Active Surveillance of the Implantable Cardioverter-Defibrillator Registry for Defibrillator Lead Failures

BACKGROUND: Several defibrillator leads have been recalled due to early lead failure leading to significant patient harm. Confirming the safety of contemporary defibrillator leads is essential to optimizing treatment for patients receiving implantable cardioverter-defibrillators (ICDs). We therefore sought to assess the comparative long-term safety of the 4 most commonly implanted ICD leads within the National Cardiovascular Data Registry ICD Registry.

METHODS AND RESULTS: A propensity-matched survival analysis of the ICD Registry was performed evaluating 4 contemporary ICD leads in patients receiving an ICD system for the first time. All patients in the ICD Registry aged ≥18 years who underwent an implant of an ICD between April 1, 2011 and March 31, 2016 were included. Monitoring of safety began with ICD implant and continued up to 5 years. A meaningful difference in ICD failure rate was defined as twice (or more) the lead failure rate observed in the propensity-matched comparator patients. Among the 374,132 patients who received a new ICD implant, no safety alerts were triggered for the primary safety end point of lead failure for any of the high energy leads studied. Estimated rates of freedom from lead failure at 5 years ranged from 97.7% to 98.9% for the 4 high-energy leads of interest.

CONCLUSIONS: Though limited by incomplete long-term outcomes ascertainment, active surveillance of the ICD Registry suggests that there were no meaningful differences in the rate of ICD high-energy lead survival for the 4 most commonly used high-energy ICD leads.
WHAT IS KNOWN

• Several defibrillator leads have been recalled due to early failures; however, systems to broadly and prospectively compare approved defibrillator lead performance have not been tested.

WHAT THE STUDY ADDS

• Active, postapproval safety surveillance of the most commonly used defibrillator leads through prospective comparative safety monitoring is feasible using a large, representative, clinical registry and prespecified surveillance methods.
• Defining a clinically meaningful difference in defibrillator lead failure, as compared with propensity-matched patients receiving alternative leads, facilitated the near real-time comparison of performance of 4 contemporary leads.
• The study validates strategy of prospective, active surveillance of accruing clinical datasets for the purpose of assuring the safety of high-risk medical devices.

Ensuring the safety of medical devices after Food and Drug Administration approval and market release is critically important but challenging for several reasons. Premarket studies of medical devices are frequently limited by small sample size, highly selected patient and provider populations, and relatively short duration of follow-up to ensure postapproval safety.1-5 Additionally, traditional postapproval safety monitoring relies primarily on voluntary reporting of adverse events by providers and hospitals, resulting in incomplete ascertainment of device safety data.6-11 Prospective, active surveillance of medical devices utilizing sequential monitoring of large, representative clinical data sources directly addresses many of these gaps and has been identified as a priority by the Food and Drug Administration.12-16 We developed a suite of active surveillance software tools, denoted as data extraction and longitudinal trend analysis system (DELTAX), to leverage data from high-quality data repositories to support active monitoring of the safety of medical devices.17-20 The methods and informatics infrastructure of DELTA have been previously validated in evaluation of medical device failure or complication rates at defined time points after initial implantation.14,15,21 However, survival methods have not been used for prospective surveillance of an accruing clinical dataset to assess the freedom from failure of a medical device.

Previous investigations have identified several examples of early failure of high energy implantable cardioverter-defibrillator (ICD) leads due to a variety of failure mechanisms22 that have led to significant morbidity and rare fatalities23,24 and device recalls that affected hundreds of thousands of patients. While contemporary ICD leads have undergone extensive evaluation to ensure that they do not have failure mechanisms that are similar to the previously recalled leads, questions regarding their safety have been raised.25 Prospective, active surveillance of ICD lead performance using real-world evidence has been proposed as a promising strategy to detect increased rates of high-energy lead failures as quickly as possible in the postmarket setting.11,26-29 The ICD Registry DELTA study (ICD-DELTA) was therefore designed to evaluate the active surveillance of a national cardiovascular registry of ICD lead survival. The primary objective of ICD-DELTA is to validate a strategy of prospective, active, safety surveillance of the NCDR ICD Registry based on prospective, propensity-matched survival analysis of contemporary high-energy ICD leads.

METHODS

Study Design and Oversight

In accordance with the AHA Journal’s implementation of the Transparency and Openness Promotion Guidelines, the investigators will share the analytic system used for this study as an open source software tool. However, because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the NCDR ICD Registry Research and Publications Committee at ncdrresearch@acc.org.

In 2014, a written protocol was developed prespecifying the clinical end points, analytic methods, sensitivity analyses, and plans for interim data reviews. As part of the protocol, a study oversight committee was established with representation from NCDR, Food and Drug Administration, and the DELTA analytic center. The institutional review board of the NCDR reviewed and approved the study protocol, and the final study protocol was approved before the review of any study data. In addition, the institutional review board of the Lahey Hospital and Medical Center waived the need for approval.

Patient Eligibility, Device Exposures, and End Point Definitions

All patients in the NCDR ICD Registry aged ≥18 years who underwent an implant of an ICD with a high-energy defibrillation lead between April 1, 2011 and March 31, 2016 were included in the study. Patients younger than 18 years old at time of implant, or those with prior ICD implantation (as documented in the registry) were excluded. We evaluated the safety of the 4 most commonly implanted high-energy leads used in contemporary cardiovascular practice. These included the following: (1) Durata (Abbott Vascular, formerly St. Jude Medical, Inc), (2) Endotak Reliance (Boston Scientific Corporation), (3) Sprint Quattro Secure (Medtronic), and the (4) Linox (Biotronik) ICD leads.

The primary safety outcome of interest was survival free of lead failure for any reason as evidenced by a record in the ICD Registry of a subsequent procedure in which the lead

Circ Cardiovasc Qual Outcomes. 2020;13:e006105. DOI: 10.1161/CIRCOUTCOMES.119.006105
was removed and/or replaced. Lead failures were identified for all records in the registry where a high energy lead was documented to be abnormal or was replaced, with documentation of implantation of a new high-energy ICD lead. Lead failure records were then matched to an initial implant case, based on exact match of the ICD Registry institution specific patient identifier and agreement between the follow-up record and the index implantation of the ICD system or lead implanted. The prespecified secondary end point evaluated late lead survival and included only those patients who did not suffer lead failure within 30 days of initial ICD implantation. The secondary end point of freedom from late lead failure thereby eliminated a common cause of procedural-related lead placement failures.

### Active Surveillance System

We performed our analysis utilizing an active clinical-data surveillance system, denoted DELTA. DELTA is composed of a collection of integrated software components linking open-source database management and statistical analytical tools. DELTA has the capability to prospectively monitor clinical data repositories for adverse safety signals and is designed to support risk-adjusted prospective safety surveillance analyses of complex clinical data sets. DELTA has been previously validated for prospective monitoring of clinical registries and clinical data sets and is available as an open-source software package with associated technical documentation.13–15

Patient-level data from the ICD Registry were fully de-identified before being provided to DELTA. Data were delivered to DELTA on a predetermined schedule of quarterly updates, and the cumulative safety analysis was automatically regenerated within DELTA at 2 prescheduled times (once after 18 and 36 months of data were available) and for a final analyses after the full 60 months of data were available. Final study results are based on the final data set and surveillance outcomes after the full 60 months of data were analyzed.

### Propensity Score Matching and Event Rate Estimation

We developed multivariable-adjusted logistic regression models to estimate the probability of being treated with each lead of interest, conditional on the included covariates. The non-parsimonious model included previously identified factors for increased risk of lead failure,22,30,31 as well as factors considered to influence the selection of a lead. A total of 10 variables were included in the final propensity score model. Demographic and comorbid variables included age, sex, body mass index, diabetes mellitus, end-stage kidney disease requiring dialysis, history of coronary bypass surgery, preprocedural left ventricular ejection fraction, history of ischemic heart disease, hypertrophic cardiomyopathy, NYHA functional classification, and whether the index ICD implantation was indicated for primary versus secondary prevention of sudden death.

For each ICD lead of interest, a propensity score matched control population was identified from the population of patients treated with any of the other ICD leads, resulting in a total of 4 device-specific comparisons. The propensity matched comparison group was selected on the basis of the propensity score model. Matched controls who underwent initial ICD implant during the same half year as the ICD implantation of the ICD lead of interest were selected in a 1:1 ratio using a fixed caliper width of 0.2 SD of the logit of the propensity score9,14,32 using a greedy matching algorithm. At each quarterly data upload, the DELTA system generated a new propensity score from the accumulating data and rematched the case sets and adverse event rates were calculated. Missing data were handled using univariate rules, assuming absence of a condition for dichotomous variables, and using the sex-specific median value for continuous variables. The relative covariate balance between the exposed (ICD lead of interest) and unexposed (alternate ICD lead) groups was assessed using the absolute standardized difference (percentile) in covariate means and proportions, with values >10% considered severely imbalanced.33

Because we anticipated that the large expected sample size might result in statistically significant differences in estimated survival despite very small absolute differences, we prespecified a threshold to determine a clinically meaningful difference in lead failure. We defined the DELTA Hazard Ratio as the ratio of estimated failure rates (namely: [1−estimated survival for the lead of interest]/[1−estimated survival of the matched control population]), at the end of the period of analysis. DELTA safety alerts were therefore triggered if the propensity score-matched Kaplan-Meier survival probability curve for the device of interest (case) demonstrated a DELTA Hazard Ratio ≥2.0, while also requiring the survival analysis stratified log-rank test to be significant at the P=0.05 level.34

In addition, prespecified subgroups were explored for evidence of uniquely increased risk of lead failure. These subgroups included: age ≥60 years, female sex, primary versus secondary prevention, patients with diabetes mellitus, patients with end-stage renal disease, and type of ICD system (CRT, dual chamber or single chamber systems). Separately, the secondary end point of freedom from late lead failure (>30 days after implantation) was assessed for each of the high-energy leads of interest.

As recommended by the study oversight committee, a prespecified falsification-hypothesis analysis was performed to assess the potential of residual confounding after propensity matching. In a propensity score-matched study, a falsification-hypothesis analysis evaluates the original matched patient cohorts for the development of postprocedural outcome for which no difference in risk is expected between the groups treated with device versus another. In this study, the original matched patient cohorts were evaluated for the subsequent upgrade of the ICD system to a biventricular resynchronization therapy system, a development that was predicted to be independent of the selection of the original high-energy lead.

Given the significant limitations, including incomplete ascertainment, in use of the ICD Registry to determine the relative frequency of lead failures, as well as the inability to perform any additional audits of the clinical outcomes using the limited analytic dataset available for analyses, the ICD Registry DELTA study oversight committee recommended that all publicly reported study results be masked. The specific ICD leads are thus denoted as lead A, B, C, or D. This masking strategy was implemented to protect against the risk of a false positive safety report on the basis of uncertain source data.
RESULTS
A total of 629,326 patients in the ICD Registry underwent a procedure related to an ICD system between March 1, 2011 and March 31, 2016. Among these, 374,132 cases involved the implantation of a new ICD system and represented the study population for this analysis (Figure I in the Data Supplement). New implants of the leads of interest ranged from 20,789 to 145,289 during the study period (Table I in the Data Supplement). The mean age of study patients was 65 years, 39% had diabetes mellitus, and 29% were female. Approximately 58% of study participants had ischemic cardiomyopathy, and 78% received the ICD for primary prevention of sudden death (Table II in the Data Supplement).

Overall, propensity score matching resulted in 99.9% of high energy leads matched with alternative leads. Post-matching standardized differences were <0.10 for each covariate within each of the leads of interest, indicating adequate distribution of risk factors between cohorts. The propensity matched results for Lead A are provided in Table 1, with the results of other high-energy leads provided in Tables III through V.

After a total of 5 years of surveillance representing 20 calendar quarters for data analysis, no DELTA safety alerts were triggered for the primary safety end point of lead failure for any of the high-energy leads studied (Figure 1; Figures II through IV in the Data Supplement). Estimated rates of freedom from lead replacement at 5 years ranged from 97.7% to 98.9% for the 4 high-energy leads of interest. While the log-rank statistic of the difference in survival curves frequently resulted in a P value <0.05, at no point in the analysis did the absolute failure rate for an individual lead exceed twice the failure rate of the comparator control population (Table 2).

Of all lead failures identified, 44% occurred within the first 30 days of initial implant, ranging from 39.5% to 52.3% for the 4 high-energy leads of interest. After 5 years of surveillance, there were no DELTA safety alerts triggered for the secondary end point of survival free from late lead failure (ie, >30 days post-implant). Estimated rates of freedom from late lead failure at 5 years ranged from 98.1% to 99.1% for the 4 high-energy leads of interest (Table VI in the Data Supplement).

The protocol-specified interim analyses were performed after 18 and 36 months of data collection and demonstrated no clinically meaningful differences in high-energy lead survival at any point in time (Table VII in the Data Supplement). Similarly, no differences in freedom from lead replacement were observed in the prespecified patient groups, including women, age less than or greater than 60 years, primary or secondary prevention, diabetics, or patients with end-stage renal disease (results for Lead A shown in Table 3).

Results of the falsification-hypothesis analysis demonstrated similar rates of ICD system upgrade to a

Table 1. Before Match and Post-Match Covariate Distribution and Standardized Differences for Lead A

| Covariate                           | Before Match | After Match | Std. Diff. | Lead A (n=145289) | Alternate ICD (n=228843) | Std. Diff. | Lead A (n=145249) | Alternate ICD (n=145249) | Std. Diff. | Lead A (n=40) | Std. Diff. |
|-------------------------------------|--------------|-------------|------------|------------------|--------------------------|------------|------------------|--------------------------|------------|-------------|------------|
| Patient age                         | 65.7±12.9    | 65.2±13.0   | 0.0        | 65.5±12.9        | 65.5±13.0                | 0.0        | 66.9±18.0        | 0.1          |
| Male                                | 72.0%        | 71.1%       | 0.0        | 72.0%            | 72.1%                    | 0.0        | 65.0%            | 0.2          |
| Diabetes mellitus                   | 38.7%        | 39.1%       | 0.0        | 38.7%            | 38.7%                    | 0.0        | 35.0%            | 0.1          |
| Current dialysis                    | 2.6%         | 3.0%        | 0.0        | 2.3%             | 2.6%                     | 0.0        | 25.0%            | 0.7          |
| Body mass index                     | 30.1±11.1    | 30.0±13.3   | 0.0        | 30.0±10.3        | 30.0±11.1                | 0.0        | 136.2±227.5      | 0.7          |
| Ischemic cardiomyopathy             | 56.8%        | 56.7%       | 0.0        | 56.8%            | 56.8%                    | 0.0        | 70.0%            | 0.3          |
| Nonischemic cardiomyopathy          | 39.4%        | 39.2%       | 0.0        | 39.4%            | 39.4%                    | 0.0        | 62.5%            | 0.5          |
| Hypertrophic cardiomyopathy         | 12.1%        | 2.0%        | 0.0        | 2.1%             | 2.1%                     | 0.0        | 15.0%            | 0.5          |
| Prior CABG                          | 27.1%        | 26.7%       | 0.0        | 27.1%            | 27.1%                    | 0.0        | 42.5%            | 0.3          |
| NYHA I-II                           | 50.2%        | 49.2%       | 0.0        | 50.2%            | 50.2%                    | 0.0        | 67.5%            | 0.4          |
| NYHA III                            | 47.1%        | 47.9%       | 0.0        | 47.1%            | 47.1%                    | 0.0        | 27.5%            | 0.4          |
| NYHA IV                             | 2.7%         | 2.8%        | 0.0        | 2.7%             | 2.7%                     | 0.0        | 5.0%             | 0.1          |
| LVEF ≤20                            | 27.4%        | 28.2%       | 0.0        | 27.4%            | 27.2%                    | 0.0        | 20.0%            | 0.2          |
| LVEF 21–30                          | 44.0%        | 44.4%       | 0.0        | 44.0%            | 44.2%                    | 0.0        | 15.0%            | 0.7          |
| LVEF 31–34                          | 4.4%         | 4.3%        | 0.0        | 4.4%             | 4.3%                     | 0.0        |                  |              |
| LVEF 35–39                          | 10.0%        | 9.8%        | 0.0        | 10.0%            | 10.0%                    | 0.0        | 2.5%             | 0.3          |
| LVEF ≥40                            | 14.3%        | 13.2%       | 0.0        | 14.2%            | 14.3%                    | 0.0        | 62.5%            | 1.1          |
| Primary prevention                  | 77.3%        | 78.7%       | 0.0        | 77.3%            | 77.5%                    | 0.0        | 42.5%            | 0.8          |

Patient age and body mass index shown as mean±SD. ICD indicates implantable cardioverter-defibrillator.
biventricular system (Figure 2) for each of the leads of interest, indicating that there was no evidence for significant residual confounding in the propensity-matched cohorts analyzed.

**DISCUSSION**

The ICD Registry DELTA study was designed to assess the feasibility of active postmarket surveillance to assess the safety of commonly used high-energy defibrillation leads using a novel, prospective, propensity-matched survival method. During the study period of 5 years, 374,132 new ICD systems were recorded in the ICD Registry, with over 99% of these procedures involving the implantation of 1 of the 4 high-energy leads of interest. Propensity score matching resulted in high match rates with adequate risk differences between groups. Our analysis showed similar high-energy lead survival, as defined as freedom from lead failure, among patients treated with the 4 most commonly used high-energy leads. Late lead failure rates were also similar among the high-energy leads studied. In prespecified subgroup analyses, no clinically meaningful differences were identified in women, diabetics, patients on chronic dialysis, those receiving the device for primary prevention, or those undergoing initial ICD implant with biventricular pacing systems.

From a medical device safety evaluation perspective, the results of the ICD Registry DELTA study are reassuring and demonstrate similarly acceptable performance of the 4 most commonly implanted contemporary leads.

### Table 2. Summary of Status of Safety Alerts for Lead Failure for Each High-Energy Lead

| Lead of Interest | Exposure | Lead Implants at Start | Lead Implants at End | Estimated Survival at End | 95% Confidence Band | P Value | DELTA Hazard Ratio | DELTA Alert |
|------------------|----------|------------------------|----------------------|--------------------------|---------------------|---------|-------------------|-------------|
| Lead A           | Lead A   | 145,249                | 6890                 | 98.9%                    | 97.8%–99.7%         | <0.001  | 0.70              | No          |
|                  | Alternative leads | 145,249              | 6864                 | 98.5%                    | 97.4%–99.3%         |         |                   |             |
| Lead B           | Lead B   | 104,968                | 5868                 | 98.3%                    | 96.9%–99.3%         | <0.001  | 1.43              | No          |
|                  | Alternative leads | 104,968              | 5908                 | 98.8%                    | 97.6%–99.6%         |         |                   |             |
| Lead C           | Lead C   | 102,340                | 4175                 | 98.8%                    | 97.6%–99.6%         | 0.0042  | 0.87              | No          |
|                  | Alternative leads | 102,340              | 4178                 | 98.6%                    | 97.1%–99.5%         |         |                   |             |
| Lead D           | Lead D   | 20,787                 | 843                  | 97.7%                    | 95.0%–99.4%         | <0.001  | 1.89              | No          |
|                  | Alternative leads | 20,787               | 844                  | 98.8%                    | 94.9%–100%          |         |                   |             |

DELTA indicates Data Extraction and Longitudinal Trend Analysis system.
high-energy ICD leads. Given several recent examples of failures in high-energy leads identified after widespread adoption following market release,1,3,35,36 rapid evaluation of high-energy lead safety after market approval is essential to minimize the risk of faulty lead design leading to patient harm or the need for lead replacement.3,27,29

A novel attribute of the methods used in this analysis was the inclusion of a protocol that defined clinically meaningful difference thresholds between patients exposed to one ICD lead as compared with propensity matched controls. Given the very large sample size available in the ICD Registry and other large clinical data sources, it is to be expected that even very small differences in outcomes may achieve statistical significance, as we observed repeatedly in this study. However, the very small differences observed in this study did not meet the predefined threshold of a doubling of the risk of failure in the patients treated with the lead of interest relative to the controls. Incorporating predefined clinically meaningful differences in safety outcomes within prospective active surveillance studies may provide regulators with objective criteria by which to consider whether a medical device warrants further evaluation (ie, signal confirmation studies) or even rapid regulatory action.

The ICD Registry DELTA study further validates the strategy of prospective, active surveillance of accruing clinical datasets, which can address many of the limitations in our current understanding of the comparative risk of new and existing medical devices. Early identification of safety signals associated with medical device use may provide opportunities to reduce device-associated morbidity and may allow early intervention to support the need for device specific training or device refinement to improve patient safety. Of equal importance, lack of signal generation indicating equivalence of real-world safety performance, as demonstrated in this study, should reassure providers using technologies initially evaluated through narrow study populations.

### Limitations

There are several important limitations of this study. The ICD Registry, while nearly comprehensive in the capture of implants of new ICD implants in the United States during the study period, has inherent limitations with respect to identification of lead failures. Before 2018, the Centers for Medicare and Medicaid Services required data collection for all ICD implants as a condition for coverage; however, there was no requirement for data collection of lead revisions. In February of 2018, after the study period covered in this analysis, Centers for Medicare and Medicaid Services removed the data collection requirement all together for ICDs, with an expected subsequent decline in the enrollment

### Table 3. Subgroup Results for Freedom From Lead Failure for Lead A

| Patient Subgroup | Exposure | Lead Implants at Start | Lead Implants at End | Estimated Survival at End | 95% Confidence Band | P Value | DELTA Hazard Ratio | DELTA Alert |
|------------------|----------|------------------------|----------------------|---------------------------|---------------------|--------|-------------------|------------|
| Female           | Lead A   | 40626                  | 1777                 | 98.7%                      | 97.0%–99.8%         | <0.001 | 0.65              | No         |
|                  | Alternative leads | 40626        | 1759                 | 98.1%                      | 96.6%–99.1%         |        |                   |            |
| Age ≥60          | Lead A   | 102102                 | 4847                 | 99.0%                      | 97.5%–99.8%         | <0.001 | 0.75              | No         |
|                  | Alternative leads | 102102       | 4828                 | 98.6%                      | 97.5%–99.4%         |        |                   |            |
| Age <60          | Lead A   | 43043                  | 2039                 | 98.8%                      | 96.8%–99.8%         | <0.001 | 0.65              | No         |
|                  | Alternative leads | 43043        | 2024                 | 98.2%                      | 96.3%–99.4%         |        |                   |            |
| Primary prevention | Lead A   | 112288                 | 5326                 | 99.9%                      | 97.6%–99.7%         | <0.001 | 0.72              | No         |
|                  | Alternative leads | 112288       | 5313                 | 98.5%                      | 96.9%–99.5%         |        |                   |            |
| Secondary prevention | Lead A   | 32906                 | 1558                 | 98.9%                      | 96.5%–100%          | <0.001 | 0.67              | No         |
|                  | Alternative leads | 32906        | 1546                 | 98.4%                      | 95.8%–99.8%         |        |                   |            |
| Diabetes mellitus | Lead A   | 56209                 | 2682                 | 99.0%                      | 96.8%–99.9%         | <0.001 | 0.75              | No         |
|                  | Alternative leads | 56209        | 2675                 | 98.6%                      | 97.0%–99.6%         |        |                   |            |
| Dialysis         | Lead A   | 3734                   | 178                  | 98.4%                      | 91.2%–100%          | 0.7640 | 1.19              | No         |
|                  | Alternative leads | 3734         | 179                  | 98.6%                      | 94.2%–100%          |        |                   |            |
| CRT device       | Lead A   | 53173                 | 2497                 | 98.9%                      | 96.6%–99.0%         | <0.001 | 0.71              | No         |
|                  | Alternative leads | 53173        | 2497                 | 98.5%                      | 96.0%–99.8%         |        |                   |            |
| Single chamber   | Lead A   | 39070                 | 1563                 | 98.8%                      | 96.0%–100%          | <0.001 | 0.75              | No         |
|                  | Alternative leads | 39070        | 1552                 | 98.4%                      | 95.8%–99.8%         |        |                   |            |
| Dual chamber     | Lead A   | 52586                 | 2807                 | 99.0%                      | 96.9%–99.9%         | <0.001 | 0.72              | No         |
|                  | Alternative leads | 52586        | 2024                 | 98.6%                      | 97.0%–99.6%         |        |                   |            |

DELTA indicates data extraction and longitudinal trend analysis system.
in the registry. Therefore, use of the ICD Registry for device safety surveillance will be even more challenging in the future, as there may be inherent bias in analyzing the registry with noncompulsory participation. The analytic dataset did not include unique patient identifiers that were valid across institutions, and we were significantly limited in our ability to match individual patients receiving a replacement ICD lead with the index ICD implant in situations where the 2 procedures occurred at different institutions. Also, while new ICD implants were comprehensively recorded in the ICD Registry, isolated lead revision or replacement procedures may have been variably documented based on local hospital practice. In addition, without routine longitudinal follow-up information, we could not ascertain which patients had died, and we assumed that any such deaths (a competing risk in the Cox model) would have been distributed equally among the exposed groups.

The primary end point of freedom from any lead failure is relatively broad and includes both early lead failures (within 30 days) that are often attributable to device implant procedure issues rather than structural lead failures. However, the secondary end point of freedom from late lead failure (>30 days) also did not demonstrate any difference in lead performance. The definition of lead failure used here required documentation that the high-energy lead was either removed or another high-energy lead was implanted. This definition would therefore not capture those patients with an abandoned lead when no additional ICD lead was implanted and may have undercounted total lead failures. Importantly, lead replacement, used in this analysis as a surrogate for lead failure, is inherently incomplete as a measure of lead performance. Monitoring the electrical performance parameters of implanted leads as well as imaging data represent the gold standard for identifying defibrillator lead dysfunction, but such information was not available within the ICD Registry for the purposes of this study. While ascertaining the cause of lead failure was not a prespecified outcome for this study, such data would be critical for regulatory application of active surveillance of ICD lead performance. In addition, nonstructural reasons for replacing the high energy lead, including sensing function failure or malposition of the lead, would have been captured in the primary end point, though such reasons do not indicate an inherent device failure. Finally, this comparative analysis of lead survival is limited to the time window of 5 years of follow-up registry data available for evaluation. If any type of lead had an increased risk of failure which became manifest more than 5 years after implantation, it would not have been captured in this study.

As with any active surveillance analyses of postmarket device performance, the results of this study must be interpreted with caution, since all such analyses are limited by their inherent observational design. We sought to minimize potential confounding through robust risk adjustment using propensity matching, which resulted in well-balanced distributions of baseline covariates.

---

**Figure 2.** Falsification hypothesis results comparing high energy Lead A with alternative high energy implantable cardioverter-defibrillator (ICD) leads for freedom from upgrade of ICD system to a CRT-D system. Quarterly propensity-matched survival analyses through 5 years of surveillance. The solid green line indicates survival of Lead A. The solid blue line indicates alternative ICD leads. The 95% confidence bands are noted as shaded color regions.
between the high-energy leads studied and their comparator groups. However, we cannot fully exclude residual confounding impacting the observed results. Therefore, we also performed prespecified falsification hypothesis analyses, in which we monitored the registry for the subsequent upgrade of the original ICD system to a cardiac resynchronization (ie, biventricular pacing) system, although we did not anticipate a difference in the rate of ICD system upgrade with any particular high-energy lead. We found that the risk of ICD system upgrade was no different among the patients receiving the various high-energy leads, supporting a low likelihood of residual risk imbalance between the propensity-matched recipients of the 4 high-energy leads. Finally, an inherent limitation of a propensity-matched analysis is that inferences can only be drawn based on the population of patients for which a matched control could be identified (referred to as common support); limiting the conclusions to the subset of patients for which there was relative equipoise for primary and comparator populations.

Conclusions

The findings of this study support the feasibility of prospective, active surveillance of a large, representative ICD registry to monitor high-energy lead failure in near real time. Despite the significant limitations of the source data, the study demonstrated no clinically significant differences in high-energy lead failure among the 4 most commonly used ICD leads in contemporary practice.

ARTICLE INFORMATION

Received August 14, 2019; accepted February 27, 2020.

The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCOUTCOMES.119.006105.

Correspondence

Frederic S. Resnic, MD MSc, Department of Cardiovascular Medicine, Lahey Hospital and Medical Center, 41 Mall Rd, Burlington, MA 01805. Email frederic.resnic@lahey.org

Affiliations

Comparative Effectiveness Research Institute, Lahey Hospital and Medical Center, Burlington, MA (F.S.R., A.M., H.S., S.R., M.R.R.). Division of Cardiovascular Medicine, Lahey Hospital and Medical Center, Burlington, MA (F.S.R., A.M., M.R.R.). Tufts School of Medicine, Boston, MA (F.S.R., M.R.R.). Brigham and Women's Hospital, Boston, MA (A.M.). UCSF School of Medicine and Section of Cardiology, San Francisco VA Health Care System (S.S.D.). Center for Devices and Radiological Health (CDRH), FDA, Silver Spring, MD (D.M.-D.). National Cardiovascular Data Registry, American College of Cardiology, Washington, DC (K.H.). Department of Biomedical Informatics, University of California San Diego Health, La Jolla (L.O.-M.). Geriatrics Research, Education, and Clinical Care Center, Tennessee Valley Healthcare System VA, Nashville (M.E.M.). Departments of Biomedical Informatics, Biostatistics and Medicine, Vanderbilt University Medical Center, Nashville, TN (M.E.M.).

Sources of Funding

This research was primarily supported through research grants from the US Food and Drug Administration (HHSF Contract 223200830058C), DASH, and the William M. Wood Foundation. In addition, the research was also partially supported by HSFS223201110172C (MDEpiNet Methodology Center), grant 1U01 FD004493-01 (MDEpiNet Medical Counter Measures Study), both from the US Food and Drug Administration. Drs. Resnic, Ohno-Machado, and Matheny's efforts were funded, in part by grant awards U54 HL108460 as well as R01 HS019913, both awarded through the National Institutes of Health. Dr Matheny's efforts were additionally supported, in part, by VA HSR&D IR 13-052, and NIH NIDDK 5R01 DK113201-02 and 1U01 FD004493-01.

Disclosures

None.

REFERENCES

1. Hauser RG, Kalininen LM, Almquist AK, Gornick CC, Katsiyanis WT. Early failure of a small-diameter high-voltage implantable cardioverter-defibrillator lead. Heart Rhythm. 2007;4:892–896. doi: 10.1016/j.hrthm.2007.03.041
2. Steele GD, Fehring TK, Oudin SM, Denneson AC, Nadaud MC. Early failure of articular surface replacement XL total hip arthroplasty. J Arthroplasty. 2009;24:666 suppl.14; doi: 10.1016/j.arth.2011.03.022
3. Maisel WH. Semper fidelis—consumer protection for patients with implanted medical devices. N Engl J Med. 2008;358:958–987. doi: 10.1056/NEJMra0800495
4. Shah JS, Maisel WH. Recalls and safety alerts affecting automated external defibrillators. JAMA. 2006;296:655–660. doi: 10.1001/jama.296.6.655
5. Maisel WH. Unanswered questions—drug-eluting stents and the risk of late thrombosis. N Engl J Med. 2007;356:981–984. doi: 10.1056/NEJMoa075638
6. Kessler DA. Introducing MEDWatch. A new approach to reporting medical device and procedure adverse effects and product problems. Gen Hosp Psychiatry. 1994;16:96–101; discussion 102.
7. Mehran R, Leon MB, Feigal DA, Jefferys D, Simons M, Chronos N, Fogarty TJ, Kuntz RE, Baim DS, Kaplan AV. Post-market approval surveillance: a call for a more integrated and comprehensive approach. Circulation. 2004;109:3073–3077. doi: 10.1161/01.CIR.0000134694.78633.86
8. O’Shea JC, Kramer JM, Califf RM, Peterson ED. Part I: Identifying holes in the safety net. Am Heart J. 2004;147:977–984. doi: 10.1016/j.ahj.2004.03.001
9. Vidi VD, Matheny ME, Resnic FS. Post-marketing device safety surveillance. Contemp Clin Trials. 2011;32:307–308. doi: 10.1016/j.cct.2011.02.002
10. Normand SL, Hatfield L, Drozda J, Resnic FS. Postmarket surveillance for medical devices: America’s new strategy. BMJ. 2012;345:e6848. doi: 10.1136/bmj.e6848
11. Resnic FS, Normand SL. Postmarketing surveillance of medical devices—filling in the gaps. N Engl J Med. 2012;366:875–877. doi: 10.1056/NEJMmp1114865
12. Majithia A, Matheny ME, Paulus JK, Marinac-Dabic D, Robbins S, Ssemaganda H, Hewitt K, Ponirakis A, Loyo-Berrios N, Moussa I, Drozda J, Normand SL, Resnic FS. Comparative safety of aspiration thrombectomy catheters utilizing prospective, active surveillance of the NCDR CathPCI registry. Circ Cardiovasc Qual Outcomes. 2019;12:e004666. doi: 10.1161/CIRCOUTCOMES.118.004666
13. Resnic FS, Majithia A, Marinac-Dabic D, Robbins S, Ssemaganda H, Hewitt K, Ponirakis A, Loyo-Berrios N, Moussa I, Drozda J, Normand SL, Matheny ME. Automated surveillance to detect postprocedure safety signals of approved cardiovascular devices. JAMA. 2010;304:2019–2027. doi: 10.1001/jama.2010.1633
14. Resnic FS, Gross TP, Marinac-Dabic D, Loyo-Berrios N, Donnelly S, Normand SL, Matheny ME. Automated surveillance to detect postprocedure safety signals of approved cardiovascular devices. JAMA. 2010;304:2019–2027. doi: 10.1001/jama.2010.1633
15. Kumar A, Matheny ME, Ho KK, Yeh RW, Piemonte TC, Waldman H, Shah PB, Cope R, Normand SL, Donnelly S, Robbins S, Resnic FS. The data extraction and longitudinal trend analysis network study of distributed automated postmarket cardiovascular device safety surveillance. Circ Cardiovasc Qual Outcomes. 2015;8:38–46. doi: 10.1161/CIRCOUTCOMES.114.001123
16. Krucoff MW, Sedrakyan A, Normand SL. Bridging unmet medical device ecosystem needs with strategically coordinated registries networks. JAMA. 2015;314:1691–1692. doi: 10.1001/jama.2015.11036
17. Matheny ME, Ohno-Machado L, Resnic FS. Monitoring device safety in interventional cardiology. J Am Med Inform Assoc. 2008;13:180–187. doi: 10.1197/jamia.M1908
18. Matheny ME, Arora N, Ohno-Machado L, Resnic FS. Rare adverse event monitoring of medical devices with the use of an automated surveillance tool. AMIA Annu Symp Proc. 2007;518–522.

19. Matheny ME, Morrow DA, Ohno-Machado L, Cannon CP, Sabatine MS, Resnic FS. Validation of an automated safety surveillance system with prospective, randomized trial data. Med Decis Making. 2009;29:247–256. doi: 10.1177/0272989X08327110

20. Matheny ME, Normand SL, Gross TP, Marinac-Dabic D, Loyo-Berrios N, Vidi VD, Donnelly S, Resnic FS. Evaluation of an automated safety surveillance system using risk adjusted sequential probability ratio testing. BMC Med Inform Decis Mak. 2011;11:75. doi: 10.1186/1472-6947-11-75

21. Hauser RG, Mugglin AS, Friedman PA, Kramer DB, Kallinen L, McGriff D, Hayes DL. Early detection of an underperforming implantable cardiovascular device using an automated safety surveillance tool. Circ Cardiovasc Qual Outcomes. 2012;5:189–196. doi: 10.1161/CIRCOUTCOMES.111.962621

22. Swerdlow CD, Kalahasty G, Ellenbogen KA. Implantable cardiac defibrillator lead failure and management. J Am Coll Cardiol. 2016;67:1358–1368. doi: 10.1016/j.jacc.2015.12.067

23. Tuohy S, Ryan P, Galvin J. Turning a blind eye to the far field: are we burying the evidence? A case of abrupt catastrophic implantable cardioverter-defibrillator lead failure causing sudden death. Heart Rhythm Case Rep. 2016;2:6–10. doi: 10.1016/j.hrcr.2015.07.004

24. Hauser RG, Abdelhadi R, McGriff D, Retel LK. Deaths caused by the failure of Riata and Riata ST implantable cardioverter-defibrillator leads failure causing sudden death. Heart Rhythm Case Rep. 2012;9:1227–1235. doi: 10.1016/j.hrcr.2012.03.048

25. Hauser RG, Sengupta J, Schloss EJ, Stanberry LJ, Wananu MK, Abdelhadi R. Internal insulation breaches in an implantable cardioverter-defibrillator lead with redundant conductors. Heart Rhythm. 2019;16:1215–1222. doi: 10.1016/j.hrthm.2019.02.019

26. Resnic FS, Matheny ME. Medical devices in the real world. N Engl J Med. 2018;378:595–597. doi: 10.1056/NEJMp1712001

27. Hauser RG. Here we go again—another failure of postmarketing device surveillance. N Engl J Med. 2012;366:873–875. doi: 10.1056/NEJMmp1114695

28. Curfman GD, Morrissey S, Drazen JM. Safer drugs for the American people. N Engl J Med. 2007;357:602–603. doi: 10.1056/NEJMep078154

29. Shuren J, Califf RM. Need for a national evaluation system for health technology. JAMA. 2016;316:1153–1154. doi: 10.1001/jama.2016.8708

30. Hauser RG, Maisel WH, Friedman PA, Kallinen LM, Mugglin AS, Kumar K, Hodge DO, Morrison TB, Hayes DL. Longevity of Sprint Fidelis implantable cardioverter-defibrillator leads and risk factors for failure: implications for patient management. Circulation. 2011;123:358–363. doi: 10.1161/CIRCULATIONAHA.110.975219

31. Borleffs CJ, van Enven L, van Bommel RJ, van der Velde ET, van der Wall EE, Bax JJ, Rosendaal FR, Schalij MJ. Risk of failure of transvenous implantable cardioverter-defibrillator leads. Circ Arrhythm Electrophysiol. 2009;2:411–416. doi: 10.1161/CIRCEP.108.834095

32. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat. 2011;10:150–161. doi: 10.1002/pst.433

33. Austin PC. The relative ability of different propensity score methods to balance measured covariates between treated and untreated subjects in observational studies. Med Decis Making. 2009;29:661–677. doi: 10.1177/0272989X09341755

34. Oakes D, Feng C. Combining stratified and unstratified log-rank tests in paired survival data. Stat Med. 2010;29:1735–1745. doi: 10.1002/sim.3921

35. Hauser RG, Retel LK. Riata implantable cardioverter-defibrillator lead failure: analysis of explanted leads with a unique insulation defect. Heart Rhythm. 2012;9:742–749. doi: 10.1016/j.hrthm.2011.12.019

36. Krebsbach A, Alhumaid F, Henrikson CA, Calkins H, Berger RD, Cheng A. Premature failure of a Riata defibrillator lead without impedance change or inappropriate sensing: a case report and review of the literature. J Cardiovasc Electrophysiol. 2011;22:1070–1072. doi: 10.1111/j.1540-8167.2011.02042.x