kontrolgruppen, men effektstørrelserne var små; der var ingen forskel for symptomer på depression; kvindekøn var en signifikant uafhængig prædiktor for, at tilbagekaldelsen af ledningen havde en stor indflydelse på det almene velbefindende; og der var kun en mindre reduktion i ICD-relaterede bekymringer (*d* = -0.17, p=0.002) over tid, og ingen signifikante ændringer i de øvrige selvrapporterede psykologiske mål.

Hovedkonklusioner: Prævalensen af EC i en komplet national screening af aktive, tilbagekaldte Riata-ledninger er på samme niveau som i sammenlignelige studier. Udviklingen af EC er en dynamisk proces med en relativ høj incidensrate og progression i størrelsen af eksisterende EC over tid. EC er associeret til en højere risiko for senere udvikling af elektriske abnormiteter. De aktuelle muligheder for at monitorere isoleringsfejl på højvoltsdelen af en ICD-ledning er begrænsede, og profylaktisk skift af tilbagekaldte Riata-ledninger bør overvejes, særligt hos patienter med forventet lang restlevetid. Tilbagekaldelsen af Riata-ledningerne har en akut effekt på patienternes almene velbefindende og psykologiske status med en vedvarende let nedsat accept af at leve med ICD'en og en let øgning i ICD-relaterede bekymringer, som kun forbedres minimalt over tid. Kvindekøn er prædiktor for en stor negativ tilbagekaldelseseffekt på det almene velbefindende. Behov for psykologhjælp kan komme på tale hos skrøbelige patienter.

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Paper I

Nationwide Fluoroscopic Screening of Recalled Riata Defibrillator Leads in Denmark

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BACKGROUND The natural history of insulation defects with inside-out conductor externalization in recalled St Jude Medical Riata defibrillator leads is not well understood.

OBJECTIVES To determine the prevalence of externalization in a nationwide screening. Secondary aims were to examine time dependence and location of externalization, association with electrical failure, and fluoroscopic diagnostic performance.

METHODS All 299 patients with recalled Riata leads in Denmark were identified, and all except one underwent fluoroscopy and device interrogation. Externalizations were confirmed by multiple investigators.

RESULTS The prevalence of externalization was 32 of 298 (11%) at a mean dwell time of 5.1 years. The prevalence was 21 of 98 (21%) for 8-F leads and 11 of 200 (6%) for 7-F leads; however, 8-F leads had longer dwell times. The degree of externalization was correlated with dwell time (Spearman's $\rho = .37$; $P = .03$). Externalization more often included the lead segment below the tricuspid annulus in dual coil leads than in single coil leads (69% vs 16%; $P = .004$). No association was observed between externalization and electrical function. Fluoroscopic diagnostic performance was good with positive and negative predictive values of 88% and 99%, respectively.

CONCLUSIONS The prevalence of externalization in a nationwide screening is at the same level as reported in previous studies with similar lead dwell times. The degree of externalization is time dependent, and location seems to differ between single and dual coil leads. Long-term lead performance and association with electrical failure need further clarification. Fluoroscopy has a good diagnostic performance in clinical practice.

KEYWORDS Riata; Implantable cardioverter-defibrillator; Defibrillation lead; Lead failure; Fluoroscopy

ABBREVIATIONS **CI** = confidence interval; **EP** = electrophysiologist; **ETFE** = ethylene tetrafluoroethylene; **ICD** = implantable cardioverter-defibrillator

(Heart Rhythm 2013;10:821–827)

This study was supported by the Department of Cardiology, Aalborg University Hospital. Dr Larsen has received speaker's fee from Biotronik. Dr Nielsen has received speaker's fee from Biotronik and research grant for the MANTRA-PAF trial from Biosense Webster. Dr Videbaek has received speaker's fee from Biotronik and advisory board fee from Boston Scientific and Cameron Health. Dr Haarbo has received advisory board fee from St Jude Medical and Boston Scientific. Dr Theuns is a consultant at Cameron Health. Dr Johansen has received speaker's fee from Biotronik, Boston Scientific, and Cameron Health. **Address reprint requests and correspondence:** Dr Jacob M. Larsen, Department of Cardiology, Aalborg University Hospital, Hobrovej 18-22, PO Box 365, 9000 Aalborg, Denmark. E-mail address: jaml@rn.dk.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2013.02.010

Paper II

Prospective nationwide fluoroscopic and electrical longitudinal follow-up of recalled Riata defibrillator leads in Denmark

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BACKGROUND Recalled St. Jude Medical Riata defibrillator leads are prone to insulation failures with externalized conductors (ECs). Longitudinal studies are needed to guide lead management.

OBJECTIVE The purpose of this study was to describe the dynamic nature of EC and the association with electrical abnormalities and lead extraction outcomes.

METHODS A nationwide cohort established in 2012 of 295 patients with recalled Riata leads with dwell time 5.1 ± 1.1 years, 34 ECs, and 19 electrical abnormalities were followed until death, lead discontinuation with fluoroscopy, or a new 2013 screening with fluoroscopy and device interrogation.

RESULTS Fluoroscopic follow-up of 239 patients with normal baseline fluoroscopy revealed incident overt EC in 8 leads and borderline EC in 2 leads after 1.1 ± 0.2 years, with an incidence rate of 3.7 per 100 person-years (95% confidence interval 2.0–6.9). Fluoroscopic follow-up in 27 patients with baseline EC showed an increase in EC length of 4 ± 1 mm ($P < .001$) after 1.1 ± 0.3 years. Electrical follow-up in 276 patients with normal baseline electrical function demonstrated 20 incident electrical abnormalities after 1.0 ± 0.3 years, with an incidence rate of 7.1 per 100 person-years (95% confidence interval 4.6–11.0). This rate was significantly higher in leads with baseline EC, with an adjusted incidence rate ratio of 4.4 (95% confidence interval 1.7–11.5, $P = .002$). In 15 extractions, all leads were removed, with 2 major complications.

CONCLUSION The development of EC is a dynamic process despite long lead dwell time. ECs are associated with a higher risk of electrical abnormalities. Therefore, lead replacement should be considered, especially in patients with a long life expectancy.

KEYWORDS Riata; Implantable cardioverter-defibrillator; Defibrillation lead; Lead failure; Recall; Advisory; Fluoroscopy; Lead extraction

ABBREVIATIONS **CI** = confidence interval; **EC** = externalized conductor; **ETFE** = ethylene tetrafluoroethylene; **ICD** = implantable cardioverter-defibrillator

(Heart Rhythm 2014;11:2141–2147)

This study was supported by the Danish Heart Foundation, the Danish Pacemaker and ICD Register, and the Department of Cardiology, Aalborg University Hospital, Denmark. Dr. Larsen has received speaker's fees from Biotronik. Dr. Nielsen has received speaker's fees from Biotronik, Actelion, and Biosense Webster, consultant's fees from Medtronic and Boston Scientific, and a research grant for the MANTRA-PAF trial from Biosense Webster. Dr. Johansen has received speaker's fees from Biotronik and Boston Scientific. Dr. Haarbo has received advisory board fees from St. Jude Medical and Boston Scientific. Dr. Hjortshøj has received speaker's fees from Biotronik. **Address reprint requests and correspondence:** Dr. Jacob M. Larsen, Aalborg University Hospital, Department of Cardiology, Hobrovej 18-22, PO Box 365, 9000 Aalborg, Denmark. E-mail address: jaml@rn.dk.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2014.07.003

Paper III

The patient perspective on the Riata defibrillator lead advisory: A Danish nationwide study

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BACKGROUND The St Jude Medical Riata lead advisory was issued owing to insulation failures. The impact of this advisory on patients' well-being is unknown.

OBJECTIVES The objectives of this study were to describe the acute impact of the Riata advisory on patients' well-being and psychological functioning and to examine changes over time.

METHODS Patients with active Riata leads completed standardized and validated patient-reported outcomes (PROs) in connection with a nationwide fluoroscopic screening with 12-month follow-up. They were matched (1:1) on age, sex, and implant indication with nonadvisory controls for baseline comparisons. Cohen's effect size *d* was used to determine the clinical relevance of the estimated adjusted mean differences (small, $d = 0.20$; moderate, $d = 0.50$; large, $d \geq 0.80$).

RESULTS Of all Riata patients, 86% (256 of 299) completed baseline PROs and 70% (210 of 299) follow-up PROs. Riata patients reported poorer device acceptance ($d = -0.28$; $P = .001$) and increased device-related concerns ($d = 0.29$; $P < .001$) as compared with matched nonadvisory controls. There were no differences in symptoms of depression ($d = 0.13$; $P = .13$). Female sex was an independent predictor of a high advisory impact on general well-being as assessed with a purpose-designed question (odds ratio 2.24; $P = .04$). Device-related concerns decreased over time ($d = -0.17$; $P = .002$), but no changes were seen for other PROs.

CONCLUSION The Riata advisory is associated with a persistent small reduction in device acceptance and a small increase in device-related concerns with minimal improvement over time. Female sex is a predictor of a high negative advisory impact on general well-being. A need for counseling may arise in vulnerable subsets of patients.

KEYWORDS Advisory; Recall; Leads; Implantable cardioverter-defibrillator; Psychology; Distress; Patient-reported outcome; Riata

ABBREVIATIONS DEFIB-WOMEN = (study acronym: Utilization of implantable cardioverter DEFIBrillator therapy in the treatment of heart disease: Clinical and psychological outcomes in WOMEN); **EC** = externalized conductor; **FPAS-12** = 12-item Florida Patient Acceptance Survey; **GAD-7** = 7-item Generalized Anxiety Disorder questionnaire; **ICD** = implantable cardioverter-defibrillator; **ICDC-8** = 8-item ICD patient Concerns questionnaire; **PHQ-9** = 9-item Patient Health Questionnaire; **PRO** = patient-reported outcome; **VAS** = visual analog scale

(Heart Rhythm 2014;11:2148–2155)

This study was supported by the Danish Heart Foundation (grant nos. 13-04-R94-A4630-22789 and 09-10-R75-A2713_10-S12-22565), the Danish Pacemaker and ICD Register, and the Department of Cardiology, Aalborg University Hospital in Denmark. Dr Larsen has received speaker's fee from Biotronik. Dr Nielsen has received speaker's fee from Biotronik, Actelion, and Biosense Webster; consultant's fee from Medtronic and Boston Scientific; and research grant for the Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation trial from Biosense Webster. Dr Johansen has received speaker's fee from Biotronik, St Jude Medical, and Boston Scientific. Dr Haarbo has received advisory board fee from St Jude Medical and Boston Scientific. Dr Pedersen has received speaker's fee from Medtronic and St Jude Medical and is currently serving as a consultant for Boston Scientific. **Address reprint requests and correspondence:** Dr Jacob M. Larsen, Department of Cardiology, Aalborg University Hospital, Hobrovej 18-22, PO Box 365, 9000 Aalborg, Denmark. E-mail address: jaml@rn.dk.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2014.09.008

Danish Riata lead management plan (September 12, 2012)

Concerning recalled St. Jude Medical Riata ICD leads

- Model no. 1560, 1561, 1562, 1570, 1571, 1572, 1580, 1581, 1582, 1590, 1591, 1592, 7000, 7001, 7002, 7010, 7011, 7040, 7041, and 7042.

Recommendations for all leads

- Remote monitoring is recommended if possible.
- Outpatient visits are recommended 4 times a year (at least once a year in case of remote monitoring). Routine test of high voltage impedance using painful low-voltage shock is not recommended.
- Fluoroscopy is recommended every 12 months in active leads in an ICD implanting center.

Patients with electrical abnormalities with/without externalization

- Electrical abnormalities are typically rising impedance, falling R-wave sensing, rising pacing threshold and noise. Lead replacement is recommended with extraction or abandonment of recalled lead.

Patients with externalization without electrical abnormalities

- **High risk**: secondary preventive ICD indication, previous relevant ICD therapy, pacing dependence and responders to cardiac resynchronization therapy. Prophylactical lead replacement is recommended with extraction or abandonment of recalled lead.
- **Low risk**: primary preventive ICD indication, no previous relevant ICD therapy, no pacing dependence and non-responders to cardiac resynchronization therapy. It is recommended to consider prophylactical lead replacement with extraction or abandonment of recalled lead. The choice is based on an individual evaluation including patients' wishes and can, if necessary, wait until planned generator replacement.

Patients without externalization or electrical abnormalities

- Strategy at elective generator exchange will depend on an individual evaluation including patients' wishes in relation to possible lead replacement with extraction or abandonment of recalled lead.

The experience with extraction of Riata leads is sparse. Externalization of conductor cables may increase difficulty of the procedure, which is the tendency described in the first small international extraction reports. In general, extraction will be more difficult and with higher risk, the longer the leads have been implanted. We therefore recommend that extraction is considered in selected patients, especially younger patients, in regard to ICD indication, comorbidity, and type of device.

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Udgivet i samarbejde med
Dansk Cardiologisk Selskab
www.cardio.dk

Dansk Cardiologisk Selskab
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1127 København K
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Tryk: AKA-PRINT A/S
Januar 2015

ISBN: 978-87-93217-16-4

ISSN: 2246-1302
E-ISBN: 978-87-7112-248-0

AALBORG UNIVERSITY PRESS