

Can machine learning complement traditional medical device surveillance? A case study of dual-chamber implantable cardioverter–defibrillators

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Background: Machine learning methods may complement traditional analytic methods for medical device surveillance.

Methods and results: Using data from the National Cardiovascular Data Registry for implantable cardioverter–defibrillators (ICDs) linked to Medicare administrative claims for longitudinal follow-up, we applied three statistical approaches to safety-signal detection for commonly used dual-chamber ICDs that used two propensity score (PS) models: one specified by subject-matter experts (PS-SME), and the other one by machine learning-based selection (PS-ML). The first approach used PS-SME and cumulative incidence (time-to-event), the second approach used PS-SME and cumulative risk (Data Extraction and Longitudinal Trend Analysis [DELTA]), and the third approach used PS-ML and cumulative risk (embedded feature selection). Safety-signal surveillance was conducted for eleven dual-chamber ICD models implanted at least 2,000 times over 3 years. Between 2006 and 2010, there were 71,948 Medicare fee-for-service beneficiaries who received dual-chamber ICDs. Cumulative device-specific unadjusted 3-year event rates varied for three surveyed safety signals: death from any cause, 12.8%–20.9%; nonfatal ICD-related adverse events, 19.3%–26.3%; and death from any cause or nonfatal ICD-related adverse event, 27.1%–37.6%. Agreement among safety signals detected/not detected between the time-to-event and DELTA approaches was 90.9% (360 of 396, $\kappa=0.068$), between the time-to-event and embedded feature-selection approaches was 91.7% (363 of 396, $\kappa=-0.028$), and between the DELTA and embedded feature selection approaches was 88.1% (349 of 396, $\kappa=-0.042$).

Conclusion: Three statistical approaches, including one machine learning method, identified important safety signals, but without exact agreement. Ensemble methods may be needed to detect all safety signals for further evaluation during medical device surveillance.

Keywords: implanted cardioverter–defibrillator, methodology, surveillance

Introduction

Implantable cardioverter–defibrillators (ICDs) may be indicated for survivors of cardiac arrest or those who have experienced prior sustained ventricular arrhythmias, and as primary prophylaxis for patients with heart failure and other conditions according to current guidelines.^{1–4} While ICD therapy has been associated with lower all-cause mortality,⁵ implantation also involves risk. Approximately 1% of ICD implantation procedures are associated with in-hospital death, and at least 5% of patients experience other complications, including device malfunctions, lead problems, and infections.^{5–7} Data from the American College of Cardiology’s National Cardiovascular Data Registry (NCDR) demonstrated that 1% of patients experience pneumothorax or hematoma formation within 30 days, and 3% have a site

infection or require ICD revision because of a mechanical complication within 90 days.⁶

However, for nearly all high-risk medical devices, including ICDs, long-term device safety, product performance, and effectiveness in improving patient outcomes are not well defined.⁸ Current medical device surveillance efforts to address these issues include mandatory reporting of certain device-related adverse events and miscellaneous product problems to the US Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience program, the hospital-based Medical Product Safety Network, and required postmarket surveillance studies. Although each has well-described limitations,^{9–12} data from these sources have contributed unique insights that have helped to inform patient and physician decision-making and improve quality of care. In particular, required studies and registries offer an opportunity to collect detailed information about patients, procedures, and devices not routinely collected by electronic health records or administrative claims data.

Importantly, the methods used to analyze data collected as part of medical device surveillance efforts have implications for the success of these efforts, and there are limitations to the traditional approaches used to analyze registry data. First, evaluations usually focus on overall product-class safety and effectiveness, rather than examining differences across manufacturers. Second, many analyses are cross-sectional and do not take time into account. However, device performance and safety are likely influenced by operator performance, which may improve with experience over time.^{13,14} Finally, risk-standardization methods used to examine and compare device performance tend to focus on patient characteristics that are prespecified to be “clinically important”, such as through propensity-matched time-to-event analyses to compare device safety and performance. However, the characteristics that most affect device use and performance are often not well understood,^{15,16} and these methods take advantage of neither the additional detailed patient information collected within registry data nor the detailed operator and hospital information that might be associated with device use and account for differences in performance, and they do not account for the clustering of patients among physicians and hospitals.

Among the best available methods for medical device surveillance is the Data Extraction and Longitudinal Trend Analysis (DELTA) system, an automated safety-surveillance tool developed and validated using medical device registries and clinical trial databases. The DELTA system has successfully identified even very low-frequency events.^{12,17–20} However, this method also relies on clinical experts to

prespecify “clinically important” patient characteristics for risk standardization, raising the question of whether novel machine learning (ML) analytic methods might complement current medical device surveillance efforts by more fully leveraging additional detailed patient, operator, and hospital information collected within registry data and employing data-driven, rather than expert-based, approaches to variable selection for risk standardization.²¹ While ML algorithms are typically applied to curated data sets where ground truth is known, in the context of real-world surveillance, the “truth” of medical device safety must be empirically investigated.

To understand potential advantages and disadvantages of applying such methods to medical device surveillance better, we used data from the NCDR-ICD registry in conjunction with Medicare administrative claims to conduct quarterly analyses of commonly used dual-chamber ICDs, surveying over 3 years of follow-up for important safety signals: death from any cause, nonfatal ICD-related adverse events, and a composite of the two. We applied three statistical approaches to safety-signal detection: time-to-event, DELTA, and embedded feature selection, each of which can be applied to registry data to evaluate multiple device types, outcomes, and evaluation periods, and compared when the three approaches identified safety signals.

Materials and methods

Data source

We used January 1, 2006, through March 31, 2010, data from the NCDR-ICD registry that collected information on ~ 90% of ICD implantations among hospitals that perform the procedure.²² These data include patient demographics and clinical comorbidities, the episode of care, and procedure information, as well as postprocedure events and complications prior to discharge.²³ The registry employs a multifaceted program to enhance data quality.²⁴ The NCDR-ICD registry data were linked using deterministic matching, as previously described,²⁵ to 2006–2011 Medicare inpatient, outpatient, and carrier standard analytic files for longitudinal follow-up information, providing a minimum of 1 year and 9 months of follow-up for ICDs implanted in March 2010. The Medicare data sets contain claims for inpatient admissions and outpatient procedures for Medicare fee-for-service patients. Additionally, we used the 2006–2011 Medicare denominator files to obtain fee-for-service enrollment and postdischarge vital status of each beneficiary. For data access, the study was approved by but did not receive financial support from the NCDR. The NCDR research and publications committee reviewed the final manuscript prior to submission, but other-

wise had no role in the design, conduct, or reporting of the study. The Yale University Human Investigation Committee approved the study (protocol MODCR0000080).

Study sample

All patients aged ≥ 65 years who had undergone dual-chamber ICD implantation and were able to be matched to Medicare fee-for-service claims data for long-term follow-up were included. We excluded patients if they were not discharged alive after ICD implantation, if they were discharged after March 31, 2010, or if data on patient age and sex or hospital-provider number were missing. Patients without both Part A and Part B Medicare fee-for-service coverage at the time of ICD implantation were also excluded. If a patient received multiple ICD implantations during the study period, they were eligible for inclusion as multiple unique observations, but follow-up for the first implantation was censored at the time of the second implantation.

Dual-chamber ICDs

For each dual-chamber ICD implanted during the study period, the device type (single chamber, dual chamber, cardiac resynchronization-therapy defibrillator) and listed manufacturer and model name and number within the NCDR-ICD registry were reviewed to ensure accuracy. Once accuracy was confirmed, a study ID was used to ensure the study team was blinded to the device manufacturer and model in accordance with the data-use agreement.

Main outcome measure

We surveyed outcomes after ICD implantation for three safety signals: death from any cause, nonfatal ICD-related adverse events, and a composite of the two. Deaths were ascertained at any time within the follow-up period after implantation, unless the patient underwent a generator reoperation, in which case death was ascertained before or up to 7 days after reoperation. A list of potential nonfatal ICD-related adverse events was developed using prior literature, using stakeholder input from regulators and manufacturers, and based on clinical expertise. Nonfatal ICD-related adverse events included ED visits and hospitalizations for complications resulting from the implantation, presence, performance, or failure of ICD therapy that did not involve reoperation, as well as any visit for ICD-site device revision or replacement (reoperation), whether inpatient or outpatient.

ED visits and hospitalizations for adverse events were identified using ICD9-CM primary discharge-diagnosis

codes. A complete list of specific coding definitions is provided in Table 1 and includes the following categories of events: device failure, infection, mental health sequelae, and other device malfunction not requiring reoperation at any time after implantation, as well as procedural complications, such as aneurysms, aortic dissections, cardioembolic events, and pneumothorax within 90 days after implantation. Inpatient and outpatient visits for ICD-site reoperation were identified using ICD9-CM procedure codes and Common Procedural Terminology codes. A complete list of specific coding definitions is provided in Table 2 and includes the following categories of events: pocket reoperation, generator reoperation (with or without lead reoperation), and lead-only reoperation at any time after implantation.

Safety-signal detection analyses

Three statistical approaches were applied to safety-signal detection for commonly used dual-chamber ICDs: time-to-event, DELTA, and embedded feature selection (ie, continuous variable selection). The objective of each approach was to determine whether any differences in dual-chamber ICD safety profiles could be identified in “real time” by comparing the most commonly used dual-chamber ICDs to the overall sample of dual-chamber ICDs. Prior to initiation of analyses, the decision was made to focus signal-detection efforts on the most commonly used devices, as we hypothesized that we would likely only be able to discriminate signals among devices with the largest number of observations. Upon inspection of the patterns of use over the overall sample period to identify a threshold of utilization, we focused on commonly used dual-chamber ICD models that had been implanted 2,000 times or more. Following accepted practice that at least 10 observations be required per propensity score (PS) model covariate, no analyses were initiated until the dual-chamber ICD of interest had been implanted 180 times. Once this threshold was reached, the three safety-signal detection approaches were independently applied to 12 consecutive quarters (ie, device performance in a prior quarter did not impact evaluation in a subsequent quarter), for a total of 3 years of safety surveillance for each device.

For all statistical analyses, significance tests were two-sided with a significance level of 0.05 and adjusted for multiple comparisons using the Sidák correction.²⁶ Time-to-event and DELTA analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA); the embedded feature selection approach was implemented in Python 3.4.3 (Python Software Foundation, Wilmington, DE, USA).

Table 1 Implantable cardioverter–defibrillator-related nonreoperation adverse events (identified from ED visits or hospitalizations)

Definition	Condition category/ICD9-CM code	Event surveillance
Device failure: cardiorespiratory failure, ventricular arrhythmias	CC78; all ICD9-CM codes CC79; all ICD9-CM codes CC92; ICD9-CM codes 426.0, 427.0, 427.1, 427.2 CC93; all ICD9-CM codes	Any time after implantation
Infections: device-related and surrounding skin, endocarditis, and other valve disease	CC2; all ICD9-CM codes CC6; ICD9-CM codes 41.00-41.9 CC85; ICD9-CM codes 420.x, 421.x, 422.x, 423.x CC86; ICD9-CM codes 397.0, 424.9x CC152; ICD9-CM codes 682.1, 682.2	Any time after implantation
Mental health sequelae: depression, anxiety, and other signals of malfunctioning device	CC55; ICD9-CM codes 296.20-296.36 CC58; all ICD9-CM codes CC59; ICD9-CM codes 300.01, 300.02, 309.81	Any time after implantation
Other device malfunctions	CC164; ICD9-CM codes 996.00, 996.01, 996.09, 996.61, 996.72	Any time after implantation
Procedural complications 1: aortic aneurysms, aortic dissections, cardioembolic events (including PE and DVT), hemorrhage, and other surgical complications (wound infection, air embolism)	CC104; ICD9-CM codes 415.1x, 441.00, 441.01, 443.21, 444.1, 444.2x, 444.89, 444.9, 445.01, 445.89, 449.x CC105; ICD9-CM codes 444.20, 444.82, 453.7x, 453.82 CC106; ICD9-CM codes 451.8x, 451.9, 453.1, 453.7x, 453.8x, 453.9, 458.29, 458.8, 458.9, 459.0, 459.2, 459.89, 459.99 CC164; ICD9-CM codes 958.0, 958.1, 958.2, 958.3, 997.1, 997.2, 997.3, 998.0, 998.6	Only within 90 days after implantation
Procedural complications 2: pneumothorax or pleural effusion	CC114; all ICD9-CM codes	Only within 90 days after implantation
Procedural complications 3: acute renal failure	CC131; ICD9-CM codes 584.x	Only within 90 days after implantation
Procedural complications 4: other surgical related	CC165; ICD9-CM codes 998.1x, 998.2, 998.3x, 998.5x, 998.7, 998.83, 998.89, 998.9, 999.1, 999.2, 999.3x, 999.9, E8700, E8705, E8706, E8708, E8709, E8710, E8718, E8719, E8720, E8725, E8726, E8728, E8729, E8733, E8744, E8745, E8750, E8752, E8758, E8759, E8762, E8798, E8799	Only within 90 days after implantation

Abbreviations: ED, emergency department; ICD9-CM, International Classification of Diseases, ninth revision, clinical modification; CC, condition category; PE, pulmonary embolism; DVT, deep vein thrombosis.

Table 2 Implantable cardioverter–defibrillator site reoperation, including partial or complete replacement (identified from inpatient or outpatient visits)

Definition	ICD9-CM PCS code or CPT code	Event surveillance
Pocket reoperation	37.79 (ICD9-CM PCS) or 33223 (CPT procedure codes)	Any time after implantation
Generator (\pm lead) reoperation	Mechanical complications with system revision: 996.0x or 996.72 (ICD9-CM) and 00.51, 0.54, 37.89, 37.94, 37.96, 37.98 (ICD9-CM PCS) or 33230, 33231, 33240, 33241, 33249, 33262, 33263, 33264 (CPT procedure codes)	
Lead reoperation only (no device replacement)	Mechanical complications with system revision: 996.0x or 996.72 (ICD9-CM) and 00.52, 37.70, 37.71, 37.72, 37.73, 37.74, 37.75, 37.77, 37.95, 37.97 (ICD9-CM PCS) or 33202, 33203, 33215, 33216, 33217, 33218, 33220, 33224, 33225, 33226, 33234, 33235, 33238, 33243, 33244 (CPT procedure codes)	

Abbreviations: ICD9-CM, International Classification of Diseases, ninth revision, clinical modification; PCS, procedure code set; CPT, current procedural terminology.

Time-to-event

The Kaplan–Meier method was used to calculate cumulative actuarial event-free incidence rates. Differences in survival curves among devices were compared using the log-rank test. For this method, we matched patients who received any of the most commonly used dual-chamber ICDs to a patient receiving any alternative dual-chamber ICD. Patients were matched 1:1 within a fixed PS caliper of 0.05 using a “greedy” matching algorithm²⁷ that accounted for the date of

implantation (within 30 days) and 13 patient characteristics (total of 18 covariates), all of which were identified prior to analyses based on clinical judgment and known associations with worse outcomes after ICD implantation.⁶ The following characteristics ascertained at the time of implantation were used: age, sex, race, clinical comorbidities, New York Heart Association class, reason for admission (admitted for ICD implantation or admitted for clinical management and ICD implanted during course of hospitalization), indication for

ICD therapy (primary versus secondary prevention, depending upon patients' prior history of cardiac arrest), and receipt of optimal medical therapy at discharge (when there was no contraindication),²⁸ including aspirin, statin, β -blocker, and angiotensin-converting-enzyme inhibitor or angiotensin II-receptor blocker. Single imputation was used for missing data; missing binary variables were imputed with 0, continuous variables were mean imputed, and categorical variables were imputed with the most frequent value.

The PS was calculated using nonparsimonious logistic regression, with the device of interest as the dependent variable. Separate models were fitted for each of the most commonly used dual-chamber ICDs, and analyses were conducted independently for each of the surveyed three safety signals. Because patients could have died prior to experiencing an ICD-related adverse event, we accounted for the competing risk of death by calculating cumulative incidence functions for these subanalyses and applied Fine and Gray testing for the equality of these curves.²⁹ A safety signal was triggered if the cumulative incidence function in a quarter differed significantly between the exposed and comparator groups, using a significance level of 0.05 adjusted for the aforementioned multiple comparisons. For each quarter, a report of percentage matches and covariate balance (standardized differences in means) was generated; balance among matched cohorts was evaluated using standardized differences of the selected covariates, and any difference >10% indicated imbalance.

DELTA

The DELTA system was developed and validated using medical device registries and clinical trial databases and shown to identify very low-frequency events, using an array of Bayesian and frequentist-inference methods.^{12,17–20} The system supports multiple, simultaneous device-specific analyses, tracking the accumulating experience of multiple devices while simultaneously monitoring multiple independent data sets. We replicated this approach,¹⁷ matching patients using the same method as discussed in the previous section for the time-to-event approach, with the exception that the date of implantation was matched within 180 days; single imputation was similarly used for missing data. Analyses were conducted quarterly for the PS-matched cohorts for each of the most commonly used dual-chamber ICDs. At least 75% of patients were required to be matched to a control patient to proceed with analysis. We used the Wilson-score method with continuity correction to calculate a confidence interval for the cumulative risk difference. As per the DELTA system,

a safety signal was triggered if the confidence interval did not cross zero, which indicates a statistically significant difference between patients receiving the ICD of interest and the PS-matched control cohorts using a significance level of 0.05. However, several modifications were made for expedience: sensitivity analyses were not performed when a safety signal was triggered, a power calculation was not performed pre hoc to determine sample size, the O'Brien–Fleming α -spending method was not employed,³⁰ and a fixed 3-year surveillance period was examined. Analyses were conducted independently for each of the surveyed three safety signals. As in the time-to-event approach, for each quarter a report of percentage matches and covariate balance (standardized differences in means) was generated; balance among matched cohorts was evaluated using standardized differences of the selected covariates and any difference >10% indicated imbalance.

Embedded feature selection

The time-to-event and DELTA approaches rely on a PS model specified by subject-matter experts (PS-SME). If the experts correctly specify the model, including the correct outcome and exposure covariates and their interactions, then we expect the PS-SME to generate reliable inferences. However, the absence of an unrecognized confounder from the PS-SME, eg, medical history of cardiac arrest or time of implant, may lead to erroneous conclusions about device safety and effectiveness. Moreover, manual specification may limit scalability of any medical device-surveillance system wherein safety signals for multiple treatment-outcome pairs are to be monitored. Therefore, some automated assistance in model specification could be desirable. Here, we considered the potential of an ML method known as embedded feature selection to create a complementary PS model (PS-ML), allowing the data to drive model specification.

Our principal aim is to periodically estimate the risk difference per device relative to a control group of individuals with a different device but of the same device class. To be precise, let I index the individuals who receive an implanted medical device of a given type in a given study period $[t_{\text{begin}}, t_{\text{end}}]$. We represent this cohort by $\{(x_i, y_i, z_i)\}_{i \in I}$ where x_i denotes preimplant covariates, y_i indicates whether a given outcome occurs in the study period, and z_i denotes the device implanted in i . We fix the device to be evaluated, and write $z_i=1$ if individual i has this device and $z_i=0$ if individual i has another device. Let I_1 index the individuals who received the device, ie, $I_1 = \{i \mid z_i = 1\}$, and put $I_0 := I \setminus I_1$.

In what follows, we make the stable-unit treatment-value assumption: 1) there is no interference between treatments and 2) treatment is fixed. Moreover, we assume that treatment assignment is individualistic, probabilistic, and unconfounded.

Given the PS $\pi(x) := P(z = 1|x)$, the matching estimator for the risk difference is given by

$$\hat{T} = \frac{1}{|I_1|} \sum_{i \in I_1} y_i - y_{m(i)},$$

where the 1-1 matching function $m: I_1 \subseteq I_1 \rightarrow I_0$ is constructed through PS matching without replacement. Here, I_1 denotes all exposed individuals who can be matched, as we place two restrictions on m , given an estimate \hat{f} of the logit of the PS: first, letting $\sigma(\hat{f})$ denote the sample standard deviation of \hat{f} over I , we fix a *caliper* $c > 0$ and require $|\hat{f}(x_i) - \hat{f}(x_{m(i)})| \leq c \sigma(\hat{f})$; second, i and $m(i)$ must have implant dates within 180 days of each other. In practice, we put $c=0.05$.

In the embedded feature-selection approach, we use a 1-norm support vector machine to estimate the PS, denoted PS-ML. In particular, we use the hinge loss, l^1 -regularized objective function:

$$F(\beta, \lambda) := \frac{1}{|I|} \sum_{i \in I} L(z_i, f(x_i)) + \lambda \|\beta\|_1,$$

where $f(x) := \sum_{j=0}^p \beta_j x_j$ and $L(z, f(x)) := (1 - \tilde{z}f(x))_+$. To be exact, $\tilde{z} := 2z - 1$; we augment the covariates as $x_0 = 1$ so that β_0

is the bias term, and $\|\beta\|_1$ does not include the intercept β_0 . Given λ , the regularization parameter, we solve $\min_{\beta} F(\beta, \lambda)$ to get $\hat{f}: I \rightarrow \mathbf{R}$, a 1-norm support vector machine, which estimates the logit of the PS π . Larger values of λ yield sparser models, ie, models with fewer selected covariates. We estimate the β -coefficients using a first-order stochastic gradient-descent learning routine, ie, Scikit-Learn’s SGDClassifier. Hyperparameters of the learning algorithm include the number of epochs ($n=10$), initialization (warm start = True), regularization penalty (as determined by the PS-ML algorithm), and shuffle (True).

The regularization parameter λ is determined according to the PS-ML algorithm (Figure 1). In this algorithm, one prespecifies a range for the number of selected covariates: $p_{\min} \leq \|\hat{\beta}\|_0 \leq p_{\max}$. Given an initial regularization penalty λ , the PS-ML algorithm adjusts the regularization penalty with an annealing rate $\delta > 1$ until the final number of selected covariates lies within the desired range and the selected covariates are balanced. The matching m is considered to be balanced if the standardized mean difference of each selected covariate (ie, covariates such that $\hat{\beta}_j \neq 0$) between exposed and matched is ≤ 0.1 .

For surveillance, preimplant covariates were extracted from the NCDR data set. These included 59 binary, 17 continuous, and 25 categorical covariates. Missing binary covariates were imputed with 0, as most corresponded to entries like “history of X: No=0, Yes=1”, and we assumed a missing value to imply nonpresence of the condition, procedure, etc. Continuous covariates were mean imputed. Levels of the categorical variables (including “missing” as a level)

Algorithm 1 PS-ML

```

1: for Several Iterations do
2:    $\hat{\beta} \leftarrow \min_{\beta} F(\beta, \lambda)$ 
3:   if  $\|\hat{\beta}\|_0 < p_{\min}$  then
4:      $\lambda \leftarrow \delta^{-1} \lambda$ 
5:     continue
6:   end if
7:   if  $\|\hat{\beta}\|_0 > p_{\max}$  then
8:      $\lambda \leftarrow \delta \lambda$ 
9:     continue
10:  end if
11:   $m \leftarrow \text{MATCHWITHOUTREPLACEMENT}(\hat{f}, c)$ 
12:  if  $\text{ISBALANCED}(m, \hat{\beta})$  then
13:    return  $m$ 
14:  else
15:     $\lambda \leftarrow \delta \lambda$ 
16:  end if
17: end for
    
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Figure 1 PS-ML algorithm to determine the regularization parameter. **Abbreviations:** PS, propensity score; ML, machine learning.

were dummy-coded, resulting in 188 main effects. These main effects and their first-order interactions were included to yield $p=17,766$ potential covariates. Each of the $p=17,766$ dimensions was standardized, ie, scaled to have mean 0 and unit standard deviation.

In running PS-ML, we set the minimum number of selected covariates to be $p_{\min}=10$ and the maximum number of selected covariates to be $p_{\max}=30$. The lower bound was chosen to prevent the model from being too lenient, and the upper bound was an heuristic chosen to limit the number of covariates that must be balanced. We chose the caliper to be $c=0.05$, which resulted in a high percentage of matches. The initial regularization penalty was set to $\lambda=0.05$, which we found to lead to quick convergence. We set the regularization annealing rate to be $\delta=1.1$, with which the algorithm consistently terminated with a number of selected features within the desired range.

In summary, the embedded feature-selection approach fits a PS model using a kind of continuous covariate selection, where the number of selected covariates is determined by a single parameter known as the regularization parameter.^{31,32} For each exposure, we searched for a regularization parameter that resulted in a PS model without limiting covariates. Next, balance between the exposed and PS-matched groups was assessed. If there was imbalance, the regularization parameter was changed to yield a model with fewer covariates. This iterative procedure was repeated until balanced, matched groups were established. Once specified according to this algorithm, the PS-ML model is used for surveillance in a manner analogous to the DELTA approach.

In the embedded feature-selection approach, most data elements collected within the NCDR-ICD registry were considered potential main-effect covariates in the PS-ML, including two-way interactions. We modeled PS-ML using a 1-norm support vector machine, with a regularization parameter chosen as described in the preceding paragraph.³³ We matched patients who had received any of the most commonly used dual-chamber ICDs to a patient receiving any alternative dual-chamber ICD. Patients were matched 1:1 within a fixed PS caliper of 0.05 using a “greedy” matching algorithm that accounted for the date of implantation (within 180 days) and the PS-ML model. Single imputation was used for missing entries, missing binary variables were imputed with 0, continuous variables were mean imputed, and categorical variables (including missing as a level) were dummy coded. Analyses were conducted quarterly for the matched cohorts for each of the most

commonly used dual-chamber ICDs. As per the DELTA approach, a safety signal was triggered if the Wilson-score confidence interval for the cumulative risk difference did not cross zero. Again, for each device and quarter, a report of percentage matches and covariate balance (standardized differences in means) was generated; balance among matched cohorts was evaluated using standardized differences of the selected covariates, and any difference $>10\%$ indicated imbalance.

Results

Between 2006 and 2010, there were 71,948 dual-chamber ICDs identified from the NCDR-ICD registry implanted among Medicare fee-for-service beneficiaries with linked administrative claims data to ascertain long-term follow-up (Figure 2). The mean patient age was 75.2 years (SD 6.4), 24% were female, and 89% were white (Table 3). Among these patients, 77% had prior ischemic heart disease, 52% had prior sustained or unsustained ventricular tachycardia, 31% had New York Heart Association class III or IV heart failure, and 71% of ICDs were implanted for primary prevention. The median duration of follow-up (ie, time from hospital discharge after implantation until death, end of study period, or lost to follow-up due to disenrollment in Medicare fee-for-service plan) was 2.7 years (interquartile range 1.9–3.8 years). There were few differences in the characteristics of patients, all of which were minimal, among the dual-chamber ICD patient populations (Table 4).

Dual-chamber ICD volume and safety signals

In total, there were 16,397 deaths within 3 years after implantation, 20,556 ED visits and hospitalizations for ICD-related adverse events within 3 years after implantation, 1,275 for procedural complications within 90 days after implantation, and 8,026 inpatient and outpatient visits for ICD-site reoperations. Figure 3 displays a Kaplan–Meier survival curve illustrating freedom from death or nonfatal ICD-related adverse events among the full sample of Medicare fee-for-service beneficiaries.

Cumulative implantation volumes for eleven dual-chamber ICDs implanted 2,000 times or more among Medicare fee-for-service beneficiaries during this period are displayed in Figure 4. While cumulative volume did not exceed 2,400 implantations for four devices, the two most commonly implanted dual-chamber ICDs had cumulative volumes of 7,891 and 18,093.

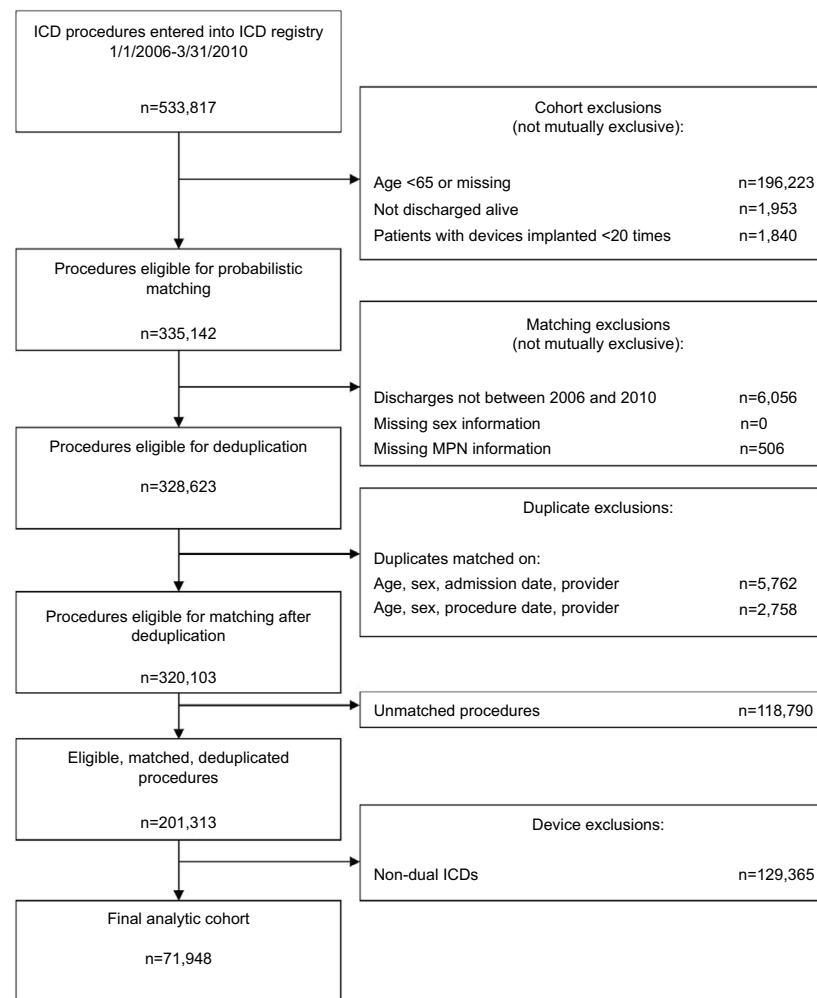


Figure 2 Cohort-derivation flowchart.

Abbreviations: ICD, implantable cardioverter-defibrillator; MPN, Medicare provider number.

Signal-detection analyses focused on the eleven dual-chamber ICDs implanted 2,000 times or more, among which cumulative unadjusted event rates following 3 years of surveillance varied. Cumulative death rates ranged from 12.8% (95% CI 12.3%–13.3%) to 20.9% (95% CI 19.3%–22.7%). Cumulative nonfatal ICD-related adverse-event rates ranged from 19.3% (95% CI 18.2%–20.5%) to 26.3% (95% CI 24.5%–28.1%). Finally, cumulative rates of death or nonfatal ICD-related adverse events ranged from 27.1% (95% CI 26.5%–27.8%) to 37.6% (95% CI 35.5%–39.8%). Among nonfatal ICD-related adverse events, the most common were ED visits or hospitalizations for device failure, infection, or device malfunction, and inpatient or outpatient visits for ICD-site generator reoperation (with or without lead reoperation) or lead reoperation only (Table 5).

Three approaches to safety-signal detection

Each of the three approaches to signal detection was applied to the eleven commonly used dual-chamber ICDs over 12

periods of analysis and for all three surveyed safety signals (396 distinct surveillance analyses). For the time-to-event approach, all patients receiving each of the eleven devices were successfully matched to controls who had received an alternative device within 30 days of the date of implant. In addition, among the 14 characteristics (18 covariates) used for the PS-SME, there were 111 instances of covariate imbalance across the 396 distinct analyses (3.6% of the 7,128 opportunities for covariate imbalance among the eleven devices evaluated over 12 quarters; Table 6). For the DELTA approach, all patients receiving each of the eleven devices were successfully matched to controls who had received an alternative device within 180 days of the date of implant. In addition, among the 14 characteristics (18 covariates) used for the PS-SME, there were 93 instances of covariate imbalance across the 396 distinct analyses (2.4% of the 7,128 opportunities for covariate imbalance). Last, for the embedded feature-selection approach, all patients receiving each of the eleven devices were successfully matched to controls

Table 3 Key characteristics of patients receiving dual-chamber ICDs, 2006–2010 (n=71,948)

Age, years, mean (SD)	75.2 (6.4)
Female sex, n (%)	17,162 (23.9)
Race, n (%)	
White	64,215 (89.3)
Black	5,017 (7.0)
Other	2,716 (3.8)
Clinical comorbidities, n (%)	
Atrial fibrillation or flutter	26,105 (36.3)
Ventricular tachycardia (sustained or unsustained)	37,127 (51.6)
Ischemic heart disease	55,149 (76.7)
Cerebrovascular disease	12,910 (17.9)
Chronic lung disease	16,476 (22.9)
End-stage renal disease on dialysis	2,571 (3.6)
New York Heart Association Class, n (%)	
I	13,861 (19.3)
II	35,936 (49.9)
III	20,597 (28.6)
IV	1,554 (2.2)
Reason for admission, n (%)	
ICD implantation	46,062 (64.0)
Heart failure ^a	5,171 (7.2)
Other cardiac ^a	18,168 (25.3)
Noncardiac ^a	2,547 (3.5)
Indication for ICD therapy, n (%)	
Primary prevention	51,241 (71.2)
Secondary prevention	20,707 (28.8)
Receipt of optimal medical therapy at discharge^b, n (%)	46,258 (64.3)

Notes: ^aAdmitted for clinical management and ICD implanted during course of hospitalization; ^breceipt of optimal medical therapy at discharge, when there was no contraindication, included aspirin, statin, β -blocker, and angiotensin-converting-enzyme inhibitor or angiotensin II-receptor blocker.

Abbreviation: ICDs, implantable cardioverter–defibrillators.

who had received an alternative device within 180 days of the date of implant. A total of 3,087 unique covariates (including interactions) were selected by the PS-ML for at least one device and quarter (Table 7), none of which was used more than five times, and there were no instances of covariate imbalance across the 396 distinct analyses.

Comparing three approaches to safety-signal detection

For the eleven commonly used dual-chamber ICDs, the application of time-to-event, DELTA, and embedded feature-selection approaches for safety-signal detection resulted in frequent agreements on the absence of safety signals, but rare agreements on their presence for individual devices and across periods of surveillance (Figure 5). A total of 60 safety signals were identified where an ICD was determined to be significantly better or worse than the group average for at least a quarter of observations for one of the three surveyed safety signals (death, nonfatal ICD-related adverse events,

or a composite of the two): 13 signals were identified by the time-to-event approach, 27 by the DELTA approach, and 20 by the embedded feature-selection approach (Figures 6–8). No signal was identified by all three statistical approaches, whereas a signal for ICD 2 was twice identified by both the time-to-event and DELTA approaches; the remaining signals were identified by only one statistical approach. Among the 396 distinct analyses, the agreement in signals detected (or lack thereof) between the time-to-event and DELTA approaches was 90.9% (360 of 396, $\kappa=0.068$, 95% CI –0.064 to 0.199), that between time-to-event and embedded feature-selection approaches was 91.7% (363 of 396, $\kappa=-0.028$, 95% CI –0.039 to –0.017), and that between the DELTA and embedded feature selection approaches was 88.1% (349 of 396, $\kappa=-0.042$, 95% CI –0.055 to –0.029).

With the exception of ICD 7, each dual-chamber ICD was identified by at least one statistical approach as being significantly better or worse than the group average for at least one quarter of observation; the most commonly identified devices were ICDs 5, 1, and 2. For instance, there were 22 quarters of observation where ICD 5 was determined to be significantly better than the group average (and two quarters where it was worse) by any of the three statistical approaches, each of which was surveying for all three safety signals. For ICD 1, there were nine quarters where it was determined to be significantly worse than the group average, always by the embedded feature-selection approach, whereas for ICD 2 there were seven quarters where it was determined to be significantly worse than the group average, but only by the time-to-event approach or DELTA.

ICDs 1 and 5 provide illustrative examples of the use of both DELTA and the embedded feature-selection approach for safety-signal detection. Figure 9 displays river plots visualizing medical device performance for ICD 1 relative to propensity-matched control devices, for the composite end point of death or nonfatal ICD-related adverse events. For this device, DELTA identified neither better nor worse than average safety performance, but for six quarters there was at least one covariate imbalanced among the propensity-matched groups. In contrast, the embedded feature-selection approach identified five consecutive quarters at the end of the observation period in which the device was identified as having worse than average safety performance, without covariate imbalance among the propensity-matched groups. Similarly, Figure 10 displays river plots for ICD 5, the most commonly implanted device in the sample. For this device, DELTA identified six quarters, many of which were consecutive, in which the device was identified as having better

Table 4 Key characteristics of patients receiving dual-chamber ICDs, 2006–2010 by device

Patient characteristics	ICD 1	ICD 2	ICD 3	ICD 4	ICD 5
n (%)	4,616 (6.4)	2,227 (3.1)	4,903 (6.8)	7,883 (11)	18,076 (25.1)
Mean age, years (SD)	75.1 (6.4)	75.7 (6.5)	75.8 (6.5)	75.5 (6.6)	75.1 (6.3)
Female sex, n (%)	1,096 (23.7)	559 (25.1)	1,274 (26)	1,934 (24.5)	4,266 (23.6)
Race, n (%)					
White	4,063 (88)	2,012 (90.3)	4,318 (88.1)	7,027 (89.1)	16,319 (90.3)
Black	374 (8.1)	151 (6.8)	353 (7.2)	531 (6.7)	1,152 (6.4)
Other	179 (3.9)	64 (2.9)	232 (4.7)	325 (4.1)	605 (3.3)
Reason for admission, n (%)					
ICD implantation	2,878 (62.3)	1,412 (63.4)	3,233 (65.9)	5,842 (74.1)	11,150 (61.7)
Heart failure ^a	336 (7.3)	147 (6.6)	377 (7.7)	365 (4.6)	1,324 (7.3)
Other cardiac ^a	1,211 (26.2)	583 (26.2)	1,141 (23.3)	1,466 (18.6)	4,916 (27.2)
Noncardiac ^a	191 (4.1)	85 (3.8)	152 (3.1)	210 (2.7)	686 (3.8)
NYHA class, n (%)					
I	821 (17.8)	439 (19.7)	969 (19.8)	1,655 (21)	3,554 (19.7)
II	2,327 (50.4)	1,023 (45.9)	2,520 (51.4)	4,245 (53.9)	9,031 (50)
III	1,379 (29.9)	705 (31.7)	1,299 (26.5)	1,882 (23.9)	5,116 (28.3)
IV	89 (1.9)	60 (2.7)	115 (2.3)	101 (1.3)	375 (2.1)
Clinical comorbidities, n (%)					
Atrial fibrillation or flutter	1,643 (35.6)	760 (34.1)	1,658 (33.8)	2,758 (35)	6,706 (37.1)
Ventricular tachycardia (sustained or unsustained)	2,280 (49.4)	1,181 (53)	2,498 (50.9)	4,371 (55.4)	9,431 (52.2)
Ischemic heart disease	3,558 (77.1)	1,673 (75.1)	3,787 (77.2)	6,079 (77.1)	13,924 (77)
Cerebrovascular disease	847 (18.3)	445 (20)	884 (18)	1,351 (17.1)	3,154 (17.4)
Chronic lung disease	1,022 (22.1)	527 (23.7)	1,124 (22.9)	1,764 (22.4)	4,068 (22.5)
End-stage renal disease on dialysis	186 (4)	96 (4.3)	154 (3.1)	252 (3.2)	579 (3.2)
Indication for ICD therapy, n (%)					
Primary	3,348 (72.5)	1,486 (66.7)	3,493 (71.2)	5,495 (69.7)	12,720 (70.4)
Secondary	1,268 (27.5)	741 (33.3)	1,410 (28.8)	2,388 (30.3)	5,356 (29.6)
Receipt of optimal medical therapy at discharge^b, n (%)	3,036 (65.8)	1,372 (61.6)	3,038 (62)	5,205 (66)	11,682 (64.6)

Notes: ^aAdmitted for clinical management and ICD implanted during course of hospitalization; ^breceipt of optimal medical therapy at discharge, when there was no contraindication, included aspirin, statin, β-blocker, and angiotensin-converting-enzyme inhibitor or angiotensin II-receptor blocker.

Abbreviations: ICDs, implantable cardioverter–defibrillators; NYHA, New York Heart Association.

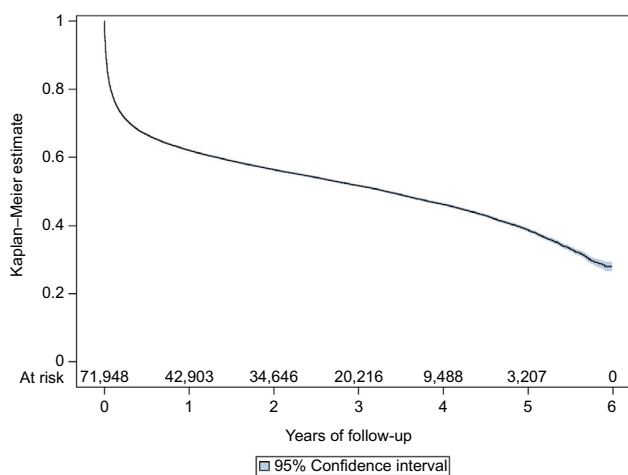


Figure 3 Kaplan–Meier survival curve.

Note: Freedom from death or nonfatal ICD-related adverse events among Medicare fee-for-service beneficiaries undergoing dual-chamber ICD implantation, 2006–2010.

Abbreviation: ICD, implantable cardioverter–defibrillator.

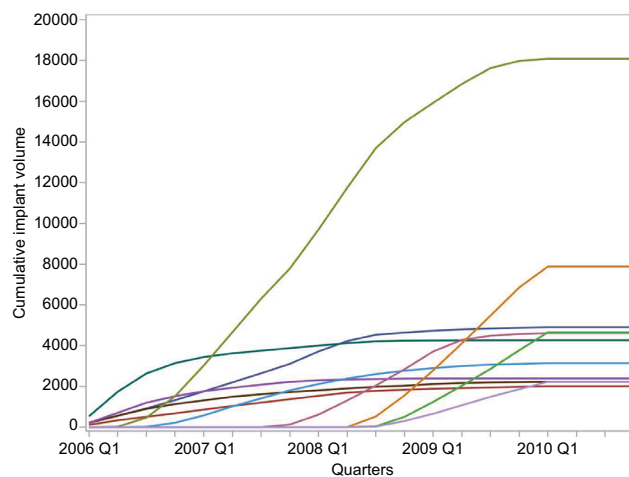


Figure 4 Cumulative implantation volume for the eleven dual-chamber ICDs.

Note: ICDs implanted 2,000 times or more among Medicare fee-for-service beneficiaries, 2006–2010.

Abbreviation: ICDs, implantable cardioverter–defibrillators.

ICD 6	ICD 7	ICD 8	ICD 9	ICD 10	ICD 11	All other ICDs
4,265 (5.9)	2,006 (2.8)	4,656 (6.5)	2,226 (3.1)	2,389 (3.3)	3,141 (4.4)	15,560 (21.6)
75 (6.1)	75.8 (6.4)	75 (6.4)	75.2 (6.5)	74.8 (6.2)	75.2 (6.4)	75.2 (6.4)
934 (21.9)	502 (25)	1,133 (24.3)	516 (23.2)	538 (22.5)	741 (23.6)	3,669 (23.6)
3,876 (90.9)	1,815 (90.5)	4,112 (88.3)	2,057 (92.4)	2,111 (88.4)	2,770 (88.2)	13,735 (88.3)
277 (6.5)	109 (5.4)	345 (7.4)	106 (4.8)	181 (7.6)	246 (7.8)	1,192 (7.7)
112 (2.6)	82 (4.1)	199 (4.3)	63 (2.8)	97 (4.1)	125 (4)	633 (4.1)
2,557 (60)	1,300 (64.8)	3,056 (65.6)	1,518 (68.2)	1,349 (56.5)	1,892 (60.2)	9,875 (63.5)
328 (7.7)	144 (7.2)	292 (6.3)	124 (5.6)	226 (9.5)	272 (8.7)	1,236 (7.9)
1,235 (29)	506 (25.2)	1,164 (25)	505 (22.7)	704 (29.5)	860 (27.4)	3,877 (24.9)
145 (3.4)	56 (2.8)	144 (3.1)	79 (3.5)	110 (4.6)	117 (3.7)	572 (3.7)
914 (21.4)	387 (19.3)	919 (19.7)	440 (19.8)	378 (15.8)	555 (17.7)	2,830 (18.2)
2,068 (48.5)	1,027 (51.2)	2,370 (50.9)	1,167 (52.4)	1,173 (49.1)	1,526 (48.6)	7,459 (47.9)
1,177 (27.6)	560 (27.9)	1,262 (27.1)	577 (25.9)	760 (31.8)	978 (31.1)	4,902 (31.5)
106 (2.5)	32 (1.6)	105 (2.3)	42 (1.9)	78 (3.3)	82 (2.6)	369 (2.4)
1,683 (39.5)	714 (35.6)	1,793 (38.5)	792 (35.6)	844 (35.3)	1,110 (35.3)	5,644 (36.3)
2,242 (52.6)	1,036 (51.6)	2,447 (52.6)	1,129 (50.7)	1,189 (49.8)	1,629 (51.9)	7,694 (49.4)
3,299 (77.4)	1,562 (77.9)	3,463 (74.4)	1,715 (77)	1,868 (78.2)	2,407 (76.6)	11,814 (75.9)
790 (18.5)	350 (17.4)	868 (18.6)	384 (17.3)	431 (18)	568 (18.1)	2,838 (18.2)
902 (21.1)	435 (21.7)	1,059 (22.7)	534 (24)	561 (23.5)	751 (23.9)	3,729 (24.0)
121 (2.8)	69 (3.4)	148 (3.2)	71 (3.2)	116 (4.9)	137 (4.4)	642 (4.1)
3,034 (71.1)	1,370 (68.3)	3,355 (72.1)	1,543 (69.3)	1,727 (72.3)	2,225 (70.8)	11,445 (73.6)
1,231 (28.9)	636 (31.7)	1,301 (27.9)	683 (30.7)	662 (27.7)	916 (29.2)	4,115 (26.4)
2,683 (62.9)	1,302 (64.9)	3,091 (66.4)	1,542 (69.3)	1,455 (60.9)	1,961 (62.4)	9,891 (63.6)

than average safety performance, without covariate imbalance among the propensity-matched groups. In contrast, the embedded feature-selection approach identified one quarter early in the observation period in which the device was identified as having worse than average safety performance, and another quarter later in the observation period in which the device was identified as having better than average safety performance, without covariate imbalance among propensity-matched groups.

Discussion

Using data from the NCDR-ICD registry in conjunction with longitudinal follow-up information obtained from Medicare administrative claims, we found that three statistical approaches to safety-signal detection, including one ML method, identified important safety signals for eleven commonly used dual-chamber ICDs. However, while these three approaches resulted in frequent agreements on the absence of signals, there were rare agreements on the quarterly presence of signals. These findings provide early insights into whether multiple methods used as an ensemble may be necessary to

detect all safety signals for further evaluation during medical device surveillance, as well as for how ML analytic methods might complement current surveillance efforts that are using traditional analytic methods.

For effective postmarket medical device-safety surveillance, three components must be in place: effective and reliable data collection, analysis, and interpretation. High-quality registry data, such as those from NCDR-ICD, offer detailed information about patients, procedures, and devices that can be used for surveillance. However, registries are costly, are not necessarily scalable across all medical devices types, and currently lack coordination.³⁴ The FDA is actively engaged in and working to enhance surveillance and life cycle medical device evaluation to monitor medical device safety and effectiveness.^{9,10,35} Ensuring effective and reliable data collection for surveillance will likely require leveraging information from that routinely collected by electronic health records or administrative claims data, once there is widespread adoption of the unique-device-identifier system.³⁶

Our analyses were focused on understanding the effectiveness and reliability of data analysis for medical device sur-

Table 5 Cumulative unadjusted rates of death, nonfatal AEs, and death or nonfatal AEs for eleven commonly used dual-chamber ICDs, 2006–2010

Event category ^a	Cumulative unadjusted event rates, % (95% CI)										
	ICD 1	ICD 2	ICD 3	ICD 4	ICD 5	ICD 6	ICD 7	ICD 8	ICD 9	ICD 10	ICD 11
Death^b	19 (17.9–20.2)	20.5 (18.8–22.3)	14.1 (13.2–15.2)	17.4 (16.6–18.3)	12.8 (12.3–13.3)	18.2 (17–19.4)	16.5 (14.9–18.3)	18.4 (17.3–19.5)	20.9 (19.3–22.7)	19.2 (17.7–20.9)	18.1 (16.8–19.5)
Any nonfatal AE^b	24.5 (23.3–25.8)	25.9 (24.1–27.9)	19.3 (18.2–20.5)	22.5 (21.6–23.5)	19.4 (18.8–20)	24.7 (23.4–26.1)	21.7 (19.9–23.6)	22.8 (21.6–24)	25.2 (23.4–27)	26.3 (24.5–28.1)	22.4 (20.9–23.9)
Device failure^b	10.4 (9.6–11.3)	11.6 (10.3–13.1)	8.2 (7.4–9)	9.9 (9.2–10.6)	8.8 (8.4–9.2)	11.7 (10.7–12.7)	8.7 (7.5–10.1)	9.9 (9–10.8)	11.3 (10–12.7)	11.2 (10–12.6)	10.2 (9.2–11.3)
Infection^b	5.1 (4.5–5.8)	5.2 (4.3–6.2)	3.7 (3.2–4.3)	4.6 (4.1–5.1)	3.5 (3.2–3.8)	4.5 (3.9–5.2)	4 (3.2–5)	5.2 (4.6–5.9)	6 (5.1–7.1)	5.6 (4.7–6.6)	4.5 (3.8–5.3)
Mental health^b	0.5 (0.3–0.7)	0.6 (0.4–1.1)	0.4 (0.2–0.6)	0.5 (0.3–0.7)	0.5 (0.4–0.6)	0.8 (0.5–1.1)	0.4 (0.2–0.9)	0.6 (0.4–0.8)	0.4 (0.2–0.7)	0.4 (0.2–0.7)	0.5 (0.3–0.8)
Other malfunction^b	3.9 (3.4–4.5)	4.6 (3.7–5.6)	3 (2.5–3.5)	3 (2.6–3.4)	3 (2.7–3.2)	3.3 (2.7–3.8)	3.3 (2.6–4.2)	2.7 (2.2–3.2)	3.8 (3.1–4.7)	5.5 (4.6–6.5)	3.3 (2.7–4)
PC 1^c	0.9 (0.6–1.2)	1.3 (0.9–1.9)	1.2 (0.9–1.5)	0.8 (0.7–1.1)	0.9 (0.8–1.1)	0.8 (0.6–1.2)	1.2 (0.8–1.9)	1.1 (0.8–1.4)	0.7 (0.4–1.1)	1.1 (0.7–1.6)	1.3 (0.9–1.8)
PC 2^c	0.2 (0.1–0.4)	0.2 (0.1–0.5)	0.3 (0.2–0.5)	0.2 (0.1–0.3)	0.2 (0.2–0.3)	0.2 (0.1–0.4)	0.3 (0.1–0.7)	0.3 (0.2–0.5)	0.4 (0.2–0.8)	0.3 (0.1–0.6)	0.3 (0.2–0.6)
PC 3^c	0	0	0	0	0	0	0	0	0	0	0
PC 4^c	1 (0.7–1.3)	0.8 (0.5–1.3)	0.6 (0.4–0.9)	0.9 (0.7–1.1)	0.9 (0.8–1.1)	1 (0.7–1.3)	1 (0.6–1.5)	0.7 (0.5–1)	1 (0.7–1.6)	1.1 (0.8–1.7)	1.1 (0.8–1.6)
Pocket reoperation^b	0.7	0.7	0.5	0.8	0.6	0.7	0.7	0.6	1	0.5	0.6
Generator reoperation^b	4.4 (3.8–5)	3.8 (3.1–4.8)	3.3 (2.8–3.9)	4.1 (3.7–4.6)	2.7 (2.4–2.9)	3.9 (3.4–4.6)	4.4 (3.5–5.4)	4.1 (3.6–4.8)	3.5 (2.8–4.4)	4.3 (3.5–5.2)	3.7 (3–4.4)
Lead reoperation^b	3.9 (3.4–4.5)	4.2 (3.4–5.2)	2.3 (1.9–2.7)	2.7 (2.3–3)	2.9 (2.7–3.2)	3.7 (3.1–4.3)	2.4 (1.8–3.3)	2.7 (2.3–3.3)	3.5 (2.8–4.4)	4.8 (4–5.8)	3.2 (2.6–3.9)
Death or any nonfatal AE^b	36 (34.6–37.4)	37.6 (35.5–39.8)	28.3 (27–29.7)	33.2 (32.2–34.3)	27.1 (26.5–27.8)	35.4 (33.9–36.8)	31.1 (29–33.2)	33.8 (32.5–35.2)	37 (35–39.1)	37 (35.1–39)	33.4 (31.7–35.1)

Notes: ^aAll event categories defined in Tables 1 and 2; ^bevent surveillance for 3 years postimplantation; ^cevent surveillance for 90 days postimplantation.

Abbreviations: ICDs, implantable cardioverter–defibrillators; AEs, adverse events; PC, procedural complication.

Table 6 Percentage of parameters imbalanced

ICD	Method	Quarter	2006		2007		2008		2009		2010		2011		Overall
			Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4		
2	TTE	55.6	0	0	5.6	11.1	0	0	0	0	0	0	0	0	6
	DELTA	38.9	0	5.6	0	5.6	0	0	0	0	0	0	0	0	4.2
	EFS	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	TTE	5.6	0	0	0	0	0	0	0	0	0	0	0	0	0.5
	DELTA	38.9	0	0	0	0	0	0	0	0	0	0	0	0	3.2
	EFS	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	TTE	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	DELTA	5.6	0	0	0	0	0	0	0	0	0	0	0	0	0.5
	EFS	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	TTE	16.7	0	0	0	0	0	0	0	0	0	0	0	0	1.4
	DELTA	22.2	0	0	0	0	0	0	0	0	0	0	0	0	1.9
	EFS	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	TTE	0	27.8	0	0	0	0	0	5.6	0	0	0	0	0	2.8
	DELTA	11.1	5.6	0	0	0	0	0	0	0	0	0	0	0	1.4
	EFS	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	TTE	0	16.7	0	0	0	0	0	0	0	0	0	0	0	1.4
	DELTA	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	EFS	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	TTE	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	DELTA	38.9	0	38.9	0	5.6	0	0	0	0	0	0	0	0	3.7
	EFS	0	0	0	0	0	0	0	0	0	0	0	0	0	1.9
1	TTE	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	DELTA	0	16.7	0	5.6	0	0	0	0	0	0	0	0	0	0
	EFS	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	TTE	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	DELTA	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	EFS	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	TTE	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	DELTA	11.1	5.6	16.7	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	10.6
	EFS	16.7	11.1	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	6.5
9	TTE	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	DELTA	27.8	16.7	16.7	0	0	0	0	0	0	0	0	0	0	5.1
	EFS	16.7	0	5.6	0	0	0	0	0	0	0	0	0	0	2.3
Overall	TTE	19.4	5.6	2.8	5.6	0.8	2.4	0	1.4	0.7	1.9	0	0	0	3.6
	DELTA	26.4	2.2	1.9	0	2.4	0.8	0	0	0.7	2.5	3.5	2.4	2.8	2.4
	EFS	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Abbreviations: ICD, implantable cardioverter-defibrillator; TTE, time-to-event (modeling); DELTA, Data Extraction and Longitudinal Trend Analysis; EFS, embedded feature selection.

Table 7 Most frequent covariates used in embedded feature selection

Covariates used 3+ times in embedded feature selection	Total covariate-usage count
EPS findings: no results induced and GovTypePrim*nan	5
EPS findings: unsustained VT and patient race – American Indian/Alaska Native	5
Family Hx sudden death and NYHA class 4 – current status	5
Nonischemic dilated cardiomyopathy: yes, <3 months and LV lead-implantation method – coronary sinus	5
PICD reason: cardiac arrest/arrhythmia – etiology unknown and previous MI within 40 days of ICD implant	5
PICD reason: monomorphic sustained VT and pacemaker insertion – atrial chamber	5
PICD reason: primary prevention/SCD and PrevICDSite*nan	5
PICD reason: syncope + high-risk characteristics and EPS findings – no results induced	5
PICD reason: ventricular fibrillation and renal failure – dialysis	5
Thoracic cardiac surgery and pacemaker insertion: biventricular	5
ACCCOCATS and primary insurance: HMO	4
Admitted for noncardiac and CBSA: micro	4
Adult electrophysiology: noncertification and pacemaker insertion – atrial chamber	4
Cardiac transplant and EPS time frame	4
Cardiac transplant and nonischemic dilated cardiomyopathy – yes, >9 months	4
Cardiac transplant and owner: public	4
Cerebrovascular disease and patient race: Asian	4
CHF hospitalization: hospitalized >6 months and previous ICD-implant site – abdominal	4
EPS findings: no results induced and patient race – other	4
EPS findings: no results induced and primary insurance – commercial	4
EPS findings: unsustained VT and bradycardia arrest	4
EPS findings: unsustained VT and patient race – other	4
EPS findings: unsustained VT and previous ICD-implant site – abdominal	4
EPS findings: results unattainable and pacemaker insertion – dual chamber	4
EPS findings: ventricular flutter induced and CHF duration <3 months	4
EPS findings: ventricular flutter induced and CHF duration 3–9 months	4
EPS findings: ventricular flutter induced and NYHA class 4 – current status	4
EPS findings: ventricular flutter induced and owner – public	4
EPS findings: ventricular flutter induced and primary insurance – none/self-pay	4
Family Hx sudden death and EPS findings: ventricular flutter induced	4
Hispanic ethnicity and LV lead-implantation method: coronary sinus	4
HTS: COTH and HTYPE – CATH	4
None of the below and tachycardia arrest reason: unknown etiology	4
Patient sex and race*nan	4
Patient race: American Indian/Alaska Native and pacemaker insertion – dual chamber	4
Patient race: Asian and admitted for cardiac CHF	4
Patient race: Asian and CBSA – micro	4
Patient race: Asian and CHF duration <3 months	4
Patient race: Asian and HTYPE: CATH	4
Patient race: Asian and previous MI within 40 days of ICD implant	4
Patient race: other and HTYPE – other	4
Pediatric electrophysiology and PICD reason: syncope with inducible VT	4
Pediatric electrophysiology and previous MI within 40 days of ICD implant	4
PICD reason: atrial fibrillation and CHF duration <3 months	4
PICD reason: cardiac arrest/arrhythmia – etiology unknown and admitted for cardiac CHF	4
PICD reason: cardiac arrest/arrhythmia – etiology unknown and HTYPE: other	4
PICD reason: polymorphic sustained VT and previous MI within 40 days of ICD implant	4
PICD reason: syncope with inducible VT and admitted for noncardiac	4
PICD reason: syncope with inducible VT and previous MI <40 days and >40 days	4
Previous ICD: biventricular and HTYPE – other	4
Previous valvular surgery and pacemaker insertion: atrial chamber	4
Renal failure: dialysis and pacemaker insertion – atrial chamber	4
Tachycardia arrest reason: acute MI and HTYPE: CATH	4
Tachycardia arrest reason: drug-induced arrhythmia and PICD reason: polymorphic sustained VT	4
Tachycardia arrest reason: unknown etiology and HCOType*Health System/Network	4
Thoracic cardiac surgery and EPS findings: ventricular flutter induced	4

(Continued)

Table 7 (Continued)

Covariates used 3+ times in embedded feature selection	Total covariate-usage count
Thoracic cardiac surgery and pacemaker insertion: atrial chamber	4
Ventricular tachycardia: yes, polymorphic sustained and nonischemic dilated cardiomyopathy 3–9 months	4
VT*nan and owner: public	4
ACCCOCATS and LV lead-implantation method: epicardial lead	3
ACCCOCATS and LV lead-implantation method: other	3
AdmissionReason*nan and HTYPE: CATH	3
Admitted for cardiac CHF and pacemaker insertion: ventricular chamber	3
Admitted for cardiac CHF and previous ICD: dual chamber	3
Adult electrophysiology: noncertification and ischemicHD*nan	3
BNP level and pacemaker insertion: dual chamber	3
BNP level and pacemaker insertion: ventricular chamber	3
Bradycardia arrest and CBSA*nan	3
Bradycardia arrest and HTS*nan	3
Bradycardia arrest and HTYPE*nan	3
Bradycardia arrest and OWNER*nan	3
Bradycardia arrest reason: acute MI and CHF duration 3–9 months	3
Bradycardia arrest reason: acute MI and EPS findings – unsustained VT	3
Bradycardia arrest reason: sinus-node dysfunction/AV block and EPS findings – unsustained VT	3
Bradycardia arrest reason: sinus-node dysfunction/AV block and EPS findings – ventricular fibrillation induced	3
Bradycardia arrest reason: unknown etiology and NYHA class 4 – current status	3
Bradycardia arrest reason: unknown etiology and previous valvular surgery	3
BUN level and CBSA: micro	3
Cardiac transplant and admitted for cardiac CHF	3
Cardiac transplant and BNP drawn	3
Cardiac transplant and CHF hospitalization: not hospitalized	3
Cardiac transplant and electrophysiology study done	3
Cardiac transplant and EPS findings: sustained monomorphic	3
Cardiac transplant and facilities previous quarter volume	3
Cardiac transplant and HTS: COTH	3
CHF duration <3 months and previous ICD: single chamber	3
CHF duration 3–9 months and pacemaker insertion: atrial chamber	3
CHF hospitalization: hospitalized within 6 months and HCOType*Private CV practice	3
Client percentage Medicare and IschemicHD*nan	3
Creatinine level and patient race: American Indian/Alaska Native	3
Creatinine level and VT*nan	3
EF% and CBSA: micro	3
EPS findings: no results induced and admitted for cardiac CHF	3
EPS findings: no results induced and admitted for noncardiac	3
EPS findings: no results induced and CHF duration 3–9 months	3
EPS findings: no results induced and pacemaker insertion – ventricular chamber	3
EPS findings: no results induced and previous ICD: biventricular	3
EPS findings: no results induced and primary insurance: HMO	3
EPS findings: results unattainable and PR interval	3
EPS findings: results unattainable and previous MI within 40 days of ICD implant	3
EPS findings: sustained monomorphic and LV lead-implantation method – coronary sinus	3
EPS findings: sustained monomorphic and previous ICD-implant site – abdominal	3
EPS findings: sustained polymorphic and EPS findings – ventricular flutter induced	3
EPS findings: sustained polymorphic and previous ICD – single chamber	3
EPS findings: sustained polymorphic and previous MI <40 days and >40 days	3
EPS findings: ventricular fibrillation induced and admitted for cardiac CHF	3
EPS findings: ventricular fibrillation induced and bradycardia arrest	3
EPS findings: ventricular fibrillation induced and CHF duration <3 months	3
EPS findings: ventricular fibrillation induced and patient race – other	3
EPS findings: ventricular fibrillation induced and previous MI <40 days and >40 days	3
EPS findings: ventricular flutter induced and CBSA*nan	3

(Continued)

Table 7 (Continued)

Covariates used 3+ times in embedded feature selection	Total covariate-usage count
EPS findings: ventricular flutter induced and CBSA – micro	3
EPS findings: ventricular flutter induced and HTS*nan	3
EPS findings: ventricular flutter induced and HTYPE*nan	3
EPS findings: ventricular flutter induced and non-ischemic dilated cardiomyopathy – yes, 3–9 months	3
EPS findings: ventricular flutter induced and OWNER*nan	3
EPS findings: ventricular flutter induced and ventricular tachycardia – yes, polymorphic sustained	3
Facilities previous quarter volume and patient race: Native Hawaiian	3
Family Hx sudden death and patient race: other	3
Family Hx sudden death and primary insurance: commercial	3
Family Hx sudden death and tachycardia arrest reason: unknown etiology	3
GovTypePrim*nan and NYHAclass*nan	3
Hispanic ethnicity and HCOType*Private CV practice	3
Hispanic ethnicity and PICD reason: atrial fibrillation	3
Hispanic ethnicity and tachycardia arrest reason: severe electrolyte disturbance	3
HRS ICD implantation and bradycardia arrest reason: acute MI	3
LV lead-implantation method – coronary sinus and HTYPE: CATH	3
None of the below and BNP level	3
None of the below and Hispanic ethnicity	3
None of the below and pacemaker insertion: atrial chamber	3
None of the below and patient race: American Indian/Alaska Native	3
None of the below and patient race: other	3
None of the below and primary insurance: commercial	3
None of the below and ventricular tachycardia: yes, polymorphic sustained	3
Nonischemic dilated cardiomyopathy: yes, <3 months and ischemic heart disease, yes other Dx tests	3
Nonischemic dilated cardiomyopathy: yes, 3–9 months and previous MI within 40 days of ICD implant	3
NYHA class I:- current status and pacemaker insertion – atrial chamber	3
NYHA class I: current status and pacemaker insertion – biventricular	3
NYHA class 4: current status and CBSA – rural	3
NYHAclass*nan and HCOType*Hospital/Health Network	3
Pacemaker insertion: biventricular and HTYPE – CATH	3
Patient race: American Indian/Alaska Native and CBSA: micro	3
Patient race: American Indian/Alaska Native and CHF hospitalization: not hospitalized	3
Patient race: American Indian/Alaska Native and HCOType*Health System/Network	3
Patient race: American Indian/Alaska Native and previous MI <40 days and >40 days	3
Patient race: American Indian/Alaska Native and tachycardia arrest	3
Patient race: American Indian/Alaska Native and ventricular tachycardia – yes, monomorphic sustained	3
Patient race: Asian and bradycardia arrest	3
Patient race: Asian and NYHA class 4 – current status	3
Patient race: Asian and pacemaker insertion – ventricular chamber	3
Patient race: black/African-American and pacemaker insertion – biventricular	3
Patient race: black/African-American and primary insurance – HMO	3
Patient race: Native Hawaiian and admitted for cardiac CHF	3
Patient race: Native Hawaiian and previous MI >40 days prior to ICD implant	3
Patient race: Native Hawaiian and sinus-node function – abnormal	3
Patient race: other and LV lead-implantation method – coronary sinus	3
Pediatric electrophysiology and admitted for cardiac CHF	3
Pediatric electrophysiology and BNP drawn	3
Pediatric electrophysiology and CHF duration <3 months	3
Pediatric electrophysiology and chronic lung disease	3
Pediatric electrophysiology and EPS findings: ventricular flutter induced	3
Pediatric electrophysiology and ischemic heart disease: no	3
Pediatric electrophysiology and NYHA class 3 – current status	3
Pediatric electrophysiology and pacemaker insertion – dual chamber	3
Pediatric electrophysiology and previous valvular surgery	3
Pediatric electrophysiology and renal failure – dialysis	3
Pediatric electrophysiology and sodium level	3

(Continued)

Table 7 (Continued)

Covariates used 3+ times in embedded feature selection	Total covariate-usage count
PICD reason: atrial fibrillation and CBSA*nan	3
PICD reason: atrial fibrillation and HTS*nan	3
PICD reason: atrial fibrillation and HTYPE*nan	3
PICD reason: atrial fibrillation and OWNER*nan	3
PICD reason: atrial fibrillation and owner – public	3
PICD reason: atrial fibrillation and pacemaker insertion – atrial chamber	3
PICD reason: atrial fibrillation and patient race – other	3
PICD reason: atrial fibrillation and Previous MI within 40 days of ICD implant	3
PICD reason: cardiac arrest/arrhythmia – etiology unknown and pacemaker insertion: ventricular chamber	3
PICD reason: cardiac arrest/arrhythmia – etiology unknown and PICD reason: atrial fibrillation	3
PICD reason: monomorphic sustained VT and admitted for noncardiac	3
PICD reason: monomorphic sustained VT and CHF duration <3 months	3
PICD reason: polymorphic sustained VT and admitted for cardiac CHF	3
PICD reason: polymorphic sustained VT and CHF duration <3 months	3
PICD reason: polymorphic sustained VT and CHF hospitalization – hospitalized within 6 months	3
PICD reason: polymorphic sustained VT and EPS findings – ventricular flutter induced	3
PICD reason: polymorphic sustained VT and primary insurance – commercial	3
PICD reason: syncope + high-risk characteristics and admitted for noncardiac	3
PICD reason: syncope + high-risk characteristics and CBSA – micro	3
PICD reason: syncope + high-risk characteristics and CHF duration <3 months	3
PICD reason: syncope + high-risk characteristics and EPS findings – ventricular fibrillation induced	3
PICD reason: syncope + high-risk characteristics and EPS findings – VT induced	3
PICD reason: syncope + high-risk characteristics and HCOType*Hospital/Health Network	3
PICD reason: syncope + high-risk characteristics and previous ICD-implant site – abdominal	3
PICD reason: syncope + high-risk characteristics and ventricular tachycardia – yes, polymorphic sustained	3
PICD reason: syncope with inducible VT and admitted for cardiac CHF	3
PICD reason: syncope with inducible VT and nonischemic dilated cardiomyopathy – yes, 3–9 months	3
PICD reason: syncope with inducible VT and previous ICD-implant site – abdominal	3
PICD reason: ventricular fibrillation and CBSA – rural	3
PICD reason: ventricular fibrillation and EPS findings – ventricular flutter induced	3
PICD reason: ventricular fibrillation and patient race – black/African-American	3
PICD reason: ventricular fibrillation and previous MI within 40 days of ICD implant	3
Previous ICD-implant site: abdominal and HCOType*Hospital/Health Network	3
Previous ICD-implant site: abdominal and HTS: COTH	3
Previous ICD: dual chamber and PrevICDsite*nan	3
Previous MI <40 days and >40 days and previous ICD: single chamber	3
Previous MI within 40 days of ICD implant and CBSA: rural	3
Previous MI within 40 days of ICD implant and LV lead-implantation method: coronary sinus	3
Previous valvular surgery and PICD reason: cardiac arrest/arrhythmia – etiology unknown	3
Previous valvular surgery and PICD reason: polymorphic sustained VT	3
Previous valvular surgery and previous ICD – biventricular	3
Previous valvular surgery and primary insurance: commercial	3
Previous valvular surgery and primary insurance: HMO	3
Previous valvular surgery and Race*nan	3
Primary government insurance: Medicaid and admitted for noncardiac	3
Primary government insurance: Medicaid and HCOType*Health System/Network	3
Primary government insurance: Medicaid and LV lead-implantation method – coronary sinus	3
Primary government insurance: Medicaid and pacemaker insertion – biventricular	3
Primary government insurance: TriCare and CBSA – division	3
Primary insurance: commercial and NYHAclass*nan	3
Primary insurance: commercial and owner – public	3
Primary insurance: HMO and HTYPE – CATH	3
Primary insurance: HMO and HTYPE – other	3
Primary insurance: HMO and ischemic heart disease – no	3
Primary insurance: HMO and nonischemic dilated cardiomyopathy – yes, >9 months	3

(Continued)

Table 7 (Continued)

Covariates used 3+ times in embedded feature selection	Total covariate-usage count
Primary insurance: HMO and NYHA class 4 – current status	3
Primary insurance: none/self-pay and CBSA – micro	3
Primary insurance: none/self-pay and CHF hospitalization – not hospitalized	3
Primary insurance: none/self-pay and previous ICD: single chamber	3
QRS duration and IschemicHD*nan	3
Race*nan and admitted for noncardiac	3
Renal failure: dialysis and EPS findings – ventricular fibrillation induced	3
Renal failure: dialysis and nonischemic dilated cardiomyopathy – yes, <3 months	3
Renal failure: dialysis and NYHAclass*nan	3
Renal failure: dialysis and patient race – Asian	3
Sinus-node function: abnormal and HCOType*Other	3
Sodium level and patient race: American Indian/Alaska Native	3
Tachycardia arrest and pacemaker insertion: atrial chamber	3
Tachycardia arrest reason: acute MI and NYHA class 4 – current status	3
Tachycardia arrest reason: acute MI and PICD reason – cardiac arrest/arrhythmia: etiology unknown	3
Tachycardia arrest reason: acute MI and PICD reason – syncope with inducible VT	3
Tachycardia arrest reason: acute MI and previous MI – no	3
Tachycardia arrest reason: drug-induced arrhythmia and BNP level	3
Tachycardia arrest reason: drug-induced arrhythmia and CBSA – division	3
Tachycardia arrest reason: drug-induced arrhythmia and CHF hospitalization – not hospitalized	3
Tachycardia arrest reason: drug-induced arrhythmia and creatinine level	3
Tachycardia arrest reason: drug-induced arrhythmia and previous PCI – yes, >3 months	3
Tachycardia arrest reason: drug-induced arrhythmia and renal failure – dialysis	3
Tachycardia arrest reason: drug-induced arrhythmia and ventricular tachycardia – yes, unsustained	3
Tachycardia arrest reason: primary VT/VF and EPS findings – no results induced	3
Tachycardia arrest reason: primary VT/VF and EPS findings – unsustained VT	3
Tachycardia arrest reason: primary VT/VF and pacemaker insertion – atrial chamber	3
Tachycardia arrest reason: primary VT/VF and patient race – American Indian/Alaska Native	3
Tachycardia arrest reason: primary VT/VF and patient race – Asian	3
Tachycardia arrest reason: severe electrolyte disturbance and CHF duration 3–9 months	3
Tachycardia arrest reason: severe electrolyte disturbance and renal failure – dialysis	3
Tachycardia arrest reason: unknown etiology and CBSA – micro	3
Thoracic cardiac surgery and CHF duration 3–9 months	3
Thoracic cardiac surgery and LV lead-implantation method: coronary sinus	3
Thoracic cardiac surgery and primary government insurance: Medicaid	3
Ventricular tachycardia: No and IschemicHD*nan	3
Ventricular tachycardia: yes, unsustained and SinusNodeFr*nan	3
Ventricular tachycardia: yes, polymorphic sustained and pacemaker insertion – ventricular chamber	3
VT*nan and HTS: other	3

Abbreviations: EPS, electrophysiology study; VT, ventricular tachycardia; NYHA, New York Heart Association; LV, left ventricular; PICD, previous implantable cardioverter-defibrillator; SCD, sudden cardiac death; CBSA, core-based statistical area; CHF, congestive heart failure; HTS, hospital teaching status; MI, myocardial infarction; HMO, health-maintenance organization; ICD, implantable cardioverter-defibrillator; HTYPE, hospital type (cardiac facility capability); CATH, catheterization (procedures performed at facility); HCO, health care organization.

veillance, examining whether different statistical approaches to analysis agree in the identification of safety issues that deserve further scrutiny and evaluation. Across three approaches, we found frequent agreements on the absences of signals, but rare agreements on their presence. There are three potential reasons for our findings. First, perhaps the eleven commonly used dual-chamber ICDs we examined all have approximately the same safety profile, resulting in the same risk-standardized rates of death and adverse events. In other words, there may have been no underlying safety issue to detect. Second, perhaps there were underlying safety issues

to detect, but none of the methods was sufficiently robust to discriminate differences accurately and consistently among ICD models. Finally, perhaps each statistical approach has inherent advantages and disadvantages for safety-signal detection accuracy, leading to differences in performance across methods. Because there is currently no “gold standard” method for safety-signal detection in surveillance, we cannot determine which method is most effective and reliable. Further work testing different methods in different data sources will be needed to understand better whether an ensemble methodological approach to medical device surveil-

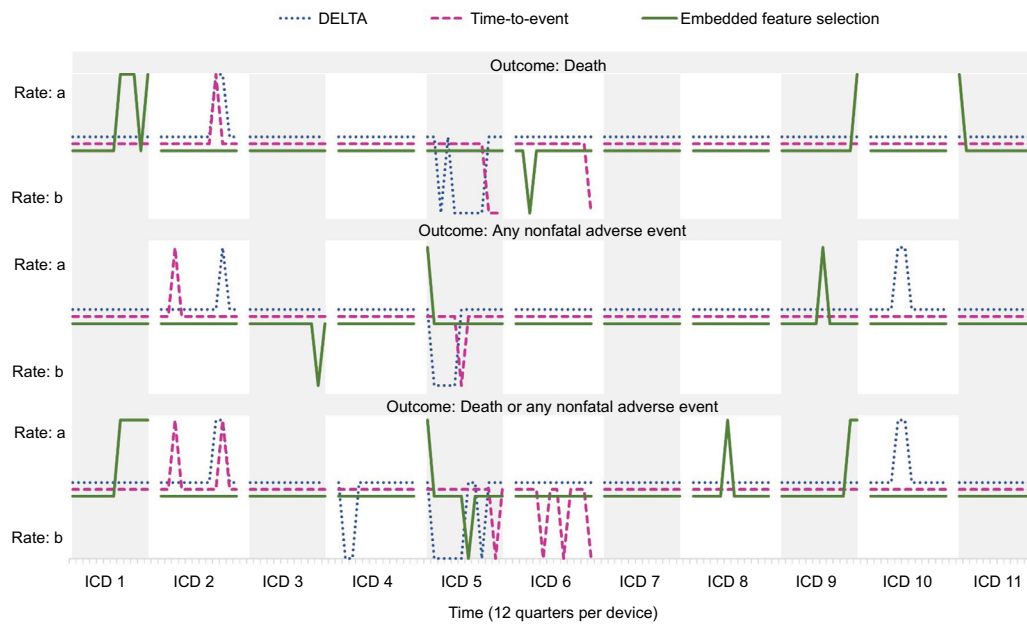


Figure 5 Time-to-event, DELTA, and embedded feature selection approaches for safety-signal detection among eleven commonly used dual-chamber ICDs, 2006–2010. **Note:** a, Rate higher than control; b, rate lower than control.

Abbreviations: DELTA, Data Extraction and Longitudinal Trend Analysis; ICDs, implantable cardioverter–defibrillators.

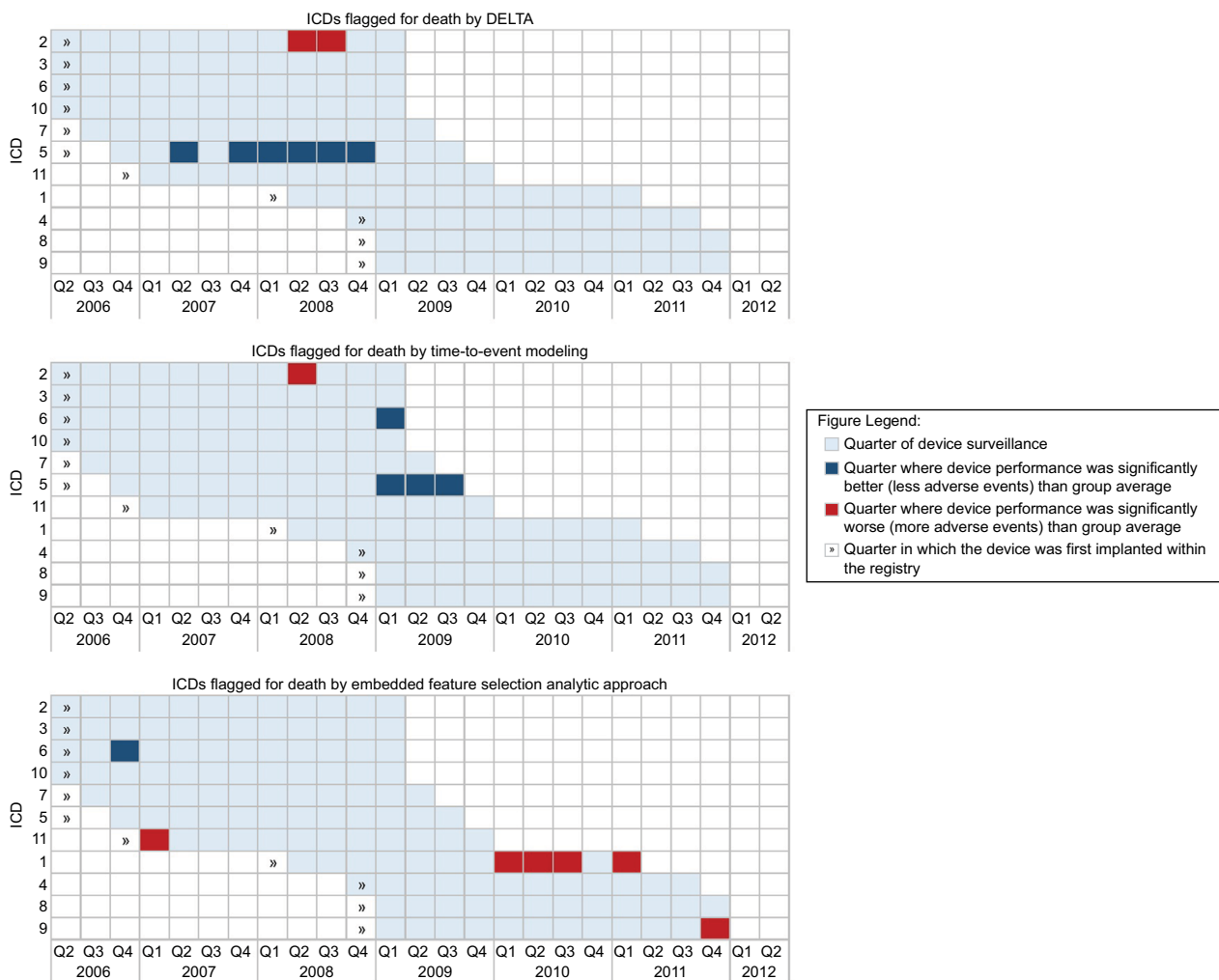


Figure 6 Time-to-event, DELTA, and embedded feature selection methods for safety-signal detection for death among eleven commonly used dual-chamber ICDs, 2006–2010. **Abbreviations:** DELTA, Data Extraction and Longitudinal Trend Analysis; ICDs, implantable cardioverter–defibrillators.

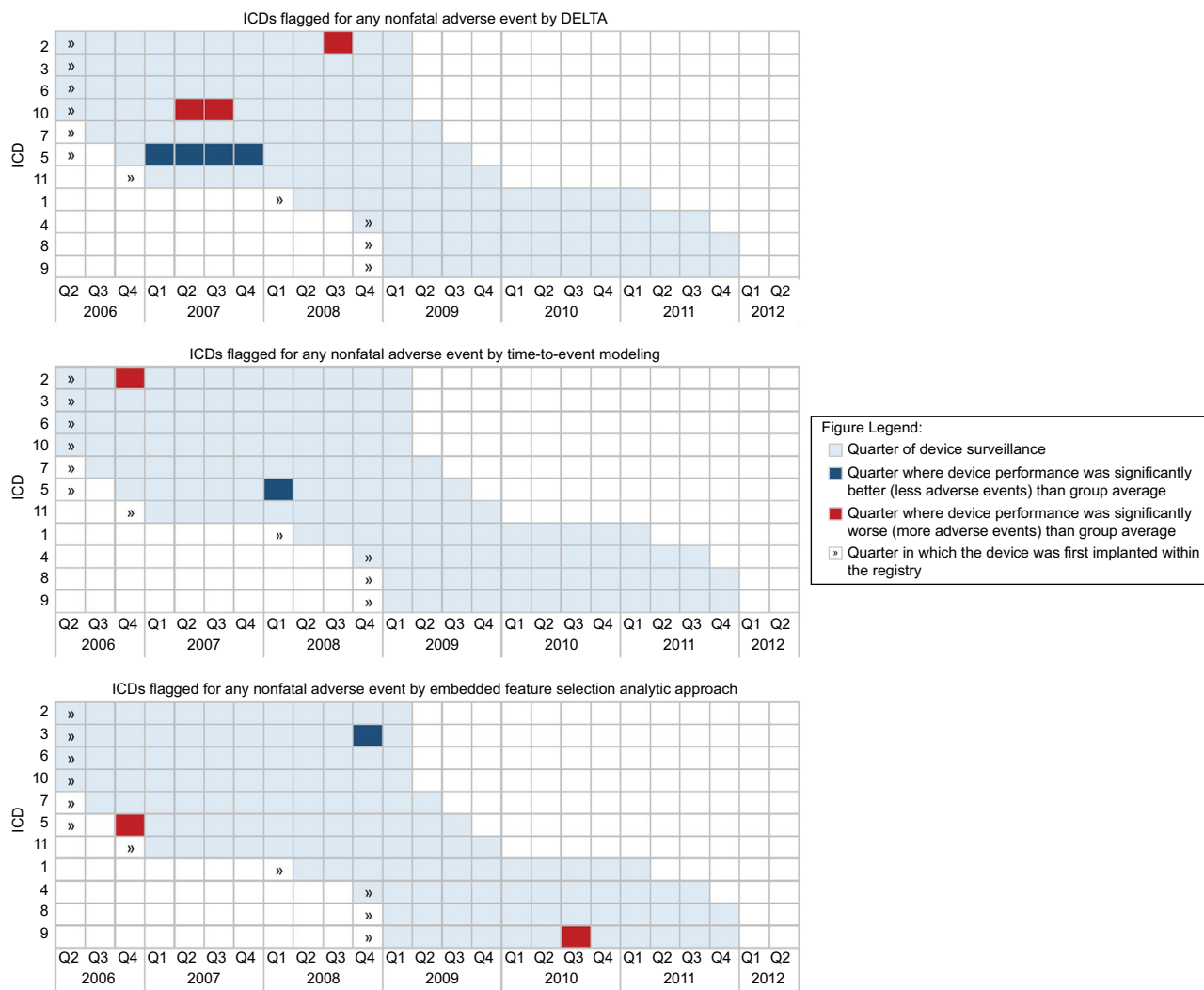


Figure 7 Time-to-event, DELTA, and embedded feature selection methods for safety-signal detection for any nonfatal adverse event among eleven commonly used dual-chamber ICDs, 2006–2010.

Abbreviations: DELTA, Data Extraction and Longitudinal Trend Analysis; ICDs, implantable cardioverter–defibrillators.

lance would best identify those important safety issues that deserve further scrutiny and evaluation, or whether multiple methods contribute to false-positive errors in signal detection.

Our findings provide important insights into statistical approaches used for medical device surveillance. First, while we observed rare agreement on the quarterly identification of safety signals for the ICD models, we did observe that those models with the lowest and highest cumulative observed death and adverse-event rates, prior to risk standardization, were identified in at least one quarterly period of surveillance as being significantly better or worse than the group by at least one statistical approach, just not consistently by all three. Despite each approach having been applied to the same quarterly cohort of devices and restricting analyses to dual-chamber ICDs implanted at least 2,000 times overall, perhaps quarterly implantation volumes may have been insufficient, resulting in false-negative errors. Safety-signal

surveillance might be enhanced by using time intervals with greater volumes of utilization, such as every 6 months instead of quarterly, or by taking into account total cumulative performance, as opposed to analyzing each quarter of data independently. Second, we used a broad definition of safety events determined to be of high clinical importance, including death from any cause and a wide range of adverse events. Perhaps a narrower approach would lead to more specific, device-related safety insights. Finally, we found that patient characteristics were not strong predictors of which dual-chamber ICD model was implanted. Safety-signal surveillance might be enhanced by selecting as many controls as possible, as opposed to one-to-one matching.

Still to be determined is how best to interpret any safety signal identified during medical device surveillance. In our analyses, few recurrent signals were identified. As part of the DELTA system, a safety signal requires confirmation in

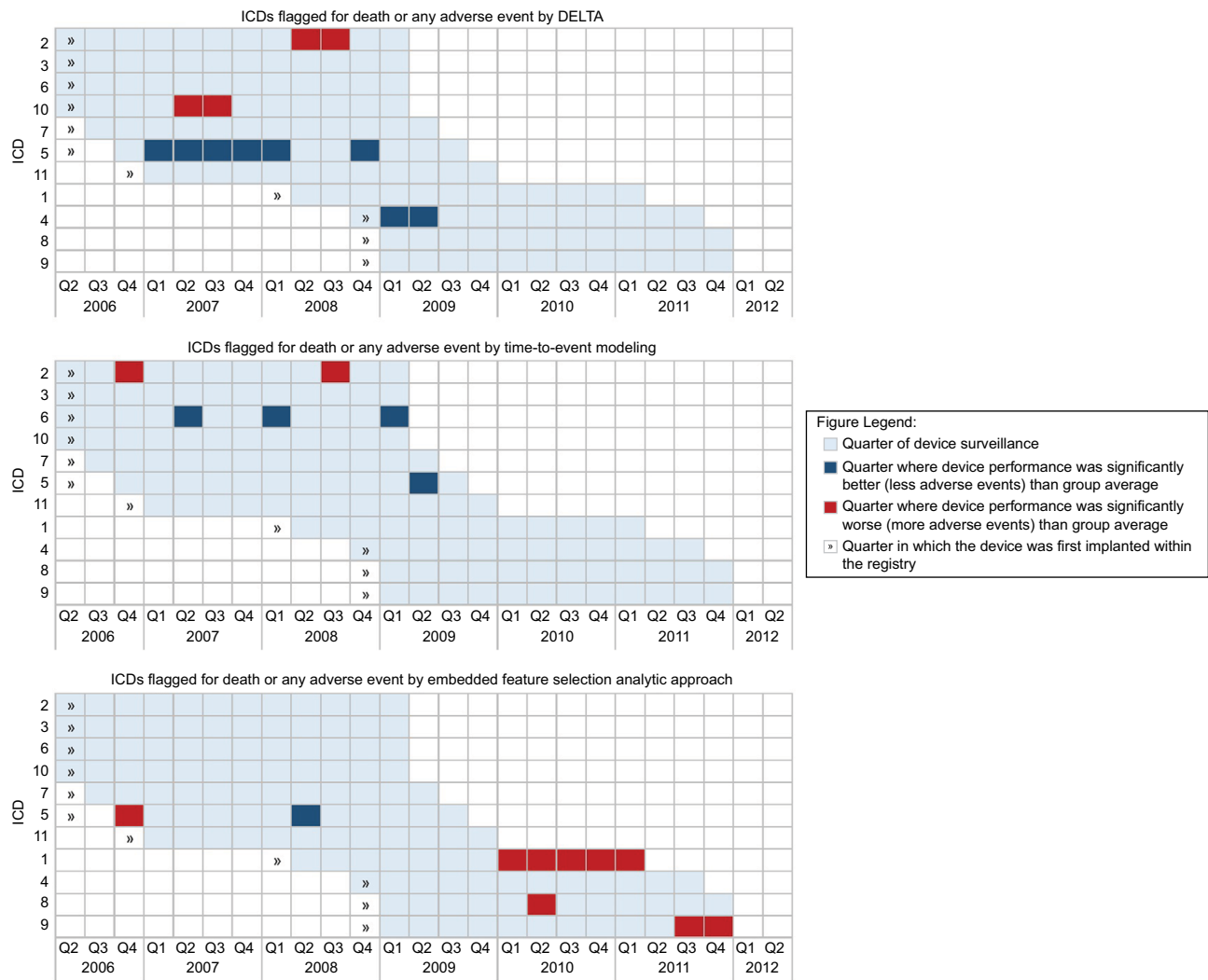


Figure 8 Time-to-event, DELTA, and embedded feature selection methods for safety-signal detection for death or any adverse event among eleven commonly used dual-chamber ICDs, 2006–2010.

Abbreviations: DELTA, Data Extraction and Longitudinal Trend Analysis; ICDs, implantable cardioverter–defibrillators.

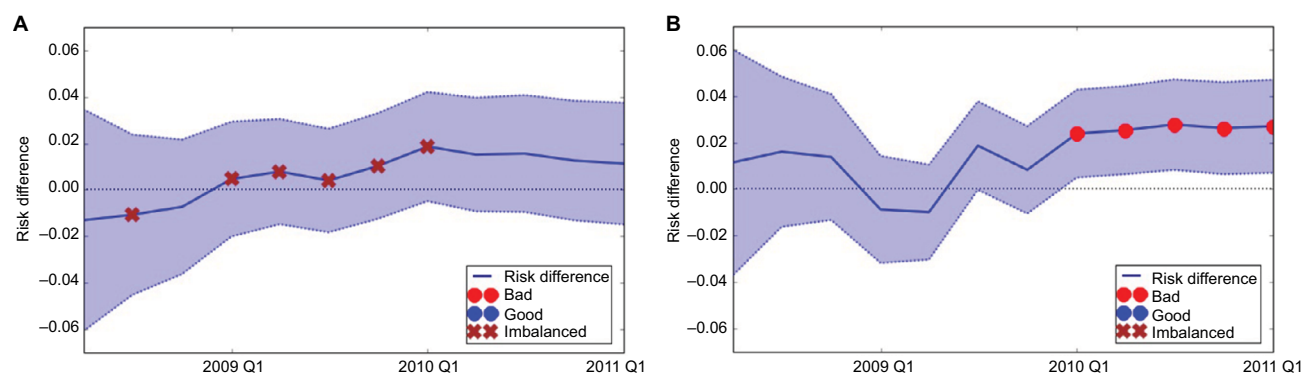


Figure 9 Medical device performance for ICD I relative to propensity-matched control devices.

Notes: Measured by composite end point of death or nonfatal ICD-related adverse events, assessed using (A) DELTA and (B) embedded feature selection. “Bad” indicates quarters where device performance was significantly worse (more adverse events) relative to propensity-matched control devices; “Good” indicates quarters where device performance was significantly better (less adverse events) relative to propensity-matched control devices; “Imbalanced” indicates quarters where at least one covariate was imbalanced among the propensity-matched groups.

Abbreviations: DELTA, Data Extraction and Longitudinal Trend Analysis; ICD, implantable cardioverter–defibrillator.

subsequent time periods prior to regulatory action. Our analyses raise the possibility of whether one statistical approach should be used to confirm another in the same time period

or in subsequent time periods. Might application of multiple statistical approaches in parallel increase sensitivity, although potentially at the expense of specificity? As our understanding

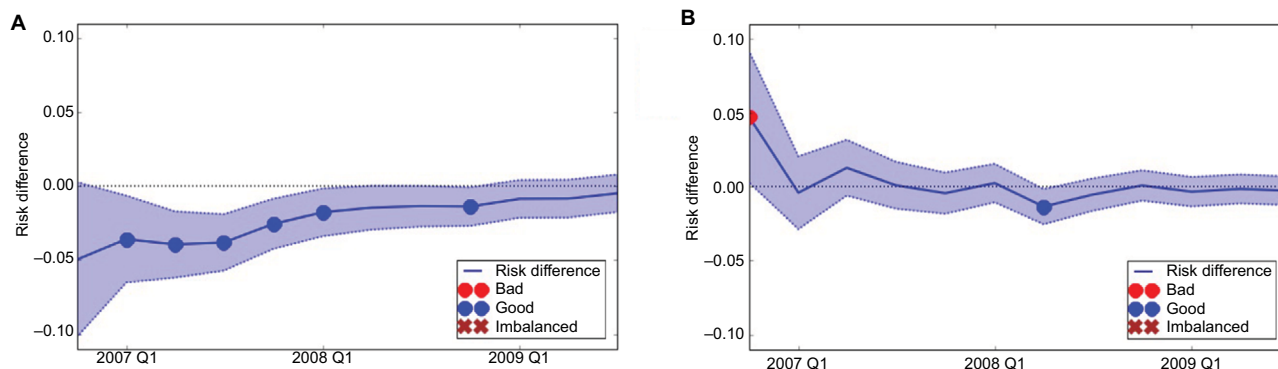


Figure 10 Medical device performance for ICD 5 relative to propensity-matched control devices.

Notes: Measured by composite end point of death or nonfatal ICD-related adverse events, assessed using (A) DELTA and (B) embedded feature selection. “Bad” indicates quarters where device performance was significantly worse (more adverse events) relative to propensity-matched control devices; “Good” indicates quarters where device performance was significantly better (less adverse events) relative to propensity-matched control devices; “Imbalanced” indicates quarters where at least one covariate was imbalanced among the propensity-matched groups.

Abbreviations: DELTA, Data Extraction and Longitudinal Trend Analysis; ICD, implantable cardioverter–defibrillator.

of how ensemble methods, including both ML and traditional analytic methods, might be used for surveillance deepens, future work can be focused on effective interpretation.

Our study has important limitations to consider. First, our analyses were limited to dual-chamber ICDs. Further work should consider other high-risk medical devices for which safety signals may be more common. Second, we used 2006–2010 NCDR-ICD registry data, which do not contain information on dual-chamber ICD leads, a potentially important cause of postmarket safety problems,³⁷ nor on how the ICDs were programmed, meaning we were unable to evaluate whether a safety event was a consequence of the ICD generator, lead, or programming. Third, the use of single rather than multiple imputation is a limitation. However, as the focus of this paper is on the comparative use of different approaches, the conclusions should remain the same. Finally, our analyses were limited to Medicare beneficiaries aged ≥ 65 years, and younger patients may experience different rates of adverse outcomes.

Conclusion

Three statistical approaches, including one ML method, successfully identified important safety signals as part of medical device surveillance. However, while there were frequent agreements on the absence of signals, there were rare agreements on their presence for dual-chamber ICDs across periods of surveillance. Further work is needed to understand better whether ensemble methods may be necessary to detect all safety signals and how ML may complement traditional analytic approaches to medical device surveillance.

Author contributions

JSR, JB, and CSP had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

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