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Registry-Based Prospective Active Medical Device Safety Surveillance

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Abstract

Background—Assuring the safety of medical devices is challenged by reliance on voluntary reporting of adverse events. We evaluated a strategy of prospective, active surveillance of a national clinical registry to monitor the safety of a vascular closure device suspected as potentially associated with increased adverse events.

Methods—We used an integrated clinical-data-surveillance system to conduct a prospective, propensity-matched analysis of the safety of the Mynx vascular closure device, as compared with alternative approved vascular closure devices, using the National Cardiovascular Data Repository CathPCI Registry. Outcomes were vascular complications including the composite of access-site bleeding, access-site hematoma, retroperitoneal bleeding, any vascular complication requiring intervention or blood transfusion.

Results—Between 1/1/2011 and 9/30/2013, 73,124 patients receiving Mynx devices used following femoral percutaneous coronary intervention (PCI) procedures were analyzed. When compared with alternative vascular closure devices, the Mynx device was associated with an

increased risk of vascular complications (absolute risk [AR]: 1.21% vs. 0.76%; relative risk [RR]: 1.59; 95% CI: 1.42-1.78), access-site bleeding (AR: 0.38% vs. 0.28%; RR: 1.34; 95% CI: 1.10-1.62) and transfusion (AR: 1.82% vs. 1.48%; RR: 1.23; 95% CI: 1.13-1.34). The initial alerts occurred within the first 12 months of monitoring. Relative risks were greater for three prespecified high-risk subsets (diabetics, elderly patients and women). These safety signals were confirmed in an independent sample of 48,992 cases between 4/1/14 and 9/30/15.

Conclusions—A strategy of prospective, active surveillance of a clinical registry was capable of rapidly identifying potential safety signals following use of an implantable medical device.

Introduction

Medical devices have revolutionized healthcare, but assurance of their post-market safety relies on voluntary reporting of adverse events, resulting in incomplete ascertainment and an inability to evaluate the safety of medical devices in an active, prospective fashion^{1–12}. Early identification of real-world differences in clinical performance may provide opportunities to support iterative device design improvements, and complement traditional pre-market evidence to refine patient selection and optimize provider training. Active surveillance of medical device safety, through the continuous monitoring of large clinical data sources, has been proposed to address these limitations^{13–15} and has been identified as a priority by the Food and Drug Administration (FDA)¹⁶.

The current study was designed to evaluate a strategy of active surveillance of a national cardiovascular registry in the assessment of the post-market safety of an implantable medical device. To test this strategy, we considered implantable devices for which previous reports had identified potential safety concerns. Prior studies had suggested important differences in the rates of post-procedural complications after the use of one vascular closure device (Mynx vascular closure device, Cardinal Health, Dublin OH) as compared to alternative, approved vascular closure devices when implanted after percutaneous coronary intervention (PCI)^{13,17}. We therefore sought to use registry data on this device to test our prospective, active data-surveillance strategy.

Methods

Study Design

We have previously validated an active clinical-data-surveillance system, denoted DELTA (Data Extraction and Longitudinal Trend Analysis), capable of prospectively monitoring clinical registries and other detailed clinical data sources for safety signals^{13,15,18–22}. DELTA is a collection of integrated software components linking open-source database management and statistical analysis tools, and is designed to simultaneously support multiple risk-adjusted prospective safety-surveillance analyses of complex clinical datasets^{13,15} (See Supplementary Appendix for additional information regarding DELTA).

The CathPCI DELTA study was designed to demonstrate the feasibility of using the DELTA system for prospective, active surveillance of medical device safety by monitoring clinical outcomes with the identified vascular closure device following PCI procedures. The National Cardiovascular Data Repository (NCDR) CathPCI Registry was used as the data

source. The Mynx vascular closure device was identified as the device of interest based on evidence from prior national registry and regional studies that suggested an increased rate of access-site bleeding, injury, or need for repeat intervention as compared to alternative vascular closure devices^{13,17}. Use of the Mynx device has been increasing since 2012 (Supplementary Appendix Figure S1), giving our analyses practical clinical importance.

A study oversight committee was established and a written protocol was approved prior to review of any study data. The protocol (available at NEJM.org) included pre-specified endpoints, analytic methods, sensitivity analyses and plans for two interim data reviews. The study protocol was reviewed and approved as per the institutional review board policies of the NCDR and the Lahey Hospital and Medical Center. The study was funded by the FDA and the William M. Wood Foundation.

Device Exposures and Adverse Outcomes

All patients who received a vascular closure device following PCI performed between 1/1/2011 and 9/30/2013 were identified from the CathPCI Registry. We excluded those patients in whom an intra-aortic balloon pump or ventricular assist device was used, cases in which non-femoral arterial access was utilized, cases in which more than one vascular closure device was deployed, and cases for which the vascular closure device used did not have an implantable component. Vascular closure devices using identical mechanisms of action and identical implanted materials were grouped together into “device families” (see Supplementary Appendix Table S1) for the study in order to increase analytic power.

The primary safety outcome was overall vascular complications, a composite endpoint that included access-site bleeding requiring treatment, access-site hematoma requiring treatment, retroperitoneal bleeding, or any vascular complication requiring intervention. Secondary safety endpoints included access-site bleeding requiring treatment alone and post-procedural blood transfusion. All endpoints and covariates were defined according to the CathPCI version 4 data element definitions (see Supplementary Appendix). All outcomes were assessed through time of hospital discharge, as limited by the CathPCI Registry dataset.

Propensity Score Matching

For each analysis, a propensity-matched concurrent control population was developed based on a non-parsimonious propensity model. The model included previously identified risk factors as well as covariates selected by the authors based on information from prior publications (see the Supplementary Appendix for details)¹³. Variables were excluded if they were found to be co-linear with covariates already included in the propensity model. Missing data were imputed using univariate rules, by assuming the absence of a clinical condition for dichotomous variables, and by using the median observed value for continuous variables. The final propensity model is shown in Supplementary Appendix Table S2.

Data Surveillance Process

Fully de-identified case-level CathPCI data were provided to DELTA based on scheduled quarterly data updates, and the cumulative safety analysis was automatically regenerated within DELTA. Propensity-score matched control patients were selected in a 1:1 ratio,

within 6 months of the date of the case device implant, using a fixed propensity probability caliper width of 0.01^{10,15,23} through a greedy matching algorithm. The relative imbalance between the exposed and unexposed groups was assessed using the absolute standardized difference in covariate means and proportions, with values less than 10% considered adequately balanced²⁴.

The primary measure of interest was the relative risk for development of an adverse safety outcome, defined as the ratio of observed event rates in the Mynx-treated patients to the observed event rates in the matched population of patients treated with other vascular closure devices. DELTA alerts were triggered if the differences between the independent proportions for the Mynx device and the alternative vascular closure devices were statistically significant, as measured by the Wilson method²⁵. Confidence intervals (CI) were established using a 95% CI corrected for multiple comparisons through use of the O'Brien-Fleming alpha-spending method adapted for use in prospective surveillance²⁶ (see the Supplementary Appendix).

Pre-Specified Sensitivity Analyses and Analyses of High-Risk Subsets

Protocol pre-specified high-risk patient subsets included patients 70 years or older, diabetics, and female patients. Sensitivity analyses included alternative event-rate estimation using logistic regression risk adjustment in place of propensity matching.

Interim Review and Additional Analyses

An early alert (after nine months of monitoring) led the study steering committee to recommend that an additional analysis be performed to address potential bias due to center-level effects. It was hypothesized that higher adverse event rates might be expected at those centers where the Mynx device was used infrequently, and where the device may have been reserved for patients with higher risk. We therefore performed a propensity-matched analysis including only those cases performed at centers that frequently used the Mynx device compared with patients from centers that used, predominantly, an alternative vascular closure device.

After review of the final study results, the FDA requested an additional analysis using the most recent data collected in CathPCI in order to assess persistence of the DELTA safety signals. A protocol amendment was finalized and CathPCI data for the period 10/1/13 through 9/30/15 were made available to DELTA. Propensity-score models were re-calibrated using cases performed from 10/1/13 through 3/31/14. An independent propensity-matched analysis was performed for cases performed between 4/1/14 and 9/30/15.

The study steering committee also recommended several post-hoc sensitivity analyses to assess the robustness of the primary findings. These included performance of a falsification hypothesis analysis in which the original matched patient cohorts were evaluated for the development of post-procedural contrast-induced nephropathy, as defined by a maximal increase of 25% or 0.5 mg/dl in pre-PCI serum creatinine²⁷. For this outcome, no difference in risk between different vascular closure devices was expected. Additional sensitivity analyses included alternative approaches to handling missing data, as well as an analysis using center-level matching, rather than global registry matching, in an effort to

address any confounding due to center-level effects. Analyses similar to that performed for the Mynx device were performed for three other commonly used vascular closure devices. Finally, event rates with vascular closure devices were compared with manual or mechanical access-site compression for hemostasis. Additional details regarding analytic methods and assumptions are provided in the Supplementary Appendix.

Results

Study Population

Between 1/1/2011 and 9/30/2013, 73,164 patients received the Mynx vascular closure device and met the inclusion criteria for the analysis from among 1,822,575 PCI cases submitted to CathPCI (Supplementary Appendix Figure S2). Missing data did not differ between the Mynx-treated patients and those receiving alternative vascular closure devices and represented 0.04% of all risk factor data (Supplementary Appendix Table S3). As shown in Table 1, propensity matching resulted in 73,124 (99.9%) Mynx cases being successfully matched with alternative vascular-closure-device cases. Matching resulted in an adequate distribution of risk factors between cohorts, with all post-match standardized differences less than the threshold for imbalance of 0.10.

Mynx Vascular Closure Device Safety Alerts

A DELTA alert was triggered after nine months of monitoring for the primary outcome of any vascular complication, and was sustained throughout the duration of the surveillance study (Figure 1). At the end of the study, the absolute risk of a vascular complication was 1.21% with use of the Mynx versus 0.76% with use of an alternate vascular closure device, with a relative risk of 1.59 (95% CI: 1.42-1.78, $p<0.001$). Each component endpoint of the primary safety outcome was significantly more common in the Mynx-treated patients, including the risk of significant access-site bleeding, vascular complication requiring intervention, significant access-site hematoma, and development of post-procedural retroperitoneal bleeding. Alerts for the secondary endpoints of significant access-site bleeding and post-procedure blood transfusion were triggered after 30 and 15 months, respectively, and were sustained through the remainder of the surveillance period (see Table 2).

Pre-Specified Sensitivity Analyses and Analyses of High-Risk Subsets

Protocol-specified propensity-matched analyses were performed for high-risk patient subsets including those age 70 years or greater, females, and diabetics, as shown in Table 2. More than 99% of identified cases were successfully matched within each subset, yielding more than 25,000 Mynx-treated patients within each high-risk subset. Safety alerts for vascular complications were triggered within 15 months of monitoring for all subsets and were sustained for the duration of the study. The relative risks for the development of any vascular complication ranged from 1.72 (95% CI: 1.42-2.10) in diabetic patients to 1.94 (95% CI: 1.63-2.29) in patients 70 years or older.

As a pre-specified sensitivity analysis, a logistic model was used to adjust for baseline risk, in place of propensity matching, and confirmed safety alerts for all outcomes within three

months of the propensity-matching analysis, thereby supporting the primary results (Supplementary Appendix Table S4).

Post-Hoc Analysis at Mynx High-Usage Centers

A total of 28,141 cases using the Mynx device were identified from those hospitals which used Mynx most frequently among available vascular closure devices, with greater than 99% of these cases matched with the AngioSeal vascular closure device from centers in which this device was preferentially used. A safety alert for vascular complications was triggered after the first twelve months of monitoring, with a relative risk of 1.43 (95% CI 1.18-1.73). Safety alerts were triggered for the secondary endpoints of access-site bleeding and transfusion within 21 months of surveillance (Table 3), and all safety alerts persisted throughout the monitored period.

Post-hoc Signal Persistence Analysis

At the request of FDA, 49,037 additional PCI procedures in which the Mynx device was used between 4/1/14 and 9/30/15 were analyzed in order to assess the persistence of the potential safety signal identified in the primary analysis. Of these cases, 48,992 (99.9%) were successfully matched to patients receiving alternative vascular closure devices, and DELTA alerts were triggered within twelve months for all endpoints (see Table 3 and Supplementary Appendix Table S5).

Additional Post-hoc Sensitivity Analyses

Repeating the primary analysis using multivariate normal imputation²⁸ in place of simple imputation rules for missing data did not lead to any significant change in alert timing or estimated relative risks. Separately, in order to assess potential confounding due to between-center differences, we repeated the primary analysis with case matching performed at the center level. Using the same propensity methods, 35,192 (48.1%) of all eligible Mynx exposures were successfully matched, resulting in a relative risk of vascular complications of 1.59 (CI: 1.40-1.78). No significant differences in estimated relative risk for any outcome or patient subset was found using center-level matching.

A falsification hypothesis analysis was performed using the outcome of contrast-induced nephropathy, which was not anticipated to differ between patients treated with the Mynx device and patients treated with alternative vascular closure devices. The relative risk for the development of contrast-induced nephropathy after receiving a Mynx device was 1.05 (CI: 0.99 – 1.11, $p=0.07$) indicating a non-significant trend toward a small increase in risk of developing contrast-induced nephropathy for the Mynx-treated patients as compared to those patients receiving alternative vascular closure device (Table 3 and Supplementary Appendix Figure S3). Analyses of three other commonly used vascular closure devices demonstrated no increase in the risk of vascular complications (Supplementary Appendix Table S6), while manual or mechanical compression was associated with a higher risk of vascular complications than the Mynx device or any vascular closure device (Supplementary Appendix Table S7).

Discussion

In our study, we evaluated the feasibility of applying active surveillance to assess the safety of a commonly used cardiovascular device through prospective monitoring of a national clinical registry. Using the CathPCI Registry, we monitored the comparative safety of a vascular closure device suspected of having increased safety risks over a three-year study period using a pre-specified, active surveillance plan. Our analysis demonstrated statistically significantly increased risks of vascular complications, access-site bleeding, and transfusion requirement following PCI with the use of the Mynx vascular closure device as compared with alternative vascular closure devices, though the absolute risk differences were small. Alerts were triggered early, persisted throughout the duration of surveillance and were present in all patient subsets (see Figure 2). In addition, the primary results were confirmed in an independent, more contemporary, cohort of patients. Analyses of other vascular closure devices did not demonstrate a similar safety signal.

An analysis restricted to those centers that preferentially utilized Mynx among available vascular closure devices demonstrated an attenuated, though persistent, safety signal as compared with the primary analysis. These findings may suggest that a portion of the difference in complications is attributable to center level experience in using the Mynx device, a finding that has previously been demonstrated with other vascular closure devices²⁹.

Potential safety signals generated through active surveillance should be interpreted with caution, as all such analyses are observational by design. Despite robust risk adjustment through propensity matching, one cannot exclude residual confounding as being responsible for some portion of the observed difference in adverse events associated with Mynx device as compared with alternative vascular closure devices. The limited number of covariates selected for inclusion in the propensity model could contribute to such residual confounding, though the covariate selection strategy employed guarded against over-fitting of the models. In addition, important clinical variables such as anatomical puncture site location may have contributed to confounding the observed relationships, but were not available in the CathPCI Registry. While the duration of follow up following the PCI procedure was limited by the CathPCI Registry to in-hospital events, the adverse events of interest would generally be expected to occur during the index hospitalization.

We attempted to assess for residual confounding through several post-hoc sensitivity analyses. Though the dataset was large, there was a small amount of missing data (<0.04%) that were imputed using both simple imputation and multivariate normal imputation. Global registry case matching, as used here, may bias results in that patients treated in different centers may have different unmeasured clinical characteristics. However, an analysis using center-specific matching resulted in no significant changes to the estimated risk differences for Mynx device as compared with alternative vascular closure devices.

Finally, we performed a falsification hypothesis analysis in which we monitored the registry for the development of contrast-induced nephropathy following PCI; an adverse outcome for which an association with exposure to a particular vascular closure device was not

anticipated. We found a trend toward developing contrast-induced nephropathy in Mynx recipients that did not meet statistical significance, indicating the possibility of a small amount of residual risk imbalance between Mynx recipients and patients treated with alternative vascular closure devices.

In conclusion, a strategy of prospective, active surveillance of a representative clinical registry was capable of rapidly identifying potential safety signals following use of an implantable medical device.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Safety analysis of “any vascular complication” following use of the Mynx vascular closure device versus propensity-matched alternative vascular closure devices among patients treated with percutaneous coronary intervention between 1/1/11 and 9/30/13.

Propensity-matched analysis of cumulative incidence of any vascular complication following use of the Mynx vascular closure device. Circles indicate observed event rates in Mynx-treated patients. Red colored circles indicate higher than expected rates (safety alerts). Solid blue squares indicate observed event rates in the matched alternative vascular closure device group. Blue vertical lines indicate 95% CI, with dashed lines indicating adjustment for multiple comparisons. The solid black line indicates cumulative sample size (with values shown on the right vertical axis).

Figure 2.
Forest plot of relative risk in all analyzed groups.

Table 1

Distribution of Clinical Covariates before and after propensity matching, in patients treated with the Mynx VCD or alternative VCD.

Covariate	Total Study Population			After Propensity Match			Unmatched Exposures		
	Mynx VCD (n=73,164)	Alternate VCD (n=603,437)	Std. Diff	Mynx VCD (n=73,124)	Alternate VCD (n=73,124)	Std. Diff	Mynx VCD (n=40)	Std. Diff	Std. Diff
Age (yrs)	65.3 ± 11.9	65.1 ± 12.1	0.0166	65.3 ± 11.9	65.3 ± 12.0	0.0007	64.4 ± 11.9	0.0007	0.075
Female Gender	34.3%	30.5%	0.0814	34.3%	34.2%	0.0022	30.0%	0.0022	0.092
Body Mass Index (kg/m ²)									
<21	3.66%	3.69%	0.0018	3.66%	3.70%	0.0022	7.50%	0.0022	0.168
25 and <30	35.4%	37.0%	0.0333	35.4%	35.4%	0.0007	37.5%	0.0007	0.043
30	45.22%	43.19%	0.0410	45.23%	45.25%	0.0005	40.00%	0.0005	0.106
Diabetes	39.8%	35.9%	0.0802	39.8%	40.2%	0.0080	45.0%	0.0080	0.105
Chronic Lung Disease	16.5%	13.6%	0.0814	16.5%	16.7%	0.0026	35.0%	0.0026	0.433
Hypertension	84.8%	81.1%	0.0992	84.8%	84.8%	0.0014	80.0%	0.0014	0.128
Baseline Creatinine (mg/dL)	1.20 ± 1.08	1.17 ± 0.98	0.0341	1.20 ± 1.08	1.20 ± 1.10	0.0004	1.39 ± 1.30	0.0004	0.177
Peripheral Arterial Disease	12.7%	9.8%	0.0918	12.6%	12.6%	0.0007	25.0%	0.0007	0.320
Emergent Procedure Status	13.0%	18.7%	0.1575	13.0%	12.9%	0.0036	17.5%	0.0036	0.126
NSTEMI on Presentation	18.9%	20.3%	0.0362	18.9%	18.9%	0.0001	27.5%	0.0001	0.205
Bivalirudin exposure	67.9%	64.4%	0.0723	67.9%	68.7%	0.0188	67.5%	0.0188	0.008
Left Main Coronary Artery PCI	2.09%	2.23%	0.0092	2.09%	2.16%	0.0049	2.50%	0.0049	0.027
Number of vessels treated during index PCI	1.42 ± 0.71	1.44 ± 0.73	0.0236	1.42 ± 0.71	1.42 ± 0.70	0.0042	1.78 ± 0.97	0.0042	0.498
Fluoroscopy time (min)	12.5 ± 9.7	14.1 ± 11.2	0.1419	12.5 ± 9.2	12.6 ± 8.9	0.0091	122.6 ± 72.2	0.0091	11.733
Total number of PCI during admission	1.05 ± 0.22	1.05 ± 0.22	0.0020	1.05 ± 0.22	1.05 ± 0.22	0.0033	1.03 ± 0.16	0.0033	0.102

Abbreviations: Standard Deviation (Std Dev), Absolute Percentile Standardized Difference (Std Diff), Percutaneous coronary intervention (PCI); Number (Num); Non-ST elevation myocardial infarction (NSTEMI); Coronary artery disease (CAD)

Summary of Outcomes and Final Alert Status for Propensity Matched Analysis of Mynx VCD for patients undergoing PCI between 1/1/11 and 9/30/13

Table 2

Cohort Analyzed	Mynx VCD	Alternative VCD	Relative Risk	(95% CI)	p-value	Absolute Risk Difference (%)	Time to Alert (Months)		
Overall Study Population									
Patients	73,124	73,124							
Vascular complications	883	1.21%	555	0.76%	1.59	(1.42-1.78)	<0.001	0.45%	9
Access-Site Bleeding	277	0.38%	207	0.28%	1.34	(1.10-1.62)	0.001	0.10%	30
Blood Transfusion	1,328	1.82%	1,080	1.48%	1.23	(1.13-1.34)	<0.001	0.34%	15
High Risk Patient Subsets:									
70 Years or Greater									
Patients	27,293		27,293						
Vascular complications	447	1.64%	231	0.85%	1.94	(1.63-2.29)	<0.001	0.79%	9
Access-Site Bleeding	142	0.52%	70	0.26%	2.03	(1.49-2.76)	<0.001	0.26%	15
Blood Transfusion	754	2.76%	621	2.28%	1.21	(1.08-1.36)	<0.001	0.49%	27
Diabetes									
Patients	29,097		29,097						
Vascular complications	307	1.06%	178	0.61%	1.72	(1.42-2.10)	<0.001	0.44%	15
Access-Site Bleeding	101	0.35%	63	0.22%	1.60	(1.14-2.25)	0.003	0.13%	24
Blood Transfusion	634	2.18%	539	1.85%	1.18	(1.04-1.33)	0.005	0.33%	24
Female									
Patients	25,065		25,065						
Vascular complications	544	2.17%	297	1.18%	1.83	(1.58-2.13)	<0.001	0.99%	9
Access-Site Bleeding	182	0.73%	100	0.40%	1.82	(1.40-2.36)	<0.001	0.33%	15
Blood Transfusion	795	3.17%	593	2.37%	1.34	(1.20-1.50)	<0.001	0.81%	15

Table 3

Summary of Outcomes and Final Alert Status for Propensity Matched Analysis for post-hoc High Mynx Utilizing centers, Signal Persistence Analysis and Falsification Hypothesis analysis.

Cohort Analyzed	Mynx VCD	Alternative VCD	Relative Risk	(95% CI)	p-value	Absolute Risk Difference (%)	Time to Alert (Months)
HI Mynx Utilizing Centers							
Patients	28,107	28,107					
Vascular complications	297	208	1.43	(1.18-1.73)	<0.001	0.32%	12
Access-Site Bleeding	101	63	1.60	(1.14-2.25)	0.003	0.14%	15
Blood Transfusion	444	364	1.22	(1.05-1.41)	0.005	0.28%	21
Signal Persistence Analysis							
Patients	48,992	48,992					
Vascular complications	704	472	1.49	(1.32-1.68)	<0.001	0.47%	6
Access-Site Bleeding	355	248	1.43	(1.21-1.69)	<0.001	0.22%	12
Blood Transfusion	725	614	1.18	(1.06-1.32)	<0.001	0.23%	12
Falsification Analysis							
Patients	73,124	73,124					
Contrast Induced Nephropathy	2,507	2,384	3.26%	1.05	(0.99-1.11)	0.070	0.17%
							n/a