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ORIGINAL REPORT

Disproportionality analysis for signal detection of implantable cardioverter–defibrillator-related adverse events in the Food and Drug Administration Medical Device Reporting System

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ABSTRACT

Background The Food and Drug Administration (FDA) became aware of lead fracture and inappropriate shock events related to Sprint Fidelis leads in January 2007. The manufacturer announced a voluntary market withdrawal in October 2007.
Aim Our aim was to retrospectively evaluate this safety signal using disproportionality analysis to estimate whether disproportionality analysis could have detected this particular safety signal earlier than actually occurred.
Materials and Methods The Manufacturer and User Facility Device Experience (MAUDE) database contains reports on device-related adverse events, of which, FDA receives several hundred thousand every year. For each manufacturer, a list of the top lead brand names was ranked by frequency of reports. We used the Multi-item Gamma Poisson Shrinker (MGPS) method for analysis. We isolated 11 top-reported implantable cardioverter defibrillator (ICD) lead brand names. Using MGPS methodology, we calculated the one-sided 95% lower confidence bound EB05 on the empirical Bayes geometric mean of the reporting ratio.
Results We performed individual MGPS analysis for each of the top reported adverse events in 2006 for ICD leads. Fidelis had the highest EB05 scores for lead fractures and inappropriate shock.
Discussion Through disproportionality analysis of the MAUDE database, we were able to identify known safety signals associated with the Medtronic Sprint Fidelis lead.
Conclusion If utilized at the time, this disproportionality analysis would have identified signals earlier for lead fractures, oversensing, high impedance, and inappropriate shock. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS—data mining; disproportionality analysis; leads; adverse events; safety; MAUDE

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INTRODUCTION

Disproportionality analysis, sometimes referred to as data mining, is the use of computerized algorithms to discover patterns of associations or unexpected occurrences (i.e., "signals") in large databases. When such signals are identified in the Food and Drug Administration's (FDA) adverse event reporting databases, they can then be evaluated for potential intervention as appropriate, such as further assessment ("signal refinement"), labeling revisions, and hypothesis testing studies.

Databases containing complex safety information for medical products (devices, drugs, vaccines, etc.) may be of particular interest for disproportionality analysis. Some contain thousands or even millions of reports, further complicating their analysis. Many of these databases collect data, which are submitted spontaneously and voluntarily. Analyzing these data is challenging because voluntary reporting systems are subject to underreporting, over-reporting (e.g., during periods of media publicity), incomplete information, variations in product name. In addition, spurious signaling because of the sheer number of product–event pairs evaluated for association may introduce bias.

Procedures for disproportionality analysis may include computational statistical methods to systematically

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identify product-event pairs reported at disproportionately high frequencies in large safety databases. The expected frequencies for each product–event pair are based on the distributions of all events and products in the database and on confounding factors such as reporting date and demographics (e.g., age, gender). Some analysis methods (e.g., Bayesian methods) additionally control for chance disproportionality because of product–event pair multiplicity.[1]

Disproportionality analysis has been shown to be a useful adjunct to traditional (manual) signal detection methods. Over the past several years, various regulatory agencies (FDA, Medicines and Healthcare Products Regulatory Agency, and European Medicines Agency) have developed disproportionality analysis methods to better identify reporting relationships in spontaneous reporting databases that could signal possible product risks. Disproportionality analysis has been preferred largely because it requires only the number of events reported. In contrast, disproportionality analysis of event rates is usually not feasible because calculation of such rates requires an estimate of the number of product units in use, a figure that is usually unobtainable.

MedWatch is the gateway for healthcare provider and public submission of adverse experience reporting for all FDA-regulated marketed medical products including drugs, biologics, and devices. This data source has been used effectively in the past to evaluate safety signals for pharmaceuticals. However, there has been limited use of disproportionality analysis in the field of medical device epidemiology, specifically applied to the Manufacturer and User Facility Device Experience (MAUDE) database of reports on device-related adverse events and product problems, of which, FDA receives several hundred thousand every year.

OBJECTIVE

Our aim was to retrospectively evaluate a well-known recent safety signal using disproportionality analysis to estimate whether this method could have detected this particular safety signal earlier than actually occurred. The signal chosen for study was associated with adverse event reports because of fracture of the Medtronic Sprint Fidelis lead, recalled in 2007.

Medtronic's Sprint Fidelis implantable cardioverter defibrillator (ICD) leads were approved by FDA in September 2004. The Sprint Fidelis is a 6.6-French bipolar lead intended as permanent implant connecting the ICD to the myocardium to provide detection of life-threatening cardiac arrhythmias and electrical pacing or shock therapy to restore normal rhythm whenever needed. Fidelis leads were designed with smaller diameters for insertion ease for physicians and less venous obstruction for patients. These four models (6930, 6931, 6948, and 6949) were preceded by six older Sprint lead models with design differences, including a larger diameter.

Significant product performance and safety concerns of lead fracture and inappropriate shock related to Fidelis leads were initially raised by the clinical community in January 2007 and published in July 2007.[2] FDA was not aware of this safety signal prior to January 2007. The manufacturer provided a Dear Doctor letter to report such failures and recommend appropriate handling and insertion of the lead according to existing labeling in March 2007.

Based on continued concerns, Medtronic announced a voluntary market withdrawal on October 15, 2007, and suspended distribution of the Sprint Fidelis. FDA classified this as a Class I Recall.[3] The manufacturer based their decision for product recall on a lead fracture rate estimate of 2.3% at 30 months, based on performance data obtained from their System Longevity Study. This rate was notably higher than those for other Medtronic ICD leads. Five patient deaths were reported to be likely related to fractures of Sprint Fidelis leads. More than 268 000 Sprint Fidelis leads had been implanted worldwide at the time of the recall.

We explored the feasibility of using disproportionality analysis for early detection of lead fracture signal associated with the use of Fidelis leads.

METHODS

MAUDE is a computerized information database designed to support the FDA's postmarket surveillance program for approved medical devices. The data consist of reports submitted since June 1993, user facility reports since 1991, distributor reports since 1993, and manufacturer reports since August 1996.[4] Medical device reporting is the mechanism used by FDA to ensure that devices already on the market remain safe and effective. FDA's reporting framework for device-related adverse events includes both mandatory and voluntary components. Manufacturers are required to report device-related deaths, serious injuries, and certain malfunctions, whereas user facilities are required to report device-related deaths to FDA and the manufacturer and to report serious injuries to the manufacturer only. Consumers, health professionals, and user facilities also may voluntarily report less serious device-related events to FDA. In this device product area, 98% of the reports are submitted to FDA by the device manufacturers. FDA scientists collect, review, and analyze reports for device-related adverse events and

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determine whether further action is needed to ensure patient safety. This analysis was conducted via direct FDA internal access to the complete MAUDE data.

The MAUDE database includes device names and events for all ICD lead-related adverse event reports. For each manufacturer, a list of the top lead brand names (generated through MAUDE) was ranked by frequency of reports. We used the Multi-item Gamma Poisson Shrinker (MGPS) method for analysis.[5,6] We examined the relative reporting rates (RRs) of the top device problems for lead fractures by brand name. Using MGPS methodology, we calculated the one-sided 95% lower confidence bound EB05 on the empirical Bayes geometric mean (EBGM) of RR. The EBGM is a reliable gauge of RR because it addresses the instability of an observed RR based on small counts and the potential for confounding arising from correlations of risk with demographic factors.[7] We use thresholds of 2, 4, and 8 when conducting disproportionality analyses at the Center for Devices and Radiological Health. Because of the frequency of lead-related events, we chose a threshold of EB05 > 8 to identify a potential problem.

The EB05 is the lower bound of the confidence interval of the EBGM. The EBGM represents the number of times a product–event pair is reported compared with the number of times the pair is expected to be reported. Therefore, the EB05 ranges that we list represent the lowest and highest EB05 in a given year for a given product–event pair. Because these devices have different times of adverse event report batch submissions, we compared these devices cumulatively (meaning that all but the first subset contains data from the previous subset to study the strength of variable associations over time) through the year 2007 to reduce signal noise associated with batch reporting. We also compared devices non-cumulatively over time. Analysis was conducted using the Empirica™ Signal software (Empirica™ Signal 7.0, Phase Forward Incorporated, Oracle Corporation, Waltham, MA, USA).

We isolated 11 top-reported ICD lead brand names; each was analyzed by disproportionality analysis against the universe comprising reports of all cardiac lead types. A custom term was created for each ICD lead brand name to consolidate names that might be misspelled or entered with different descriptors (such as model number) in the MAUDE database.

The most frequent lead problems were identified for each manufacturer. The top four lead-related events reported overall in 2006 were high impedance, inappropriate shock, lead fracture, and oversensing. These also were the top reported events for Medtronic leads for the entire period 2006–2009. We performed disproportionality analyses for all 2006 (the year prior to the recall) ICD lead reports for each of these event problems (high impedance, inappropriate shock, lead fracture, and oversensing).

RESULTS

We examined lead reports received September 2004 to December 2006. The period was selected to cover the data that the Sprint Fidelis lead was first approved (September 2004) to the time that the FDA was made aware of a problem (January 2007). During this period, the most frequently reported device problem codes were lead fracture, (370 events), oversensing (724 events), high impedance (1,034 events), and inappropriate shock (629 events). Note that each report can have more than one device problem code. The lead models for which device problem codes were reported were as follows: Sprint Fidelis (2765), Endotak and/or Reliance (3686), and Riata (1479). These lead brand names accounted for 94% of the MAUDE device problem codes for the top ICD leads reported from September 2004 to December 2006. There were very few reports received in 2005, so the emphasis of our disproportionality analysis was for the 2006 calendar year because more data points were available.

Individual MGPS analyses were performed for each of the top reported adverse events in 2006 for ICD leads, which included "Lead(s), Fracture of", "Oversensing", "High Impedance", and "Inappropriate shock". This enabled us to look at signal scores based on spontaneous report data available 1 year in advance of FDA being notified of this problem.

When looking at the subsets by month cumulatively, non-Fidelis Sprint leads had the highest EB05 scores in 2006 for lead fractures, ranging from 43.2 to 67.0 but below 1.9 in January and February (Figure 1). The cumulative EB05 range of Fidelis leads for 2006 was 14.3–55.1 but below 1.9 in January and February. Five of the 11 ICD lead brand names had an EB05 > 2. We did not observe elevated EB05's for the Transvene or TVL leads. Riata lead fractures had an EB05 < 6.5 from January to July but ranged from 6.9 to 10.3 from August to December.

When looking at the subsets by month cumulatively, Fidelis had the highest EB05 score in 2006 for oversensing, ranging from 8.1 to 24.0, with an EB05 of 2.9 in February (Figure 2). The range for non-Fidelis Sprint leads was EB05 7.3–20.3. Of the 11 ICD lead brand names, seven had an EB05 > 2. Transvene ranged from 1.3 to 13.3, and Endotak and/or Reliance ranged from 15.1 to 21.5. We did not observe elevated EB05's for the Riata, TVL, Kentrox, or SPL leads.

Three of the 11 brand name devices had an EB05 > 2 in 2006 for high impedance and inappropriate shock.

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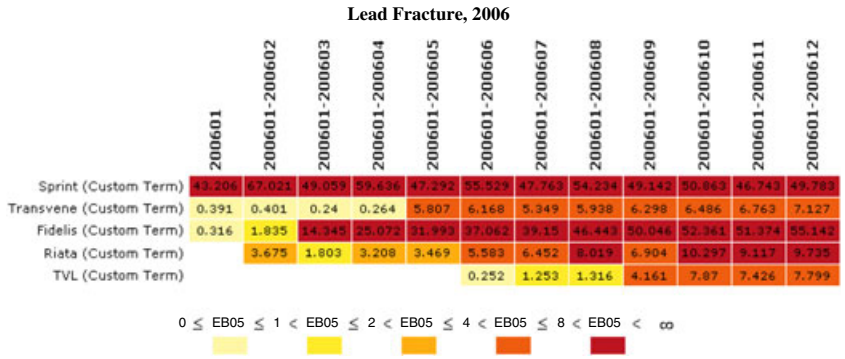

Figure 1. One-sided 95% lower confidence bound EB05 on the empirical Bayes geometric mean (EBGM) of the relative reporting rate, by cardiac lead brand name, manufacturer and user facility device experience, cumulative, 1 January 2006 through 31 December 2006, lead fracture reports

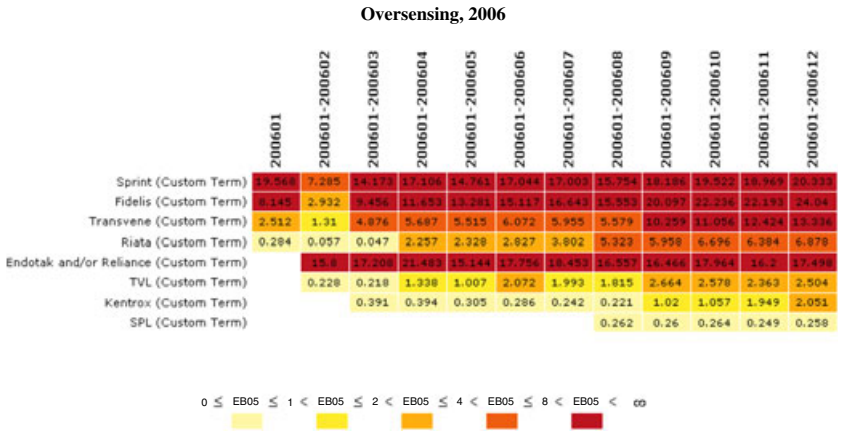

Figure 2. One-sided 95% lower confidence bound EB05 on the EBGM of the relative reporting rate, by cardiac lead brand name, manufacturer and user facility device experience, cumulative, 1 January 2006 through 31 December 2006, oversensing reports

For high impedance, the Sprint and Endotak and/or Reliance leads had the highest EB05 scores for the majority of 2006, ranging from 7.8 to 22.6 and 11.3 to 16.0, respectively (Figure 3). The EB05 for Fidelis ranged from 7.5 to 14.9. The Riata, Transvene, TVL, Kentrox, SPL, and TVL leads all generated an EB05 < 1.4.

In 2006, Fidelis leads had the highest EB05 score for inappropriate shock at a maximum of 65.2 in December (minimum of 7.6 in January). The EB05 for other Sprint leads ranged from 18.6 to 30.7, and the EB05 for Transvene leads ranged from 15.2 to 42.5 (Figure 4). The EB05 for Endotak and/or Reliance leads ranged from 9.6 to 13.3. TVL leads ranged from 0.3 to 41.6; Kentrox and SPL had EB05 scores ≤ 5.5.

An overview of the number of reports and EB05 scores for each event in 2006 is shown in Table 1. This table demonstrates cases in which a relatively low number of reports generated a high EB05 (e.g., Transvene inappropriate shock). A low frequency of a rare event can generate a high signal score. The table also shows brands with an equal number of reports but different EB05 (Riata and Sprint inappropriate shock).

To examine the trend of reported events over time, we analyzed the Fidelis lead reports for inappropriate shock from 1 May 2005 through 31 January 2008 in a non-cumulative graph (Figure 5). May 2005 was selected because of the low device distribution in months after device release. In January 2007, the FDA was informed of a potential problem occurring in Fidelis leads by an outside source (non-cumulative EB05 = 28.2). Medtronic sent a "Dear Doctor" letter in March 2007 (non-cumulative EB05 = 35.5), and Hauser's article on the issue was published in July 2007 (non-cumulative EB05 = 22.3). The non-cumulative EB05 score in March 2006, prior to FDA notification of the problem, was 47.6.

COMMENT

The potential utility of disproportionality analysis to identify important safety signals within MAUDE data

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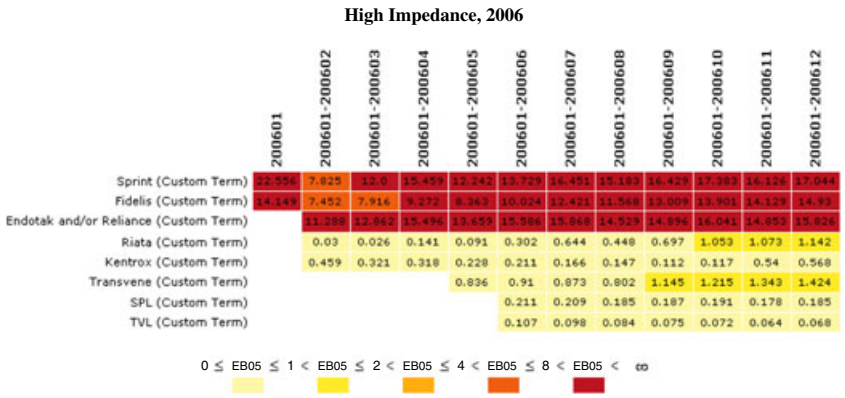

Figure 3. One-sided 95% lower confidence bound EB05 on the EBGM of the relative reporting rate, by cardiac lead brand name, manufacturer and user facility device experience, cumulative, 1 January 2006 through 31 December 2006, high impedance reports

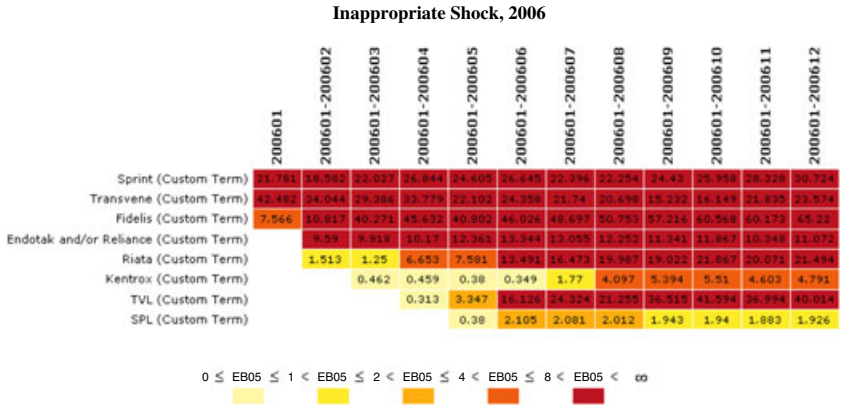

Figure 4. One-sided 95% lower confidence bound EB05 on the EBGM of the relative reporting rate, by cardiac lead brand name, manufacturer and user facility device experience, cumulative, 1 January 2006 through 31 December 2006, inappropriate shock reports

Table 1. Number of events and cumulative EB05 for top 4 events by brand name in 2006

Device product code	High impedance *N* (EB05)	Inappropriate shock *N* (EB05)	Lead fracture *N* (EB05)	Oversensing, *N* (EB05)
TVL	1 (0.068)	16 (40.3)	6 (7.84)	4 (2.51)
SPL	1 (0.185)	2 (1.93)	0	1 (0.258)
Kentrox	2 (0.569)	4 (4.81)	0	3 (2.06)
Transvene	5 (1.42)	16 (23.8)	7 (7.17)	16 (13.4)
Riata	16 (1.14)	69 (21.3)	32 (9.81)	40 (6.71)
Sprint	123 (17.1)	69 (30.9)	93 (49.6)	78 (20.4)
Fidelis	138 (14.9)	170 (64.7)	129 (54.5)	113 (23.8)
Endotak and/or Reliance	262 (15.8)	62 (11.1)	0	152 (17.5)

has been demonstrated by this study. We were able to identify known safety signals associated with the Medtronic Sprint Fidelis lead. If utilized at the time, this disproportionality analysis would have identified signals for lead fractures, oversensing, high impedance, and inappropriate shock. In 2006, Fidelis leads had the highest EB05 score for inappropriate shock at a maximum of 65.2 in December (minimum of 7.6 in January). The non-cumulative EB05 score in March 2006, prior to FDA notification of the problem, was 47.6 (Figure 5). This is the first time a signal is seen. The use of disproportionality analysis of the MAUDE database not only confirms evidence reported by others[2] but also suggests that the potential risk of the

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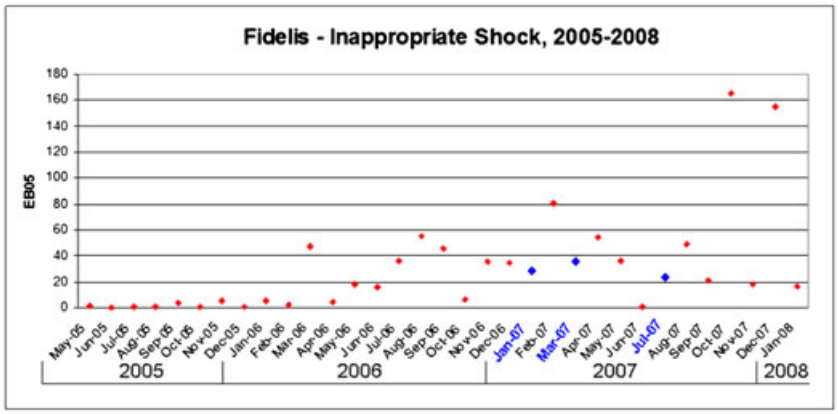

Figure 5. One-sided 95% lower confidence bound EB05 on the EBGM of the relative reporting rate, manufacturer and user facility device experience, monthly, 1 May 2005 through 31 January 2008, inappropriate shock for Fidelis cardiac leads. The dates in blue mark: January 2007 when the Food and Drug Administration was informed of a potential problem occurring in Fidelis leads by an outside source; March 2007 when Medtronic sent a "Dear Doctor" letter; and July 2007, when Hauser's article on the issue was published. This figure is available in colour online at wileyonlinelibrary.com/journal/pds

device could have been detected earlier had this methodology been used. This analysis would have generated signals for which further investigations and active surveillance could have been carried out.

High EB05 values also occurred for two other leads in the analysis. The EB05 for Sprint leads may be high because, although the Fidelis custom term contains only Fidelis leads, when users enter "Sprint" into MAUDE, they might be referring to Fidelis leads without specifying the term "Fidelis". Endotak and/or Reliance leads generated a high EB05 for high impedance, ranging from 11.2 to 16.0. The Riata lead had a high EB05 throughout the second half of 2006 for inappropriate shock with a maximum score of 21.9. TVL leads had an increased EB05 for inappropriate shock throughout the second half of 2006 with a maximum score of 41.6. These elevated values serve as an indicator of when the Agency should further investigate a potential problem. They do not serve to prove any hypotheses. The Endotak and TVL signals were evaluated. The signals for Endotak and/or Reliance were high impedance and oversensing. Because these are a non-specific measure and can be the symptom of many different problems, they are not stand-alone signals. Although high impedance and oversensing often are seen with lead fractures, they were not found to be associated with fractures for the Endotak and Reliance leads and not deemed to be safety signals. False-positive signals such as these are to be expected in any prospective analysis. This data mining instrument is useful for early detection and evaluation of signals where it is desirable to have high sensitivity with the possibility of over-detection. These signals, although not actionable on their own, would be further evaluated by a team of experts before any regulatory action is taken.

Disproportionality analysis has the potential to clarify the many complex interdependent factors (e.g., concomitant products and/or diseases) that can play a role in the development of adverse events. Traditional methods, such as manually reviewing individual reports, may not be able to detect these complex relationships. Also, accurate product exposure data and background rates of adverse events of interest are usually impossible to obtain in a systematic manner. Thus, a postmarket analyst may have difficulty in placing counts of reported events into context. The application of computerized algorithms offers the opportunity to analyze these large databases in a timely and consistent manner. Moving forward in a prospective analysis, a postmarket analysis could be expected to use disproportionality analysis to triage significant safety signals of interest. The safety analysts may start disproportionality analysis on devices in the same class and limit it to high risk devices to focus their analyses. If a safety signal is detected, FDA may ask the device manufacturer to further investigate the association. This also may lead to a directed inspection from the field to review manufacturing design, risk analyses, and an evaluation of the complaint review processes that are in place by the manufacturer.

The limitations of this analysis are those inherent to a spontaneous reporting system. These include underreporting of adverse events, incomplete or nonvalidated data, and various reporter and device biases. Additionally, no incidence rates can be generated in the absence of true denominator data. The limited information in the adverse event reporting form may

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lead to uncertainty about causality. Device manufacturers can be generally relied on to provide quality data and details about their medical device, whereas the clinician provides valuable details related to the patient's experience with the reported device. Medical devices such as implanted defibrillators are life-saving, individually registered, and regularly evaluated by specialized clinicians; it would be reasonable to expect a higher level of reporting for them compared with lower-profile medical devices. The MAUDE data may not be timely in some cases because of delays in reporting and data entry. Disproportionality analysis would serve as a helpful tool for analysis of large data sets but would not help fix any of these data-related concerns.

The retrospective disproportionality analysis runs may have been biased because of our knowledge of the Sprint Fidelis issue. Although we attempted to keep the analysis simple and based on what potential runs would have looked like at the time, we may have inadvertently introduced bias. Prospectively, there would be a concern for false-positive safety signals. Finally, reporting also may be biased because of publicity of a known device problem, which may result in over-reporting. However, in our analysis, this effect was minimized by selecting time frames covering the period before any publicity because of the lead problem described here.

CONCLUSION

Disproportionality analysis has had limited utility in medical device data thus far. This methodology has significant potential in the pharmacovigilance of medical devices and should be further explored. MGPS is particularly suited for large, government, pharmacovigilance databases.[8,9] The early detection of failure-prone devices can mitigate the exposure of large patient populations to potentially hazardous products.

Specifically, disproportionality analysis offers systematic, automated, and practical means of analyzing large datasets; improved efficiency by focusing signal detection efforts on key reporting associations; positive contributions to public health by identifying potential safety issues more quickly than traditional signal detection methods; and better decision support for regulators because of broader insight/knowledge of product–event combinations that are disproportionately reported in the data after consideration of confounding factors and chance disproportionality because of product–event pair multiplicity.

CONFLICT OF INTEREST

H. J. D., N. D. H., D. A. C., R. A. S., E. P., and D. M. D. declare no conflicts of interest. Phase Forward Inc. (now Oracle America Inc.) provided services under contract to FDA to maintain the Empirica Signal software, which was used to produce the disproportionality analysis results. R. S. is an employee of Oracle. FDA is the sponsor of this work.

KEY POINTS

- Disproportionality analysis was able to identify known safety signals associated with Sprint Fidelis leads.
- This analysis was conducted via direct FDA internal access to complete Manufacturer and User Facility Device Experience data.
- Limitations are those inherent to a spontaneous reporting system including underreporting of adverse events and incomplete or non-validated data.
- Disproportionality analysis offers systematic, automated, and practical means of analyzing large datasets; potential safety issues can be identified more quickly than traditional signal detection methods.

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