

# Long-Term Evaluation of Biotronik Linx and Linx<sup>smart</sup> Implantable Cardioverter Defibrillator Leads

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**Long-Term Evaluation of Biotronik Linx Family of ICD Leads.** *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 Linx and Linx<sup>smart</sup> 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 Linx leads and 96.6% at 4 years after implant for Linx<sup>smart</sup> leads. A comparison of the Linx and Linx<sup>smart</sup> 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:* Linx and Linx<sup>smart</sup> 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 Linx family of ICD leads. (*J Cardiovasc Electrophysiol*, Vol. 27, pp. 735-742, June 2016)

*lead, implantable cardioverter defibrillator, cardiac resynchronization therapy, adverse event, reliability, survival, Performance, Biotronik, Linx 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).<sup>1-6</sup> Benchtop 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 underreporting 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.<sup>7-10</sup> 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.<sup>11</sup> To this end, the current study addresses ICD lead performance by prospective analysis of 2 large, multicenter prospective lead performance registries.

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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 Linx family of ICD leads.

## Methods

### Background

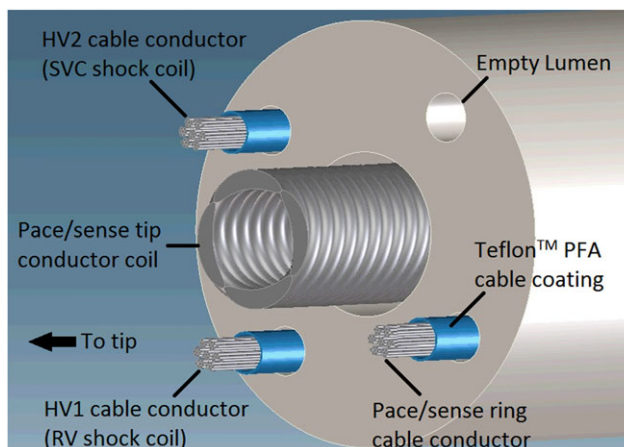
The GALAXY registry is an ongoing multicenter, prospective, non-randomized, 5-year data collection registry designed to gather long-term safety and reliability data on Biotronik's Linx family of ICD leads. A total of 1,997 patients were enrolled at 98 United States (US) sites. The institutional review 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 Linx 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 Linx 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 Linx 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 Linx 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, or inability to provide data on the implanted system, demographics, and adverse events since implant.

The Linx family of ICD leads is differentiated into Linx and Linx<sup>smart</sup> models. Biotronik first received FDA approval for the Linx ICD lead on January 27, 2006 and



**Figure 1.** Cross-section of Linx family SD ICD lead. HV = high voltage; SVC = superior vena cava; PFA = perfluoroalkoxy. For a high quality, full color version of this figure, please see *Journal of Cardiovascular Electrophysiology's* website: [www.wileyonlinelibrary.com/journal/jce](http://www.wileyonlinelibrary.com/journal/jce)

for the Linx<sup>smart</sup> 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 Linx and 67,490 Linx<sup>smart</sup> ICD leads.<sup>12</sup>

All Linx family leads are implantable, transvenous ICD leads with dedicated sensing and pacing bipoles. The tip and ring electrodes comprise 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 Linx family leads have 1 shock electrode that is positioned in the right ventricle. The Linx SD, Linx TD, Linx<sup>smart</sup> SD, and Linx<sup>smart</sup> TD leads have an additional proximal shock electrode for placement in the superior vena cava. All Linx family leads have silicone insulation. Linx<sup>smart</sup> models are additionally treated with a surface treatment, Silglide<sup>®</sup>. Silglide<sup>®</sup> 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 Linx family leads have a lead diameter of 7.8 F. The pace/sense cable conductor is made of 7 × 7 filars of MP35N<sup>®</sup> (a nickel-cobalt based proprietary alloy) material and the shock coil cable conductor is made of 7 × 7 filars of MP35N<sup>®</sup>/silver. The pace/sense and shock coil cable conductors are wrapped with a Teflon<sup>™</sup> Perfluoroalkoxy (PFA) coating. The inner conductor is a 4 filar wire conductor made of MP35N<sup>®</sup>. The Linx family has 4 cable lumens to provide a symmetric cross-sectional design. A cross-section of a Linx family SD ICD lead is shown in Figure 1. A summary of the Linx lead models included in this analysis is shown in Table 1.

### 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

**TABLE 1**  
Linx Family of ICD Leads

Name	Fixation	Coils	Insulation
Linx S	Active	Single	Silicone
Linx SD	Active	Dual	Silicone
Linx T	Passive	Single	Silicone
Linx TD	Passive	Dual	Silicone
Linx <sup>smart</sup> S	Active	Single	Silicone with Silglide® surface treatment
Linx <sup>smart</sup> SD	Active	Dual	Silicone with Silglide® surface treatment
Linx <sup>smart</sup> TD	Passive	Dual	Silicone with Silglide® surface treatment

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 2 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 Linx 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 Linx 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.<sup>13</sup> 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  $< 200 \Omega$  or  $> 3,000 \Omega$  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 Linx and Linx<sup>smart</sup> ICD leads. The standard error (SE) for the estimated survival (freedom from AEs) was calculated using the method of Greenwood,<sup>14</sup> and corresponding upper and lower confidence limits were calculated using the log–log transformation of Kalbfleisch and Prentice.<sup>15</sup> All leads were assigned a censor or event date and status categorization per ISO 5841-2 (Third edition).<sup>13</sup> 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 Linx and Linx<sup>smart</sup> survival function estimates were compared using a log-rank test (Mantel–Haenszel).<sup>16</sup> 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 (2-sided).<sup>17</sup> General tests of association were done comparing AE event categories using Fisher’s exact (2-sided) test.<sup>18</sup>

## 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  $67.0 \pm 12.2$  years old and a mean left ventricular ejection fraction (LVEF) of  $28.0 \pm 9.7\%$  ( $n = 3,564$ ). 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 Linx leads and 2.3 years for Linx<sup>smart</sup> 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 Linx 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  $12.6 \pm 5.46$  mV for Linx leads and  $13.2 \pm 5.83$  mV for Linx<sup>smart</sup> leads. The mean pacing threshold value at 0.5 ms pulse width was  $0.6 \pm 0.34$  V for Linx leads and  $0.6 \pm 0.39$  V for Linx<sup>smart</sup> leads. The mean impedance was  $560 \pm 139.3$  ohms for Linx leads and  $556 \pm 132.3$  ohms for Linx<sup>smart</sup> leads.

### Adverse Events

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).<sup>13</sup>

The estimated cumulative survival probability is 96.3% at 5 years after implant for Linx leads and 96.6% at 4 years after implant for Linx<sup>smart</sup> leads. A comparison of the Linx and Linx<sup>smart</sup> survival functions did not identify evidence of a survival difference ( $P = 0.2155$ ). Figure 2 displays a Kaplan–Meier actuarial graph of Linx and Linx<sup>smart</sup> 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 the venous access method used during the initial implant procedures for the Linx and Linx<sup>smart</sup> 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 Linx family (Linx and Linx<sup>smart</sup>) leads between females and males was not statistically significant ( $P = 0.3537$ ), nor were comparisons between genders within the individual Linx models ( $P = 0.8567$ ) or Linx<sup>smart</sup> models ( $P = 0.1049$ ). A comparison of the survival functions for all males with Linx leads and all males with Linx<sup>smart</sup> 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 Linx<sup>smart</sup> and Linx 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 ( $P = 0.5748$ ).<sup>19</sup> 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 ( $P = 0.8946$ ).<sup>19</sup>

### Discussion

To our knowledge, this study represents the most extensive description of performance, safety, and longevity of the Linx family of ICD leads published to date: It is large in 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 Linx and Linx<sup>smart</sup> 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 Linx and Linx<sup>smart</sup> 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

TABLE 3  
Adverse Event Details

Adverse Events	Results				P-Value*		
	Total	Male	Female				
<b>Chronic events, n (%)</b>							
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
<b>Total</b>	<b>91</b>	<b>(2.31%)</b>	<b>63</b>	<b>(2.20%)</b>	<b>28</b>	<b>(2.63%)</b>	<b>0.4061</b>
<b>Acute events, n (%)</b>							
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
<b>Total</b>	<b>14</b>	<b>(0.36%)</b>	<b>8</b>	<b>(0.28%)</b>	<b>6</b>	<b>(0.56%)</b>	<b>0.2256</b>

Linx and Linx<sup>smart</sup> ICD leads, with an estimated cumulative survival probability of 96.3% at 5 years for the Linx ICD leads and 96.6% at 4 years for the Linx<sup>smart</sup> leads.

### Comparisons with Other Studies

The lead survival estimates for the Linx 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.<sup>12</sup> The lead survival estimates for the Linx<sup>smart</sup> 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 Linx and Linx<sup>smart</sup> leads ( $P = 0.2155$ ).

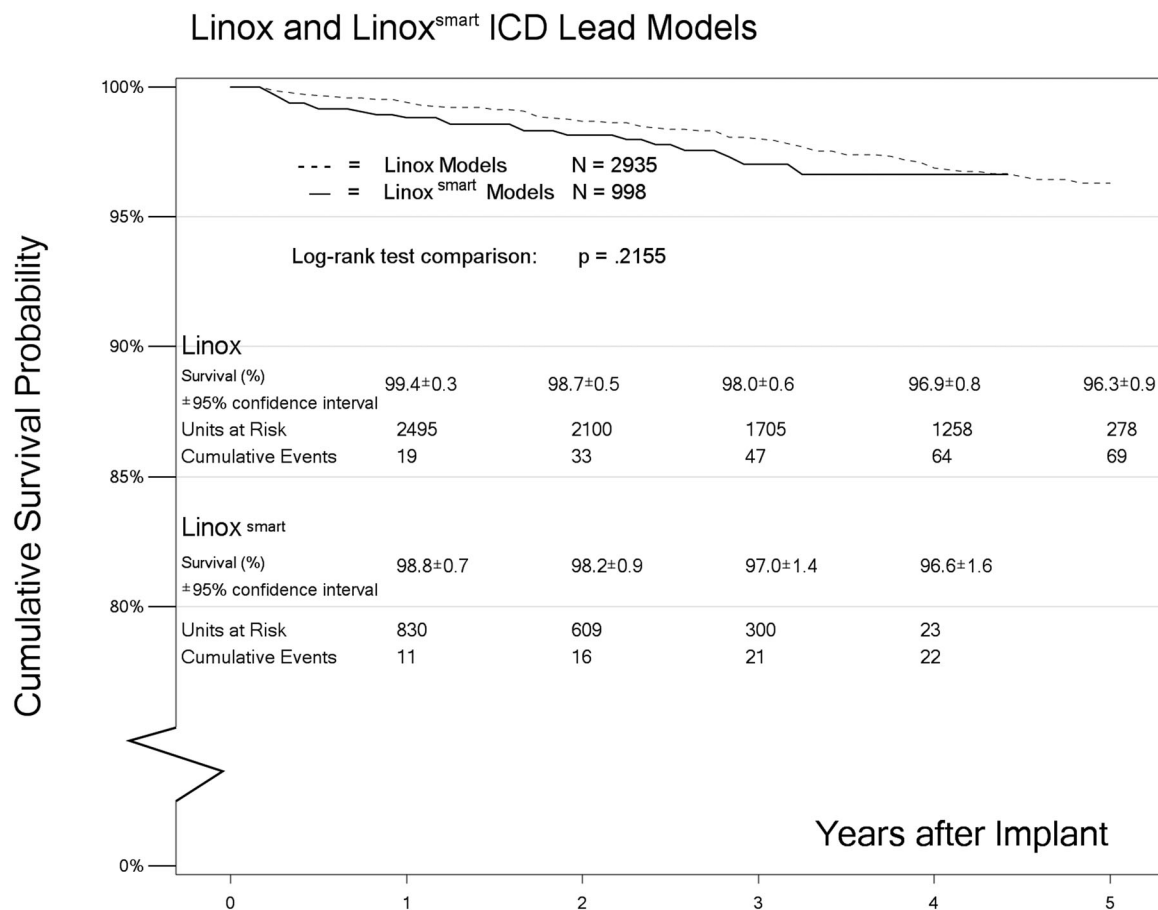
Few studies of ICD lead survival have included similar large numbers of ICD leads as the current study. Reported ICD lead survival rates vary significantly between studies, but generally fall within a range of 85–95% at 5 years.<sup>7-9,20-22</sup> Disparities in study design, definitions of lead performance, 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 Linx and Linx<sup>smart</sup> lead performance, keeping in mind these comparative limitations.

The Linx and Linx<sup>smart</sup> leads in this study demonstrated favorable lead survivability when compared to 4,078 Medtronic (Sprint family); Boston Scientific (Endotak family), and St. Jude (Riata and Durata family) ICD leads (93–97% estimated at 5 years) evaluated in a large-scale retrospective, single center study by Cohen *et al.*<sup>23</sup> In addition, Linx and Linx<sup>smart</sup> 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%).<sup>22</sup>

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.<sup>24</sup> 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 Linx and Linx<sup>smart</sup> 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 1 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 Linx and Linx<sup>smart</sup> ICD leads in the current study (< 1% and 1.22%).<sup>25</sup> 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 US and 5 German sites, which showed similarly low individual (< 1%) and overall (1.70%) AE rates.<sup>26</sup>



**Figure 2.** Linix family cumulative survival probability.

A few studies, however, have called into question the performance of the Linix leads in particular.<sup>27-29</sup> 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).<sup>27</sup> 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 Linix ICD leads compared to the current study ( $n = 2,935$ ), and a disparate proportion of patients receiving Linix 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 Linix group.

Another concern with the BCCR study is that the Linix 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 majority (11/16 cases, or 69%) of “true lead failures” in the Linix 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, USA) devices employ a proprietary Lead Integrity Alert<sup>TM</sup> (LIA) algorithm, which is sensitive to detecting non-physiologic intervals, short V-V

sensing intervals (NPVVI)—a factor that may have biased the Linix 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 NPVVI. 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, NPVVI, without an associated higher rate of true lead malfunction.<sup>30</sup> In fact, none of the patients with integrated bipolar lead sensing and NPVVI 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 NPVVI (73%) exhibited no true lead failures over a mean follow-up of 86.5 months. It is possible, therefore, that the Linix 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.<sup>31-43</sup> 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,

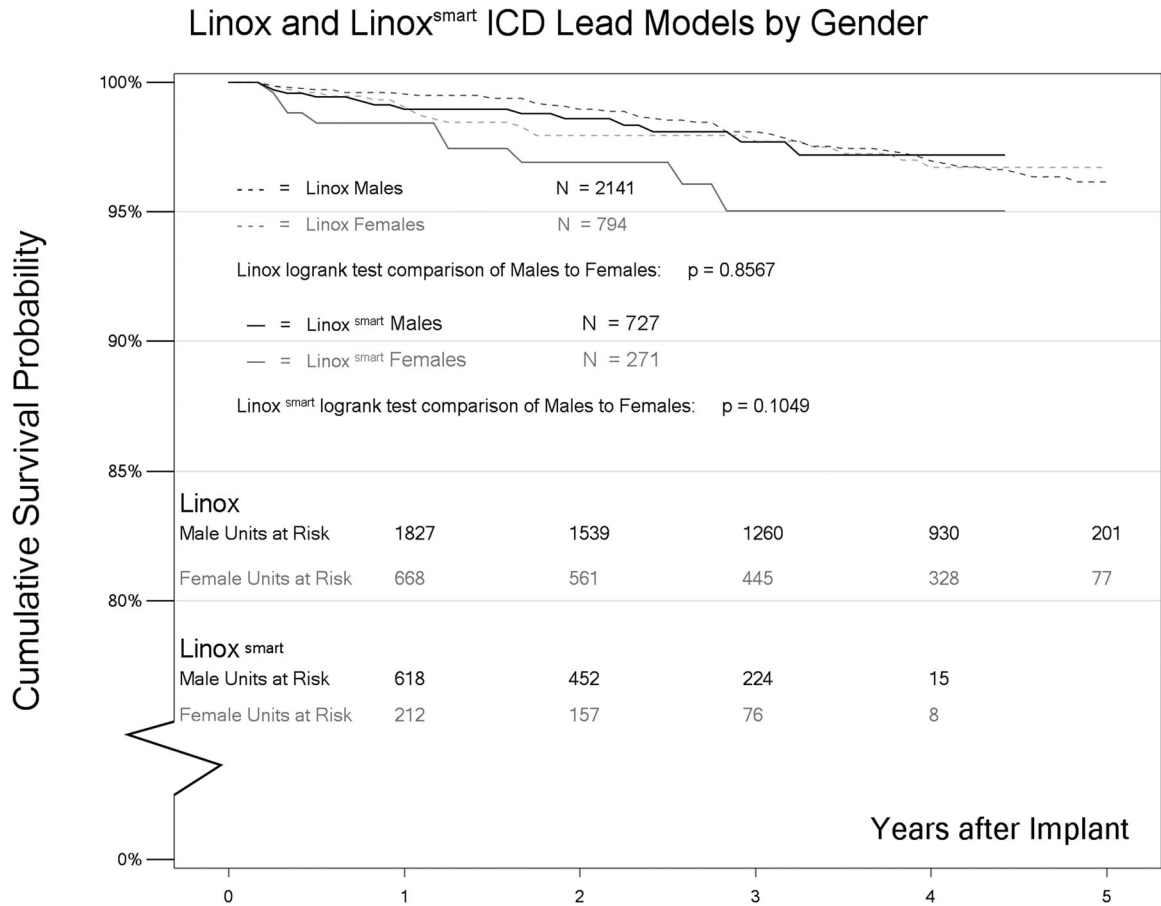


Figure 3. Linx family cumulative survival probability by gender.

being more likely to have had ventricular fibrillation, and having lower defibrillation thresholds.<sup>43</sup> 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.<sup>20,44-46</sup> 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 Linx and Linx<sup>smart</sup> 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.<sup>20,47,48</sup> This correlation was not observed in the current study for Linx and Linx<sup>smart</sup> ICD leads: Although it included only adult patients ( $\geq 18$  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, Linx and Linx<sup>smart</sup> 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 indus-

try standards.<sup>8,9,22,45</sup> Ongoing data collection will confirm longer-term safety and performance of the Linx family of ICD leads.

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