Long-Term Evaluation of Biotronik Linox and Linox^{smart} Implantable Cardioverter Defibrillator Leads

Short Title: Long-Term Evaluation of Biotronik Linox Family of ICD Leads

Authors: *Eric D. Good, DO, FHRS,[1] Ivan Cakulev, MD, FHRS,[2] Michael V. Orlov, MD, PhD,[3] David Hirsh, MD,[4] John Simeles, BS,[5] Kelly Mohr, BS,[5] Phil Moll, MS,[5] Heather Bloom, MD[6]*

[1]University of Michigan, [2]University Hospitals of Cleveland, [3]Steward St. Elizabeth's Medical Center, [4]Emory University, [5]Biotronik, [6]Emory University and Atlanta VA Medical Center

Corresponding Author Information:

Eric D. Good, DO

P.O. Box 530818

Livonia, MI 48153

Telephone 734-904-7891

Email dogood9112@gmail.com

_

Clinical Trials Registration Information: ClinicalTrials.gov NCT00836589 and NCT00810264

Biotronik, Inc. provided funding for the CELESTIAL & GALAXY trial and is the manufacturer of the implantable cardioverter defibrillator systems used in these trials.

E.D. Good reports consulting fees/honoraria (Biotronik), research grants (Biotronik, Boston Scientific Corp.); I. Cakulev reports honoraria (Biotronik); M.V. Orlov reports honoraria (Biotronik), consulting fees (Philips); research grants (BSCi); D. Hirsh reports honoraria (Biotronik); J. Simeles, K. Mohr, P. Moll report salary (Biotronik); H. Bloom reports honoraria (Biotronik).

Abstract

Introduction

Expert consensus holds that post-market, systematic surveillance of ICD leads is essential to ensure confirmation of adequate lead performance. GALAXY (NCT00836589) and CELESTIAL (NCT00810264) are ongoing multicenter, prospective, non-randomized registries conducted to confirm the long-term safety and reliability of Biotronik leads.

Methods and Results

ICD and CRT-D patients are followed for Linox and Linox^{smart} ICD lead performance and safety for 5 years post-implant. All procedural and system-related adverse events (AEs) were assessed at each follow-up, along with lead electrical parameters. An independent CEC of EPs adjudicated AEs to determine AE category and lead relatedness. The analysis used categories of lead observations per ISO 5841-2 (Third edition).

A total of 3,933 leads were implanted in 3,840 patients (73.0% male, mean age 67.0 ± 12.2 years) at 146 US centers. The estimated cumulative survival probability was 96.3% at 5 years after implant for Linox leads and 96.6% at 4 years after implant for Linox^{smart} leads. A comparison of the Linox and Linox^{smart} survival functions did not find evidence of a difference (p = 0.2155). The most common AEs were oversensing (23, 0.58%), conductor fracture (14, 0.36%), failure to capture (13, 0.33%), lead dislodgement (12, 0.31%), insulation breach (10, 0.25%), and abnormal pacing impedance (8, 0.20%).

Conclusions

Linox and Linox^{smart} ICD leads are safe, reliable and infrequently associated with lead-related AEs. Additionally, estimated cumulative survival probability is clinically acceptable and well within industry standards. Ongoing data collection will confirm the longer-term safety and performance of the Linox family of ICD leads.

Keywords: lead; implantable cardioverter defibrillator; cardiac resynchronization therapy; adverse event; reliability; survival; Performance; Biotronik; Linox lead

Introduction

In the three and one-half decades since its inception, implantable cardioverter-defibrillator (ICD) therapy has revolutionized the management of patients with or at risk for malignant ventricular arrhythmias and in the process has saved numerous patient lives. Advances in ICD lead design have led to improvements in implant technique, reliability, extractability and clinical outcomes in patients with heart disease. Some design changes, however, have led to clinically significant and highly publicized performance and patient safety issues (e.g., Sprint Fidelis (Medtronic, Minneapolis, MN, USA) and Riata leads (St. Jude Medical, Sylmar, CA, USA)).[1-6] Bench-top analysis is one means of assessing ICD lead performance, but lacks the myriad of 'real-world' factors that might influence actual clinical performance (e.g., implant technique, patient and physician variables). Product performance reports are another means of identifying ICD lead issues, but are typically based on analysis of voluntary product returns and are not necessarily subject to the scrutiny of systematic data collection and unbiased adjudication. Thus, they have a propensity for under-reporting of performance issues. Expert consensus holds that post-market, systematic surveillance of ICD leads is essential to ensure confirmation of adequate lead performance; this must be independent of returned product, or lead approval and labeling evaluations.[7-10] In 2008, in response to a congressional mandate, the FDA launched the 'Sentinel Initiative', which advocated active post market safety surveillance of (among other things) medical device technologies utilizing 'secondary use' protocols.[11] To this end, the current study addresses ICD lead performance by prospective analysis of two large, multicenter prospective lead performance registries.

The GALAXY (NCT00836589) and CELESTIAL (NCT00810264) registries are ongoing multicenter, prospective, non-randomized, observational studies conducted to confirm the long-

term safety and reliability of Biotronik leads. These registries provide a means of evaluating adverse events based on clinical data collected on the Biotronik Linox family of ICD leads.

Methods

Background

The GALAXY registry is an ongoing multicenter, prospective, non-randomized, 5-year data collection registry designed to gather long-term safety and reliability data on Biotronik's Linox family of ICD leads. A total of 1,999 patients were enrolled at 98 United States (US) sites. The institutional review board at each participating site approved the registry protocol. Enrollment began in January 2009 and was completed in November 2011.

The CELESTIAL post-approval registry is an ongoing multicenter, prospective, non-randomized, 5-year data collection registry designed to gather long-term safety and reliability data on Biotronik's Corox family of bipolar left ventricular pacing leads. However, many CELESTIAL patients also have a Linox family ICD (right ventricular) lead implanted and these patients were included in the current study. A total of 2,499 CELESTIAL patients were enrolled at 97 US sites, with 1,843 of these patients receiving a Linox family ICD lead on or after the start date of study data collection. The institutional review board at each participating site approved the registry protocol. Enrollment began in December 2008 and was completed in October 2013.

A total of 3,933 Linox family ICD leads were implanted for both registries and all implanted leads and generators were Federal Drug Administration (FDA) approved and non-investigational. Inclusion criteria for both registries required that patients were implanted with the study lead and a Biotronik generator. GALAXY patients were enrolled within 1-45 days post-successful study lead implant and were implanted with a Biotronik ICD generator.

CELESTIAL patients were enrolled 7-180 days post-successful study lead implant and were implanted with a Biotronik Cardiac Resynchronization Therapy Defibrillator (CRT-D) or Cardiac Resynchronization Therapy Pacemaker (CRT-P). All CELESTIAL patients in the current analysis were implanted with a Linox family ICD lead connected to a Biotronik CRT-D generator. Additional inclusion criteria included patients being at least 18 years of age, able to understand the nature of the registry and provide informed consent, and being available for follow-up visits on a regular basis at the investigational site.

Exclusion criteria at the time of enrollment for both registries included enrollment in an investigational device exemption (IDE) clinical study, planned cardiac surgical or interventional measures within the next 6 months, expected to receive a heart transplant within 1 year, life expectancy less than 1 year, presence of another life-threatening illness separate from their cardiac disorder, pregnancy, inability to provide data on the implanted system, demographics, and adverse events since implant.

The Linox family of ICD leads is differentiated into Linox and Linox^{smart} models. Biotronik first received FDA approval for the Linox ICD lead on January 27, 2006 and for the Linox^{smart} ICD lead on September 17, 2010. As of December 31, 2014, the worldwide distribution for the ICD lead models represented in this study was 103,380 Linox and 67,490 Linox^{smart} ICD leads.[12]

All Linox family leads are implantable, transvenous ICD leads with dedicated sensing and pacing bipoles. The tip and ring electrodes are comprised of a platinum/iridium alloy base with a fractal iridium surface. The distal tip has a steroid-eluting collar, which contains up to 1.3 mg of dexamethasone acetate (DXA). All Linox family leads have one shock electrode that is positioned in the right ventricle. The Linox SD, Linox TD, Linox^{smart} SD, and Linox^{smart} TD leads have an

additional proximal shock electrode for placement in the superior vena cava. All Linox family leads have silicone insulation. Linox^{smart} models are additionally treated with a surface treatment, Silglide®. Silglide® is a silicone-based surface treatment similar to the silicone based-tubing substrate, but made unique by a polymerization process that allows it to acquire a different chemical structure that is responsible for its improved gliding characteristics and reduced friction within the introducer sheath and between leads.

All Linox family leads have a lead diameter of 7.8 F. The pace/sense cable conductor is made of 7x7 filars of MP35N® (a nickel-cobalt based proprietary alloy) material and the shock coil cable conductor is made of 7x7 filars of MP35N®/silver. The pace/sense and shock coil cable conductors are wrapped with a Teflon™ Perfluoroalkoxy (PFA) coating. The inner conductor is a four filar wire conductor made of MP35N®. The Linox family has four cable lumens to provide a symmetric cross-sectional design. A cross-section of a Linox family SD ICD lead is shown in Figure 1. A summary of the Linox lead models included in this analysis is shown in Table 1.

Figure 1: Cross-section of Linox Family SD ICD Lead

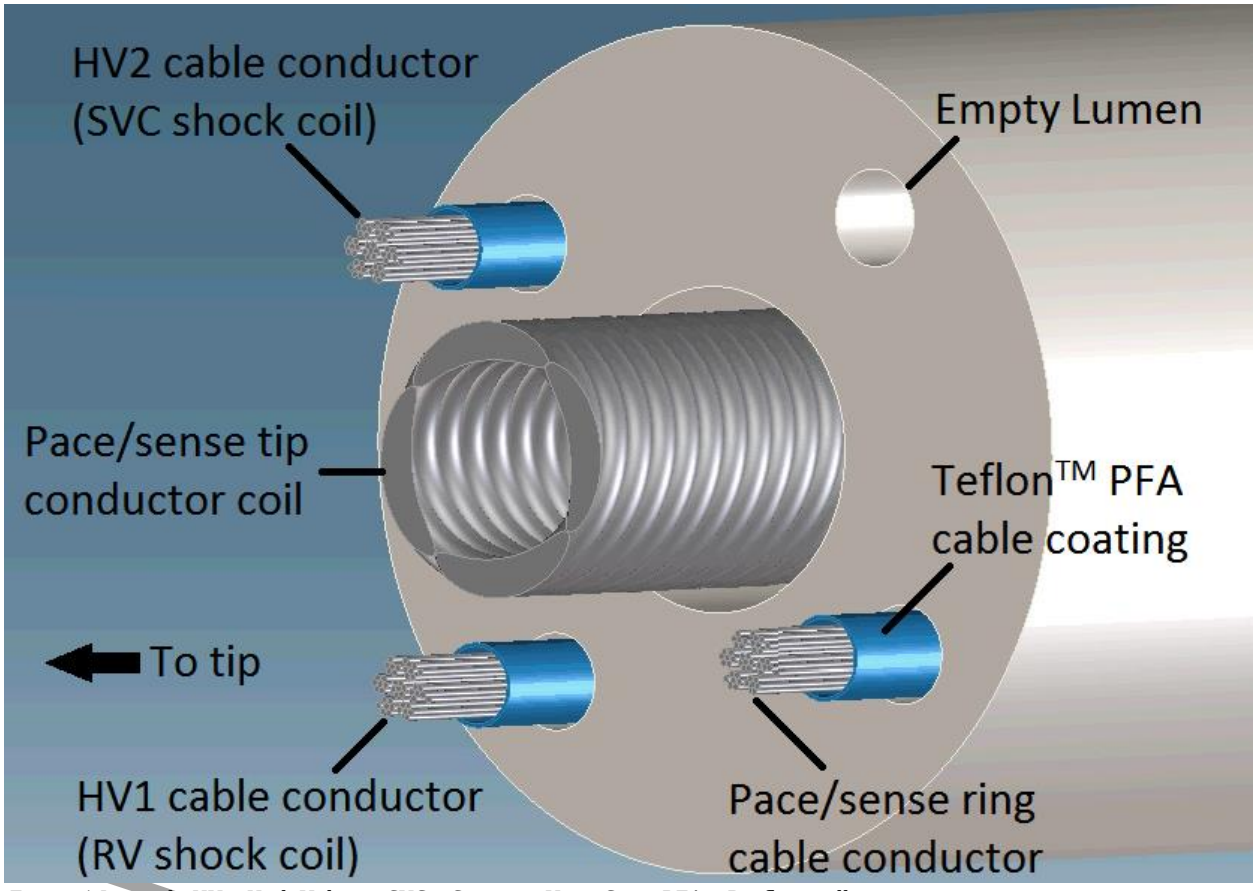


Figure 1 Legend: HV = High Voltage, SVC = Superior Vena Cava, PFA = Perfluoroalkoxy

Table 1: Linox Family of ICD Leads

Name	Fixation	Coils	Insulation
Linox S	active	single	silicone
Linox SD	active	dual	silicone
Linox T	passive	single	silicone
Linox TD	passive	dual	silicone
Linox^{smart} S	active	single	silicone with Silglide® surface treatment
Linox^{smart} SD	active	dual	silicone with Silglide® surface treatment
Linox^{smart} TD	passive	dual	silicone with Silglide® surface treatment

Study design and data collection

Patients were seen for in-office follow-up visits per the study site's standard of care at the time of study start-up, typically every 3 or 4 months (the maximum study visit interval in this analysis is 6 months). Follow-up data collection included assessments of adverse events (AEs); collection of sensing, threshold, and impedance measurements for Biotronik leads; and collection of shock information. This included the most recent shock impedance, charge time, and energy for Biotronik ICD leads. All interim device interrogations occurring at the site were required to be documented and have the same requirements as a study visit. Data collected during remote monitoring visits were not used for these registries.

The GALAXY and CELESTIAL registry protocols collected AEs related to the implanted system or implant procedure. An adverse event was considered to be 'implant related' if an event occurred

during or as a result of the implant procedure (e.g., cardiac perforation, hematoma, etc.). A 'system-related' AE was considered to have occurred if both of the following conditions were met: 1) an event related to the implanted system occurred and 2) an action was taken to address the event (e.g., surgical intervention, lead pacing polarity or pacing mode reprogramming due to a suspected lead failure, lead abandonment and pacing disabled), or lead use was continued based on medical judgment despite a known clinical performance issue, which would have otherwise dictated action to be taken (e.g., patient too ill for intervention).

An independent Clinical Events Committee (CEC) consisting of 5 electrophysiologists (EPs) was responsible for reviewing and adjudicating all AEs to classify the AE's relatedness to the study lead and the AE category (i.e., lead dislodgement, potential conductor fracture, etc.). Source documentation was collected on each protocol defined AE. Patient and site identifiers were redacted from the source documents provided to the CEC for adjudication. Two CEC members reviewed each AE. If the two reviewers disagreed on the relatedness or category of the AE, the AE was also reviewed by the CEC chairperson or brought to a meeting of a quorum of committee members for discussion. In the event of a full CEC committee review, each member voted and the majority vote was entered into the database as the final adjudication.

The current analysis included AEs that the CEC adjudicated as being related to the Linox family ICD leads. Additionally, one cardiac perforation occurring during ICD lead implant that was adjudicated as being related to the implant procedure was considered to be related to the Linox family ICD lead in this analysis. The analysis was performed using the categories of lead observations (i.e., cardiac perforation, conductor fracture, lead dislodgement, etc.) as defined in the third edition of the international standard ISO 5841-2.[13] ISO 5841-2 is used by all cardiac rhythm management device manufacturers for reporting of clinical performance of populations

of leads. The standard provides descriptions for each of the lead observation categories: Conductor fracture was observed visually, electrically, or radiographically, and in some cases via returned lead analysis. Failure to capture was intermittent or complete non-capture or sudden or significant increase in pacing threshold. Insulation breach was observed visually, electrically, or radiographically, and in some cases via returned lead analysis. Pacing impedance was considered abnormal if a measurement was <200 Ω or >3000 Ω or there was a sudden or significant change in impedance, without evidence to corroborate conductor fracture or insulation breach. In accordance with ISO 5841-2, the analysis excluded AEs that were resolved with successful lead repositioning. This standard defines acute AEs as occurring within 30 days post-implant and chronic as occurring more than 30 days post-implant.

Statistical Analysis

Kaplan-Meier actuarial graphs were created for the Linox and Linox^{smart} ICD leads. The standard error (SE) for the estimated survival (freedom from AEs) was calculated using the method of Greenwood,[14] and corresponding upper and lower confidence limits were calculated using the log-log transformation of Kalbfleisch and Prentice.[15] All leads were assigned a censor or event date and status categorization per ISO 5841-2 (Third edition).[13] For patients who were exited from the study for any reason (i.e., death, lost to follow-up, withdrawn) without a previous censor or event date, the patient's study exit date was used as the lead's censor date. Leads still in service without a previous censor or study exit date were assigned a March 23, 2015 censor date. If a lead had more than 5 years of follow-up time, the lead was censored at 5 years. The Linox and Linox^{smart} survival function estimates were compared using a log-rank test (Mantel-Haenszel).[16] Age group survival functions were compared using a log-rank test (Mantel-Haenszel) with a Sidak adjustment for multiple comparisons. The age group at lead implant and the prevalence of AEs were compared using the Cochran-Armitage Trend Test (two-sided).[17]

General tests of association were done comparing AE Event Categories using Fisher's Exact (two-sided) Test.[18]

Results

Patient Population

A total of 3,933 leads were implanted in 3,840 patients at 146 US centers. At enrollment, the patient population had a mean age of 67.0 ± 12.2 years old and a mean left ventricular ejection fraction (LVEF) of 28.0 ± 9.7% (n=3,564). A summary of patient demographics is provided in

Table 2. There were 570 (14.8%) patients with single chamber ICDs, 1,382 (36.0%) patients with dual chamber ICDs, and 1,888 (49.2%) patients with CRT-Ds. The median duration of follow-up was 3.6 years for Linox leads and 2.3 years for Linox^{smart} leads. The implanted system history of all patients was reviewed and any patients with no record of prior devices and with the generator and all leads implanted on the same day were classified as de novo implants. There were 3,440 (89.6%) patients who received a de novo implant and 400 (10.4%) patients who received an upgrade at the time of their Linox family ICD lead implant.

Table 2: Patient Demographics

Demographics	Results n = 3,840	
Gender, n (%)		
Male	2,802	(73.0%)
Female	1,038	(27.0%)
NYHA, n (%)		
I	100	(2.6%)
II	1,197	(31.2%)
III	2,046	(53.3%)
IV	100	(2.6%)
Not Available or Not Reported	397	(10.3%)
Venous Access (side), n (%)		
Left	3,661	(95.3%)
Right	174	(4.5%)
Not Reported	5	(0.1%)
Venous Access (details), n (%)		
Left		
Subclavian	2,817	(73.4%)
Axillary	586	(15.3%)
Cephalic	256	(6.7%)
Internal Jugular	1	(0.03%)
Not Reported	1	(0.03%)
Right		
Subclavian	133	(3.5%)
Axillary	27	(0.7%)
Cephalic	14	(0.4%)
Not Reported	5	(0.1%)
Race, n (%)		
White	2,594	(67.6%)
Black or African American	460	(12.0%)
Hispanic or Latino	433	(11.3%)
Asian	50	(1.3%)
Native Hawaiian or Other Pacific Islander	10	(0.3%)
American Indian or Alaska Native	7	(0.2%)
Unknown / Not reported	286	(7.4%)

Electrical Performance

The overall lead electrical parameters (sensing, threshold, and impedance measurements) assessed at all study visits were within standard clinically acceptable values. The mean sensing value was 12.6 ± 5.46 mV for Linox leads and 13.2 ± 5.83 mV for Linox^{smart} leads. The mean pacing threshold value at 0.5 ms pulse width was 0.6 ± 0.34 V for Linox leads and 0.6 ± 0.39 V for Linox^{smart} leads. The mean impedance was 560 ± 139.3 ohms for Linox leads and 556 ± 132.3 ohms for Linox^{smart} leads.

Adverse Events

There were 14 acute AEs in 14 leads (0.36% of all leads) and 91 chronic AEs reported in 91 leads (2.31% of all leads).

Table 3 provides a summary of AEs. The most common acute AEs were cardiac perforation (6, 0.15%), lead dislodgement (4, 0.10%), and failure to capture (2, 0.05%). The most common chronic AEs were oversensing (23, 0.58%), conductor fracture (14, 0.36%), failure to capture (13, 0.33%), lead dislodgement (12, 0.31%), insulation breach (10, 0.25%), and abnormal pacing impedance (8, 0.20%). There were 52 additional AEs that were resolved with successful lead repositioning that were not included in this analysis per ISO 5841-2 (Third edition) (46 lead dislodgements, 4 failures to capture, 1 oversensing AE immediately following implantation due to chatter with another lead, and 1 other AE in which lead was repositioned due to sub-optimal superior vena cava (SVC) coil positioning).[13]

The estimated cumulative survival probability is 96.3% at 5 years after implant for Linox leads and 96.6% at 4 years after implant for Linox^{smart} leads. A comparison of the Linox and Linox^{smart} survival functions did not identify evidence of a survival difference ($p = 0.2155$).

Figure 2 displays a Kaplan-Meier actuarial graph of Linox and Linox^{smart} ICD lead model groups.

There were 41 AEs in the 1,933 leads implanted with a CRT-D system (2.12%) and 63 AEs in the 2,000 leads implanted with dual or single chamber ICD (3.15%). Leads implanted with CRT-D systems had a statistically significantly lower proportion of AEs than leads implanted with ICD systems (p=0.0470).

There was no statistical difference between venous access method and the prevalence of AEs. For example, cephalic venous access accounted for 7.0% of all patients, and 6.9% of all AEs (p=1.000). Sub-group analysis of oversensing AEs, specifically, compared to venous access method used during the initial implant procedures for the Linox and Linox^{smart} showed no statistically significant difference. For example, subclavian venous access was used in 73.9% of patients with lead oversensing AEs compared to 76.8% in the general population (p=0.8041).

Gender did not influence lead performance: A comparison of the survival functions for all Linox family (Linox and Linox^{smart}) leads between females and males was not statistically significant (p=0.3537), nor were comparisons between genders within the individual Linox models (p=0.8567) or Linox^{smart} models (p=0.1049). A comparison of the survival functions for all males with Linox leads and all males with Linox^{smart} leads was not statistically significant (p=0.5987), nor was the same comparison for females (p=0.1516).

Figure 3 displays a Kaplan-Meier actuarial graph of Linox^{smart} and Linox ICD model groups separated by gender. There was also no statistically significant difference between or within AEs category according to gender (Table 3).

There was no statistical difference between subject age at lead implant and the prevalence of AEs using the REPLACE DARE study age thresholds (p=0.5748).[19] Additionally, there was no evidence of a difference in lead survival by DARE age group based on a log rank test of equality over all age groups (p=0.8946).[19]

Table 3: Adverse Event Details

Adverse Events	Results						
	Total		Male		Female		p-value*
Chronic Events, n (%)							
Oversensing	23	(0.58%)	18	(0.63%)	5	(0.47%)	0.6462
Conductor fracture	14	(0.36%)	11	(0.38%)	3	(0.28%)	0.7708
Failure to capture	13	(0.33%)	9	(0.31%)	4	(0.38%)	0.7582
Lead dislodgement	12	(0.31%)	8	(0.28%)	4	(0.38%)	0.7450
Insulation breach	10	(0.25%)	5	(0.17%)	5	(0.47%)	0.1468
Abnormal pacing impedance	8	(0.20%)	5	(0.17%)	3	(0.28%)	0.4535
Abnormal defibrillation impedance	4	(0.10%)	2	(0.07%)	2	(0.19%)	0.2972
Failure to sense (undersensing)	3	(0.08%)	3	(0.10%)	0	(0.00%)	0.5678
Cardiac perforation	2	(0.05%)	1	(0.03%)	1	(0.09%)	0.4683
Other	2	(0.05%)	1	(0.03%)	1	(0.09%)	0.4683
Total	**91**	**(2.31%)**	**63**	**(2.20%)**	**28**	**(2.63%)**	**0.4061**
Acute Events, n (%)							
Cardiac perforation	6	(0.15%)	3	(0.10%)	3	(0.28%)	0.3536
Lead dislodgement	4	(0.10%)	2	(0.07%)	2	(0.19%)	0.2972
Failure to capture	2	(0.05%)	2	(0.07%)	0	(0.00%)	1.0000
Insulation breach	1	(0.03%)	1	(0.03%)	0	(0.00%)	1.0000
Other	1	(0.03%)	0	(0.00%)	1	(0.09%)	0.2708
Total	**14**	**(0.36%)**	**8**	**(0.28%)**	**6**	**(0.56%)**	**0.2256**

Figure 2: Linox Family Cumulative Survival Probability

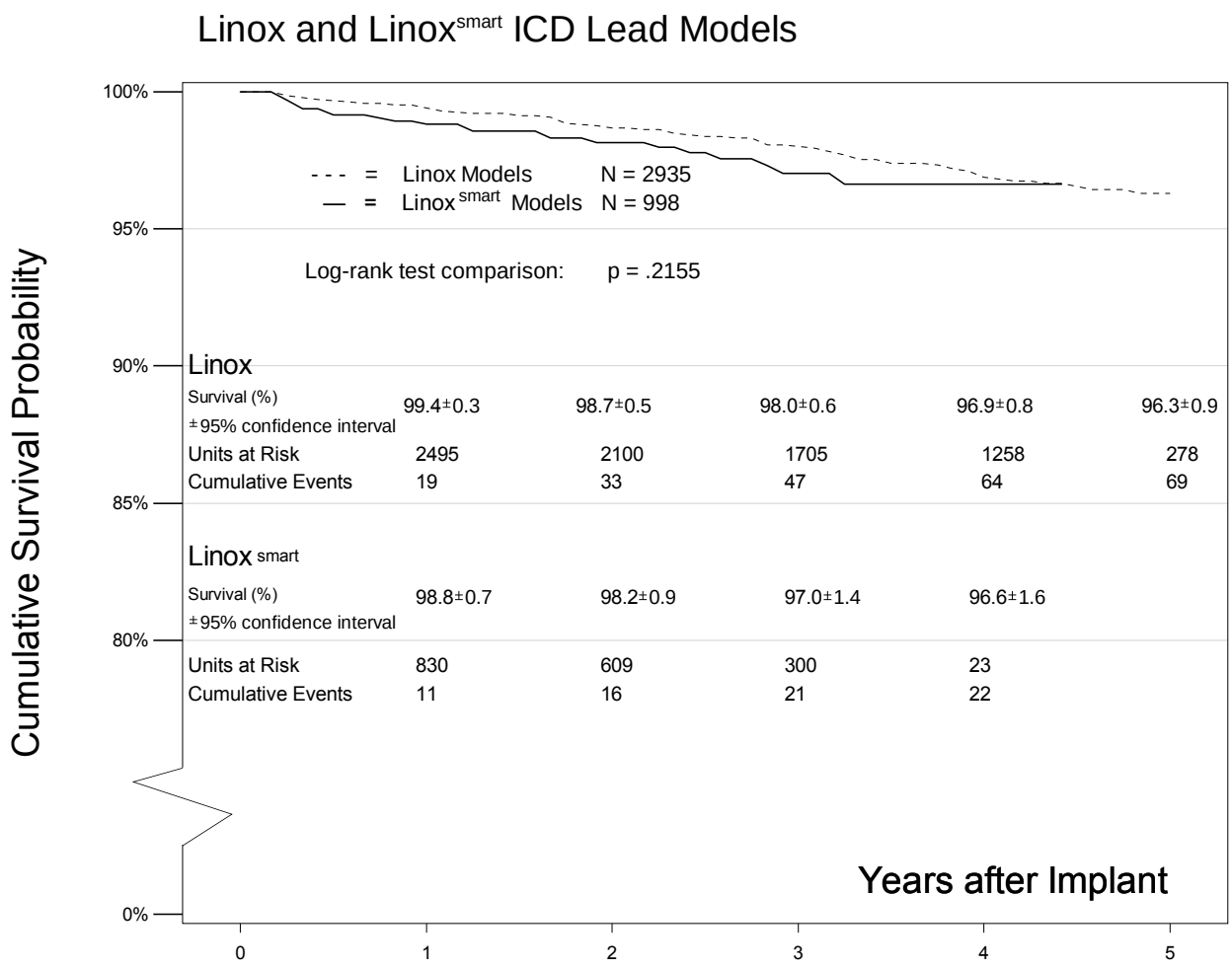
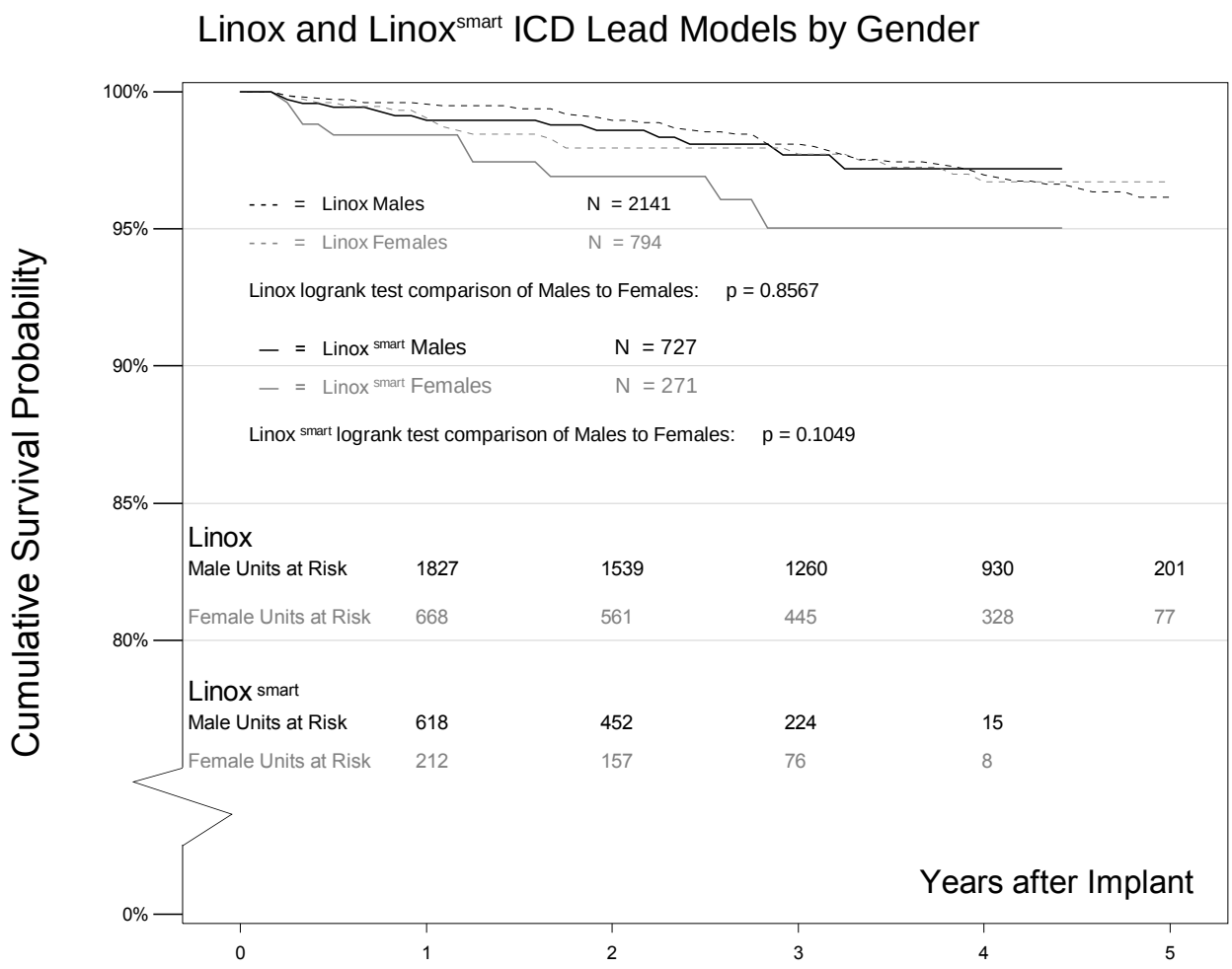


Figure 3: Linox Family Cumulative Survival Probability by Gender



Discussion

To our knowledge, this study represents the most extensive description of performance, safety and longevity of the Linox family of ICD leads published to date: It is large scale (n=3,933 leads), prospective in design, and incorporates a wide sampling of clinical sites (n=146) in both the academic and private practice arenas. In addition, its results are buttressed by having all AEs adjudicated by members from an independent panel of 5 EPs not participating in the indexed clinical trials.

This study concludes that the performance of Linox and Linox^{smart} ICD leads, as determined by electrical parameters is excellent: Measures of sensing, impedance and pacing thresholds met or exceeded clinically acceptable values. Further, this study validates that Linox and Linox^{smart} ICD leads can be implanted safely with a low overall rate of acute AEs (0.36%) and a correspondingly low overall rate of chronic AEs (2.31%). Finally, this study confirms the durability of Linox and Linox^{smart} ICD leads, with an estimated cumulative survival probability of 96.3% at 5 years for the Linox ICD leads and 96.6% at 4 years for the Linox^{smart} leads.

Comparisons With Other Studies

The lead survival estimates for the Linox lead models in this study were within a comparable range to manufacturer product performance report (MPPR) values (96.3-97.4%) at 5 years for each lead.[12] The lead survival estimates for the Linox^{smart} lead models in this study were slightly lower than the range reported in the MPPR (97.8-98.9%) at 3 years, although the this study had longer-term follow-up than that reported in the MPPR. This study found no significant difference in lead survivability between the Linox and Linox^{smart} leads (p=0.2155).

Few studies of ICD lead survival have included similar large numbers of ICD leads as the current study. Reported ICD lead survival rates vary significantly between studies, but generally fall within a range of 85 -95% at 5 years.[7-9,20-22] Disparities in study design, definitions of lead performance, patient characteristics, implant methodology and duration of follow-up among other variables confound direct comparisons between studies, manufacturers and specific lead models. Nonetheless, the authors think that such comparisons are necessary to enhance the general understanding of Linox and Linox^{smart} lead performance, keeping in mind these comparative limitations.

The Linox and Linox^{smart} leads in this study demonstrated favorable lead survivability when compared to 4,078 Medtronic (Sprint family); Boston Scientific (Endotak family) and St. Jude (Riata & Durata family) ICD leads (93 – 97% estimated at 5 years) evaluated in a large-scale retrospective, single center study by Cohen et al.[23] In addition, Linox and Linox^{smart} leads had better survivability when compared to a University of Pittsburgh Medical Center study of 5,288 Medtronic, Boston Scientific, or St. Jude Medical transvenous ICD leads as a whole (89.3% at 5 years, with a mean follow-up of 3.7 years), and were similar to the single best individual lead survival rate reported in the same study (98.5%).[22]

A pooled analysis of 3 large-scale, prospective SJM registries (OPTIMUM, SCORE and SJ4 PAS) evaluated 10,835 patients who received 11,016 SJM leads with Optim insulation (8,147 Durata and 2,869 Riata ST Optim) attached to a matched manufacturer ICD or CRT-D device found a mechanical failure- free survival rate of 99.0% (95% CI 98.4–99.3) at 5 years.[24] Although this value seems significantly better than the lead survival values reported in the current study, it is important to distinguish that the SJM registry studies defined lead survival narrowly by strict mechanical criteria (i.e., failure of the structural integrity of the lead), whereas the current study incorporated broader, system-related AE criteria (e.g., lead dislodgment, oversensing, etc.) to determine lead survival. If the current study were to include only those AEs with lead failures defined by mechanical criteria similar to the SJM registries, estimates of lead survivability for all Linox and Linox^{smart} ICD leads in this study would increase to 99.1% (95% CI: 98.6,99.4) at 4 years.

Another pooled analysis of 4 prospective, SJM-sponsored studies (Advancements in ICD Therapy (ACT), OPTIM Lead InsUlation Material (OPTIMUM), Resynchronization HemodYnamic

Treatment for Heart Failure Management (RHYTHM), and the Post Approval Study (PAS) by Epstein et al. reported lead-related AE rates over a median follow-up of 22 months in 7,497 patients with one of 27 different Riata model of leads: the individual and overall lead-related AE rates for conductor fracture, insulation damage, dislodgement, and perforation (<1% and 1.41%, respectively) were comparable to those for the Linox and Linox^{smart} ICD leads in the current study (<1% and 1.22%).[25] These findings were also congruent with the results of the Porterfield et al. evaluation of 15,387 patients with SJM Riata leads (1500 and 7000 series models) followed over a mean of 18 months at 23 U.S. and 5 German sites, which showed similarly low individual (<1%) and overall (1.70%) AE rates.[26]

A few studies, however, have called into question the performance of the Linox leads in particular.[27,28,29] A recent British Columbian Cardiac Registry (BCCR) study suggested that these leads had a higher-than-expected rate of failure (3.4%) and lower-than-expected 5-year survivability (91.6%) at a median follow-up of 39-months as compared to Durata leads (SJM) (0.4% and 99.4%, respectively).[27] Several significant and potentially confounding issues with the BCCR study exist that may help explain the differences in results compared to the current study: First, the BCCR study had a relatively small sample size (n=477) of Linox ICD leads compared to the current study (n=2,935), and a disparate proportion of patients receiving Linox leads were not only reported to already have multiple leads in situ, but also to have had prior documentation of lead failures compared to the Durata group. Thus, sampling bias may have negatively influenced the results for the Linox group.

Another concern with the BCCR study is that the Linox lead patients predominately received a Medtronic ICD generator, while most Durata lead patients received a St. Jude Medical generator. All of the patients in the current study received a matched-manufacturer generator (i.e.,

Biotronik). This is significant, since the vast majority (11/16 cases, or 69%) of "true lead failures" in the Linox group were attributed to high rate, non-physiological sensing for which no cause could be identified in 45% of the cases at the time of reoperation. Medtronic (Minneapolis, MN) devices employ a proprietary Lead Integrity Alert™ (LIA) algorithm, which is sensitive to detecting non-physiologic intervals, short V-V sensing intervals (NPVVIs)—a factor that may have biased the Linox group toward AEs reporting in the BCCR study.

It is also important to note that Medtronic ICD generators allow both integrated and true bipolar sensing configuration as a programming feature, an uncontrolled factor that may have influenced detection of NPVVIs. In a study of randomly selected patients with Medtronic generators with LIA, Ng et al found that integrated bipolar lead sensing had a higher incidence of one component of the LIA, NPVVIs, without an associated higher rate of true lead malfunction.[30] In fact, *none* of the patients with integrated bipolar lead sensing and NPVVIs demonstrated any clinical evidence of lead malfunction over a mean follow-up of 115.2 months. Moreover, the vast majority of patients with true bipolar lead sensing and NPVVIs (73%) exhibited no true lead failures over a mean follow-up of 86.5 months. It is possible, therefore, that the Linox lead failures were significantly overestimated in the BCCR study by being connected to a Medtronic generator and that Durata lead failures might have been underestimated by not having been connected to Medtronic generators.

Effects of Gender

Important gender differences exist in the incidence, risk factors, and other clinical factors of women with heart disease.[31-43] Clinical characteristics and ICD implant data of women tend to be different than those for men, with women typically being younger at age of ICD implant, having higher LVEF, being less likely to have coronary artery disease, being more likely to have

had ventricular fibrillation, and having lower defibrillation thresholds.[43] Prior studies have suggested an increase in AEs among female patients implanted with ICD leads as compared to men, as well as higher rates of lead failure.[20,44-46] This study analyzed the effect of gender on AEs and found no significant gender interaction. Another similarly unique but encouraging finding of the current study was that measures of Linox and Linox^{smart} lead performance and survivability were similar both between genders and between lead types within a gender.

Effects of Age

Younger patient age (especially pediatric) has been correlated with decreased ICD lead performance, increased AEs and poorer lead survivability when compared to older patients.[20,47-48] This correlation was not observed in the current study for Linox and Linox^{smart} ICD leads: although it included only adult patients (≥18 years), there was no statistical difference between subject age at lead implant and the incidence of AEs (p=0.5748) or lead survivability (p=0.8946) using the REPLACE DARE study age thresholds.

Conclusion

Based on the results of this large-scale study, Linox and Linox^{smart} ICD leads are safe, reliable and infrequently associated with lead-related AEs. Additionally, intermediate-term (4-5 year) estimated cumulative survival probability is favorable, clinically acceptable and within industry standards.[8-9,22,45] Ongoing data collection will confirm longer-term safety and performance of the Linox family of ICD leads.

Acknowledgements

We would like to thank the investigators and centers participating in the GALAXY and CELESTIAL registries.

References

1. Hauser RG, Kallinen LM, Almquist AK, Gornick CC, Katsiyiannis WT: Early failure of a small-diameter high-voltage implantable cardioverter-defibrillator lead. Heart Rhythm 2007; 4:892-896.

2. Hauser RG, Hayes DL: Increasing hazard of Sprint Fidelis implantable cardio-verter defibrillator lead failure. Heart Rhythm 2009; 6:605-610.

3. Farwell D, Green MS, Lemery R, Gollob MH, Birnie DH: Accelerating risk of Fidelis lead fracture. Heart Rhythm 2008; 5:1375-1379.

4. US Food and Drug Administration. FDA Classifies Voluntary Physician Advisory Letter on Riata and Riata ST Silicone Defibrillation Leads as Class I Recall (Urgent Medical Device Advisory) 2011.

5. Hayes D, Freedman R, Curtis AB, Niebauer M, Neal Kay G, Dinerman J, Beau S: Prevalence of externalized conductors in Riata and Riata ST silicone leads: results from the prospective, multicenter Riata Lead Evaluation Study. Heart Rhythm 2013 Dec; 10(12):1778-82.

6. Hauser RG, McGriff D, Retel LK: Riata implantable cardioverter-defibrillator lead failure: analysis of explanted leads with a unique insulation defect. Heart Rhythm 2012 May; 9(5):742-9.

7. Goette A, Cantu F, van Erven L, Geelen P, Halimi F, Merino JL, Morgan JM: Scientific Initiative Committee of the European Heart Rhythm Association. Performance and survival of transvenous defibrillation leads: need for a European data registry. Europace 2009 Jan; 11(1):31-4.

8. Maisel WH, Kramer DB: Implantable Cardioverter-Defibrillator Lead Performance. Circulation 2008; 117:2721-2723.

9. Maisel WH, Hauser RG, Hammill SC, Hauser RG, Ellenbogen KA, Epstein AE, Hayes DL, Alpert JS, Berger RD, Curtis AB, Dubin AM, Estes NA 3rd, Gura MT, Krahn AD, Lampert R, Lindsay BD, Wilkoff BL: Heart Rhythm Society Task Force on Lead Performance Policies and Guidelines; American College of Cardiology (ACC); American Heart Association (AHA). Recommendations from the Heart Rhythm Society Task Force on Lead Performance Policies and Guidelines: developed in collaboration with the American College of Cardiology (ACC) and the American Heart Association (AHA). Heart Rhythm 2009; 6(6):869-85.

10. Love C, Estes NA 3rd: Following leads to improve patient outcomes: it's about time. Heart Rhythm 2014; 11(12):2163-4.

11. Robb MA, Racoosin JA, Sherman RE, Gross TP, Ball R, Reichman ME, Midthun K, Woodcock J: The US Food and Drug Administration's Sentinel Initiative: Expanding the horizons of medical product safety. Pharmacoepidemiol Drug Saf 2012; 21:9-11.

12. Biotronik Product Performance Report July 2015. (2015, July). Retrieved from http://www.biotronik.com/files/38E6CFB4E275DE2CC1257EC800531F89/$FILE/Product_Performance_Report_July_2015.pdf

13. International Standard ISO 5841-2 (Third edition) Implants for surgery – Cardiac pacemakers – Part 2: Reporting of clinical performance of populations of pulse generators or leads. (2014, August 1). Retrieved from http://www.iso.org

14. Greenwood M: *The natural duration of cancer. Reports on Public Health and Medical Subjects, No 33*. London: H M S O, 1926, p. 1-26.

15. Kalbfleisch JD, Prentice R: *The Statistical Analysis of Failure Time Data*. New York: John Wiley & Sons, 1980.

16. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemotherapy Reports 1966; 50:163-170.

17. Margolin BH: *Test for Trend in Proportions* In Kotz S, Johnson NL, eds: Encyclopedia of Statistical Sciences, vol. 9, New York: John Wiley & Sons, 1988, pp, 334–336.
18. Mehta C, Patel N: A Network Algorithm for Performing Fisher's Exact Test in Contingency Tables. Journal of the American Statistical Association 1983; 78:427-434.
19. Chung MK, Holcomb RG, Mittal S, Steinberg JS, Gleva MJ, Mela T, Ulsan DZ, Mitchell K, Poole J: REPLACE DARE (Death After Replacement Evaluation) Score Determinants of All-Cause Mortality After Implantable Device Replacement or Upgrade From the REPLACE Registry. Circ Arrhythm Electrophysiol 2014; 7:1048-1056.
20. Kleemann T, Becker T, Doenges K, Vater M, Senges J, Schneider S, Saggau W, Weisse U, Seidl K: Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of 10 years. Circulation 2007; 115:2474-2480.
21. Eckstein J, Koller MT, Zabel M, Kalusche D, Schaer BA, Osswald S, Sticherling C: Necessity for surgical revision of defibrillator leads implanted long-term: causes and management. Circulation 2008; 117(21):2727-2733.
22. Liu J, Brumberg G, Rattan R, Patel D, Adelstein E, Jain S, Saba S: Longitudinal Follow-Up of Implantable Cardioverter Defibrillator Leads. Am J Cardiol 2014; 113:103-106.
23. Cohen T, Asheld W, Germano J, Islam S, Patel D: A comparative Study of Defibrillator Leads at a Large-Volume Implanting Hospital: Results From the Pacemaker and Implantable Defibrillator Leads Survival Study ("PAIDLESS"). J Invasive Cardiol 2015; 27:292-300.
24. Cairns JA, Epstein AE, Rickard J, Connolly SJ, Buller C, Wilkoff BL, Pogue J, Themeles E, Healey JS: Prospective long-term evaluation of Optim-insulated (Riata ST Optim and Durata) implantable cardioverter-defibrillator leads. Heart Rhythm 2014; 11(12):2156-62.
25. Epstein AE, Baker JH 2nd, Beau SL, Deering TF, Greenberg SM, Goldman DS: Performance of the St. Jude Medical Riata leads. Heart Rhythm 2009; 6(2):204-9.

26. Porterfield JG1, Porterfield LM, Kuck KH, Corbisiero R, Greenberg SM, Hindricks G, Wazni O, Beau SL, Herre JM: Clinical performance of the St. Jude Medical Riata defibrillation lead in a large patient population. J Cardiovasc Electrophysiol 2010; 21(5):551-6.
27. Padfield GJ, Steinberg C, Karim SS, Tung S, Bennett MT, Le Maitre JP, Bashir J: Early failure of the Biotronik Linox Implantable Cardioverter Defibrillator Lead. J Cardiovasc Electrophysiol 2015; 26:274-281.
28. Howe AJ, McKeag NA, Wilson CM, Ashfield KP, Roberts MJ: Insulation Failure of the Linox Defibrillator Lead: A Case Report and Retrospective Review of a Single Center Experience. J Cardiovasc Electrophysiol. 2015; 26(6):686-9.
29. Manfredi JA, Smithgall SM, Kircher CM, Lollis MA: Insulation failure with externalized conductor of a Linox SD lead: a case report. J Cardiovasc Electrophysiol. 2014; 25(4):440-1.
30. Ng J, Chopra N, Barbhaiya C, Reichlin T, Nof E, Nagashima K, Tadros T, Koplan BA: Incidence of nonphysiologic short VV intervals detected by the sensing integrity counter with integrated bipolar compared with true bipolar leads: clinically inconsequential or cause for concern? J Interv Card Electrophysiol 2014; 39:281-285.
31. Chandra NC, Ziegelstein RC, Rogers WJ, Tiefenbrunn AJ, Gore JM, French WJ, Rubison M: Observations of the treatment of women in the United States with myocardial infarction: a report from the National Registry of Myocardial Infarction-I. Arch Intern Med 1998; 158:981-988.
32. Marrugat J, Sala J, Masia R, Pavesi M, Sanz G, Valle V, Mollina L, Seres L, Elousa R: Mortality Differences Between Men and Women Following First Myocardial Infarction. JAMA 1998; 280:1405-1409.
33. Maynard C, Every NR, Martin JS, Kudenchuk PJ, Weaver WD: Association of gender and survival in patients with acute myocardial infarction. Arch Intern Med 1997; 157:1379-1384.
34. Larsen JA, Kadish AH: Effects of Gender on Cardiac Arrhythmias. J Cardiovasc Electrophysiol 1998; 9:655-664.
35. Wolbrette D, Patel H: Arrhythmias and women. Curr Opin Cardiol 1999; 14:36-43.

36. Cupples LA, Gagnon DR, Kannel WB: Long- and short-term risk of sudden coronary death. Circulation 1992; 85:11-18.
37. Kannel WB, Wilson PWF, D'Agostino RB, Cobb J: Sudden coronary death in women. Am Heart J 1998; 136:205-212.
38. Lerner DJ, Kannel WB: Patterns of coronary heart disease morbidity and mortality in the sexes: A 26-year follow-up of the Framingham population. Am Heart J 1986; 111:383-390.
39. Dittrich H, Gilpin E, Nicod P, Cali G, Henning H, Ross J: Acute myocardial infarction in women: Influence of gender on mortality and prognostic variables. Am J Cardiol 1988; 62:1-7.
40. Albert CM, McGovern BA, Newell JB, Ruskin JN: Sex Differences in Cardiac Arrest Survivors. Circulation 1996; 93:1170-1176.
41. Ho KKL, Anderson KM, Kannel WB, Grossman W, Levy D: Survival After the Onset of Congestive Heart Failure in Framingham Heart Study Subjects. Circulation 1993; 88:105-115.
42. Adams KF Jr, Dunlap SH, Sueta CA, Clarke SW, Patterson JH, Blauwet MB, Jensen LR, Tomasko L, Koch G: Relation between gender, etiology and survival in patients with symptomatic heart failure. J Am Coll Cardiol 1996; 28:1781-1788.
43. Pires LA, Sethuraman B, Guduguntla VD, Todd KM, Yamasaki H, Ravi S: Outcome of Women Versus Men with Ventricular Tachyarrhythmias Treated with the Implantable Cardioverter Defibrillator. J Cardiovasc Electrophysiol 2002; 13:563-568.
44. Russo AM, Daugherty SL, Masoudi FA, Wang Y, Curtis J, Lampert R: Gender and outcomes after primary prevention implantable cardioverter-defibrillator implantation: Findings from the National Cardiovascular Data Registry (NCDR). Am Heart J 2015; 170(2):330-8.
45. Masoudi FA, Go AS, Magid DJ, Cassidy-Bushrow AE, Gurwitz JH, Liu TI, Reynolds K, Smith DH, Reifler LM, Glenn KA, Fiocchi F, Goldberg R, Gupta N, Peterson PN, Schuger C, Vidaillet H, Hammill SC, Greenlee RT: Age and sex differences in long-term outcomes following implantable cardioverter-defibrillator placement in contemporary clinical

practice: findings from the Cardiovascular Research Network. J Am Heart Assoc 2015; 4(6):e002005.

46. MacFadden DR, Crystal E, Krahn AD, Mangat I, Healey JS, Dorian P, Birnie D, Simpson CS, Khaykin Y, Pinter A, Nanthakumar K, Calzavara AJ, Austin PC, Tu JV, Lee DS: Sex differences in implantable cardioverter-defibrillator outcomes: findings from a prospective defibrillator database. Ann Intern Med 2012; 156(3):195-203.

47. Atallah J, Erickson CC, Cecchin F, Dubin AM, Law IH, Cohen MI, Lapage MJ, Cannon BC, Chun TU, Freedenberg V, Gierdalski M, Berul CI: Pediatric and Congenital Electrophysiology Society (PACES). Multi-institutional study of implantable defibrillator lead performance in children and young adults: results of the Pediatric Lead Extractability and Survival Evaluation (PLEASE) study. Circulation 2013; 127(24):2393-402.

48. Alexander ME, Cecchin F, Walsh EP, Triedman JK, Bevilacqua LM, Berul CI: Implications of implantable cardioverter defibrillator therapy in congenital heart disease and pediatrics. J Cardiovasc Electrophysiol 2004; 15(1):72-6.