Impact of early surveillance on safety signal identification in the CathPCI DELTA study

Arjun Majithia 1,2,3, Michael E Matheny,4 Sourbha S Dani,1,2,3 Jessica K Paulus,5 Danica Marinac-Dabic,6 Susan Robbins,2 Henry Ssemaganda,7 Kathleen Hewitt,8 Angelo Ponirakis,8 Nilsa Loyo-Berrios,6 Issam Moussa,9 Joseph Drozda 10, Sharon-Lise Normand,11 Frederic S Resnic1,2,3

ABSTRACT

Objectives The CathPCI Data Extraction and Longitudinal Trend Analysis study was designed to determine the feasibility of conducting prospective surveillance of a large national registry to perform comparative safety analyses of medical devices. We sought to determine whether the complementary use of retrospective case data could improve safety signal detection time.

Design We performed a simulated surveillance study of the comparative safety of the Mynx vascular closure device (VCD) with propensity score matched alternate VCD recipients, using both retrospective and prospective cohort data.

Setting Centers within the USA using the National Cardiovascular Data Registry (NCDR) CathPCI Registry.

Participants Percutaneous coronary intervention cases captured within the NCDR CathPCI Registry from July 1, 2009 to September 30, 2013 were included in the analysis.

Interventions None.

Main outcome measures Absolute and relative risk (RR) of any vascular complication (a composite of bleeding at access site, hematoma at access site, retroperitoneal bleeding, and other vascular complications requiring treatment); time to signal detection.

Results A safety alert was detected for the primary outcome of “any vascular complication” after 15 months of surveillance and was sustained for the study duration (absolute risk of any vascular complication, 1.20% vs 0.73%, RR 1.63; 95% CI 1.50 to 1.79; p<0.001). The safety signal was identified 12 months earlier with the use of retrospective case data than during the initial study.

Conclusions Prospective, active surveillance of cardiovascular registries is feasible to perform comparative analyses of medical devices. Retrospective data may complement prospective surveillance to improve time to signal detection, indicating the need for earlier prospective application of safety surveillance for devices new to the market.

BACKGROUND

Assuring public safety after medical device approval and widespread adoption is critically important. However, current pre-market safety evaluations are constrained by small sample size and short duration of follow-up, limiting the ability to detect low frequency safety events over the life-cycle of a medical device. Additionally, post-market safety evaluations rely heavily on voluntary reporting of safety events, leading to incomplete ascertainment of safety events.1–10 Prospective, active surveillance of large, high quality clinical data repositories addresses these limitations, and has been identified as a strategic priority by the Food and Drug Administration. We developed a set of active surveillance tools, referred to as DELTA (Data Extraction and Longitudinal Trend Analysis system), to support near real-time safety monitoring. The methods and informatics infrastructure of DELTA have been previously described and validated.11–14

The CathPCI DELTA study was conducted to evaluate the feasibility of prospective...
active surveillance of a National Cardiovascular Data Registry (NCDR) for assessment of the post-market safety of implantable medical devices. We assessed the relative safety of a vascular closure device (VCD) (Mynx, Cardinal Health) using data from the NCDR CathPCI Registry, and identified a sustained safety alert after 9 months of surveillance. However, it is unknown whether a safety alert associated with this device could have been detected earlier in the device life-cycle. We therefore sought to explore whether earlier safety signal detection was feasible using complementary prospective and retrospectively identified Mynx VCD cases within the CathPCI Registry.

METHODS
Study design and oversight
A simulated prospective surveillance study of the comparative safety of the identified VCD using both retrospective and prospective data was designed, anticipating improvement in safety signal detection time. The study was completed using data from the NCDR CathPCI Registry. The NCDR CathPCI Registry is cosponsored by the American College of Cardiology and Society for Cardiovascular Angiography and Interventions, and is a large, contemporary national registry of patients undergoing cardiac catheterization procedures and/or percutaneous coronary intervention (PCI). The database included more than 15,000 hospitals and capture ~90% of PCI procedures. Internal quality assurance protocols and quality checks, as well data auditing are conducted to ensure data completeness, validity, and reliability.

For this study, patient-level data from the CathPCI Registry were fully deidentified in accordance with recommendations of the Health Insurance Portability and Accountability Act and the Office of the National Coordinator for Health Information Technology prior to being uploaded to DELTA. Analysis parameters were retained and applied to the expanded dataset.

Patient eligibility, device exposures, and endpoint definitions
We identified all patients in the CathPCI Registry aged ≥18 years who received treatment with VCD after PCI performed with femoral arterial access from January 1, 2011 to September 30, 2013 for the initial (prospective only) analysis. For this extended study, cases in the CathPCI Registry beginning July 1, 2009, representing the cumulative safety analysis of integrated software components linking statistical analytic tools with data repositories. DELTA has been previously validated for prospective monitoring of clinical registries and data sets to support risk-adjusted prospective safety surveillance analyses.

Active surveillance system
The analysis was performed using the DELTA suite of active surveillance tools. DELTA is an open-source collection of integrated software components linking statistical analytic tools with data repositories. DELTA has been automatically regenerated within DELTA.

Propensity score matching and event rate estimation
We developed multivariable adjusted logistic regression models to estimate the probability of being treated with the Mynx or an alternate VCD of interest, conditional on the included covariates. The model included previously identified risk factors for the adverse outcomes of interest, as well as factors considered to influence the selection of a specific device. A total of 15 variables were included in the final propensity score model. All covariates were defined in accordance with the NCDR CathPCI Coder’s Data Dictionary, versions 4.4 (online supplemental appendix). Demographic and comorbid variables included age, body mass index, sex, diabetes, history of chronic lung disease, hypertension, pre-procedure creatinine, and history of peripheral artery disease. Variables related to clinical presentation and angiographic findings in the final propensity score model included emergent cardiac catheterization, non-ST elevation myocardial infarction on presentation, bivalirudin exposure, left main coronary artery PCI, number of coronary vessels
treated during index presentation, fluoroscopy time, and total number of PCI procedures during admission.

A propensity score matched control population was identified from the population of patients treated with non-Mynx family, alternative VCDs. The propensity matched comparison group was selected on the basis of a non-parsimonious propensity model. Matched controls were selected in a 1:1 ratio, within 6 months of the date of the case device implant/use, using a fixed propensity probability caliper width of 0.01 using a greedy matching algorithm. At each quarterly data upload, the DELTA system re-matched the case sets and adverse event rate were calculated.

Missing data were handled using univariate rules, assuming absence of a condition for dichotomous variables, and using the median value for continuous variables. Absolute standardized difference (per cent) in covariate proportions and means were calculated to assess the relative imbalance between the exposed (Mynx VCD recipients) and unexposed (alternate VCD) groups with values greater than 10% considered severely imbalanced.

Adverse event rates were calculated quarterly for the propensity score matched cohorts in each analysis. Safety alerts were triggered if the CIs around the differences between two independent proportions, as measured by the Wilson method, did not cross zero, indicating a statistically significant difference between the exposed and control cohorts. CIs were corrected for multiple comparisons through use of the adapted O’Brien-Fleming method.

RESULTS

The final study population included 109,857 cases of Mynx device recipients from 1479 centers between July 1, 2009 and September 30, 2013. Compared with the initial cohort, the study population included 36,693 additional earlier Mynx cases, with an additional 18 months of surveillance time compared with the initial analysis. Propensity score matching resulted in 100% of Mynx cases being matched to alternate VCD cases, with adequate distribution of risk factors as evidenced by post-matching absolute standardized differences less than 0.10 (table 1).

After 15 months of surveillance, a safety alert for was detected for the primary outcome of “any vascular complication” during the third calendar quarter of 2010 and was sustained for the study duration (absolute risk of any vascular complication, 1.20% vs 0.73%, relative risk (RR), 1.63; 95% CI 1.50 to 1.79; p<0.001) (figure 1 and table 2).

### Table 1 Population covariate comparison (pre-match and post-match)

| Covariate                        | Total study population | After propensity match |
|----------------------------------|------------------------|------------------------|
|                                  | Mynx VCD (n=109,857)   | Alternate VCD (n=925,355) | Std. Diff. | Mynx VCD (n=109,857)   | Alternate VCD (n=109,857) | Std. Diff. |
| Age (years)                      | 65.19±11.90            | 64.95±12.09            | 0.0200     | 65.19±11.90            | 65.22±11.89            | 0.0026     |
| Female gender                    | 34.12%                 | 30.49%                 | 0.0777     | 34.12%                 | 34.47%                 | 0.0072     |
| Body mass index (kg/m²)          |                        |                        |            |                        |                        |            |
| <21                              | 3.52%                  | 3.67%                  | 0.0080     | 3.52%                  | 3.55%                  | 0.0014     |
| ≥25 and <30                      | 35.7%                  | 37.0%                  | 0.0282     | 35.7%                  | 35.7%                  | 0.0003     |
| ≥30                              | 45.31%                 | 43.21%                 | 0.0423     | 45.31%                 | 45.38%                 | 0.0014     |
| Diabetes                         | 39.1%                  | 35.3%                  | 0.0795     | 39.1%                  | 39.5%                  | 0.0084     |
| Chronic lung disease             | 16.3%                  | 13.5%                  | 0.0783     | 16.3%                  | 16.3%                  | 0.0022     |
| Hypertension                     | 84.7%                  | 80.9%                  | 0.1001     | 84.7%                  | 84.8%                  | 0.0037     |
| Baseline creatinine (mg/dL)      | 1.19±1.03              | 1.16±0.95              | 0.0627     | 1.19±1.03              | 1.20±1.06              | 0.0095     |
| Peripheral arterial disease      | 12.7%                  | 9.7%                   | 0.0964     | 12.7%                  | 12.9%                  | 0.0047     |
| Emergent procedure status        | 11.7%                  | 17.7%                  | 0.1693     | 11.7%                  | 11.8%                  | 0.0018     |
| NSTEMI on presentation           | 17.17%                 | 19.25%                 | 0.0540     | 17.17%                 | 17.01%                 | 0.0040     |
| Bivalirudin exposure             | 66.9%                  | 61.8%                  | 0.1062     | 66.9%                  | 67.5%                  | 0.0119     |
| Left main coronary artery PCI    | 2.06%                  | 2.11%                  | 0.0037     | 2.06%                  | 2.00%                  | 0.0043     |
| Number of vessels treated during index PCI | 1.42±0.70          | 1.44±0.73              | 0.0292     | 1.42±0.70              | 1.42±0.71              | 0.0049     |
| Fluoroscopy time (min)           | 12.33±9.77             | 14.04±11.15            | 0.1340     | 12.33±9.77             | 12.46±9.42            | 0.0102     |
| Total number of PCI during admission | 1.0481               | 1.0467                 | 0.0062     | 1.0481                 | 1.0483                 | 0.0006     |

Plus–minus values are means±SD. The standardised difference (the mean between-group difference divided by the SD) and was calculated to assess the relative imbalance between the exposed and unexposed groups, with values of less than 0.100 considered to be adequately balanced. The body mass index is the weight in kilograms divided by the square of the height in meters. CAD, coronary artery disease; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; Std. Diff., absolute percentile standardized difference; VCD, vascular closure device.
Compared with the initial analysis which did not include retrospective cases, the safety signal was identified 12 months earlier. During this interval, 24,949 Mynx implants following PCI were captured in the CathPCI Registry.

For the outcome of post-procedure access site bleeding, a safety alert was identified 18 months after study initiation (absolute risk 0.37% vs 0.26%, RR 1.43, 95% CI 1.23 to 1.67), 27 months earlier compared with the initial analysis. For the outcomes of transfusion, a safety alert was identified 21 months after study initiation (absolute risk 1.73% vs 1.45%, RR 1.19, 95% CI 1.12 to 1.28), 9 months earlier compared with the initial analysis. Among prespecified high-risk subgroups including age >70, female sex, and those with diabetes, safety alerts were generated for the primary outcome of "any vascular complication" as well as the secondary endpoints of access site bleeding and need for transfusion (table 2). For all the outcomes, and among each of the subgroups, safety alerts were generated earlier in the current analysis compared with the initial cohort.

**DISCUSSION**

The CathPCI DELTA study was designed to assess the feasibility of prospective, active safety surveillance of a large clinical data repository to support safety outcomes monitoring of post-market medical devices. We performed a large, propensity score matched, safety surveillance study of a national cardiovascular clinical registry and identified a safety alert for vascular complications associated with use of the Mynx VCD. In the current analysis, we were able to improve safety signal detection time by 12 months through inclusion of 36,693 retrospective Mynx VCD cases over an additional analysis period of 18 months. This analysis confirmed a higher risk of vascular complications, access site bleeding, and transfusion requirement among a larger cohort of Mynx VCD recipients compared with those treated with alternate VCDs.

The RR for vascular complications associated with the Mynx VCD was 1.63 (95% CI 1.50 to 1.79; p<0.001) with an absolute event rate of 1.20% versus 0.73% with alternate devices. Had the device of interest been recalled after identifying the first safety alert in this study, between 952 and 1035 additional vascular complications may have been avoided.

The appropriate actions following detection of a safety alert have not been fully established. Given the large sample sizes available in national data registries, alerts that achieve statistical significance should be interpreted in the context of their clinical significance. Depending on estimations of absolute event rates, risk thresholds that prompt additional action should be prespecified. The regulatory actions that follow should depend not only on risk estimates, but on the gravity of the clinical outcome event of interest, and the confidence in this signal. For example, a safety signal indicating higher rates of death associated with the use of...
| Event                        | Mynx (N=109,857) (%) | Alternate device (N=109,857) (%) | Relative risk (95% CI) | Time to alert | Improvement in time to alert |
|------------------------------|----------------------|---------------------------------|------------------------|---------------|-----------------------------|
| Vascular complications       | 1.20                 | 0.73                            | 1.63 (1.50 to 1.79)    | 15 months     | 12 months                   |
| Access-site bleeding         | 0.37                 | 0.26                            | 1.43 (1.23 to 1.67)    | 21 months     | 27 months                   |
| Blood transfusion            | 1.73                 | 1.45                            | 1.19 (1.12 to 1.28)    | 24 months     | 9 months                    |

| Event                        | Mynx (N=40,617) (%) | Alternate device (N=40,616) (%) | Relative risk (95% CI) | Time to alert | Improvement in time to alert |
|------------------------------|---------------------|---------------------------------|------------------------|---------------|-----------------------------|
| Vascular complications       | 1.59                | 0.90                            | 1.77 (1.55 to 2.01)    | 15 months     | 12 months                   |
| Access-site bleeding         | 0.53                | 0.30                            | 1.76 (1.41 to 2.20)    | 15 months     | 18 months                   |
| Blood transfusion            | 2.64                | 2.09                            | 1.29 (1.16 to 1.39)    | 9 months      | 36 months                   |

| Event                        | Mynx (N=37,488) (%) | Alternate device (N=37,488) (%) | Relative risk (95% CI) | Time to alert | Improvement in time to alert |
|------------------------------|---------------------|---------------------------------|------------------------|---------------|-----------------------------|
| Vascular complications       | 2.14                | 1.22                            | 1.75 (1.56 to 1.96)    | 12 months     | 15 months                   |
| Access-site bleeding         | 0.68                | 0.41                            | 1.67 (1.37 to 2.04)    | 21 months     | 12 months                   |
| Blood transfusion            | 3.04                | 2.27                            | 1.33 (1.22 to 1.46)    | 24 months     | 9 months                    |

| Event                        | Mynx (N=42,977) (%) | Alternate device (n=42,976) (%) | Relative risk (95% CI) | Time to alert | Improvement in time to alert |
|------------------------------|---------------------|---------------------------------|------------------------|---------------|-----------------------------|
| Vascular complications       | 1.03                | 0.64                            | 1.61 (1.38 to 1.86)    | 21 months     | 6 months                    |
| Access-site bleeding         | 0.31                | 0.26                            | 1.23 (0.95 to 1.58)    | 21 months     | 21 months                   |
| Blood transfusion            | 2.07                | 1.71                            | 1.21 (1.10 to 1.33)    | 24 months     | 18 months                   |
a medical device may prompt more immediate action at a lower risk ratio with lower confidence. The specific actions that follow should integrate several variables including the frequency of events, seriousness of safety events, and necessity of using the device in consideration. Actions might be limited to manufacturers simply considering device modifications or improving education regarding the use of a specific device or may extend to withdrawal or recall of a device if serious safety concerns are demonstrated.

This study specifically focused on safety of arterial VCDs which were initially brought to market in 1996 in the USA to support safe and expedient hemostasis following femoral arterial access for PCI. Several devices are currently available, and differ with respect to the mechanical, pharmacological, and biomaterial components used. Most have been approved through small pre-market studies, and no data currently supports an improvement in rates of post-procedural bleeding or other complications with their use. However, given the improvement in patient comfort compared with prolonged manual compression, and significant improvement in time to achieve hemostasis, VCDs remain widely available and are commonly used. While VCDs offer a convenient solution for arterial hemostasis, the use of such devices, and new devices, should be held to rigorous standards with little tolerance for excess in adverse event rates given their non-essential role in most PCI procedures.

This study has several important limitations. Safety signals, once identified, should be interpreted with caution. We performed robust risk adjustment through the use of propensity score matching. However, the possibility of residual confounding cannot be excluded. Additionally, the variables included in the propensity score matched analysis are limited to those available in the CathPCI data collection tool. Additional anatomic variables such as arterial puncture site, which may contribute to residual confounding, were not available in the CathPCI Registry. Finally, study endpoints were limited to in-hospital events available in the Cath PCI registry.

This study demonstrates the feasibility of automated surveillance within a large, high quality data sources to support post-market monitoring of medical devices. Among existing medical devices, using prospective active surveillance methods, augmented by retrospective registry data may improve early identification of safety differences. For novel medical devices, surveillance should begin early in the device life-cycle to allow rapid and actionable safety alert identification. Overall, our analysis demonstrates that prospective, active surveillance within a large clinical registry is feasible to detect safety differences among commonly used cardiovascular devices.

Author affiliations

1Cardiovascular Medicine, Lahey Hospital and Medical Center, Burlington, Massachusetts, USA

2Comparative Effectiveness Research Institute, Lahey Hospital and Medical Center, Burlington, Massachusetts, USA

3Tufts School of Medicine, Boston, MA, United States

4Center for Population Health Informatics, Departments of Biomedical Informatics, Biostatistics, and Medicine, Vanderbilt University Medical Center, Nashville, TN, United States

5Predictive Analytics and Comparative Effectiveness (PACE) Center, Institute for Clinical Research and Health Policy Studies (ICRPHS), Tufts Medical Center, Boston, Massachusetts, USA

6Center for Devices and Radiological Health, Food and Drug Administration, Silver Spring, MD, United States

7Comparative Effectiveness Research Institute, Lahey Hospital and Medical Center, Burlington, Massachusetts, USA

8National Cardiovascular Data Registry, American College of Cardiology, Washington DC, United States

9Heart and Vascular Institute, Carle Illinois College of Medicine, Urbana, IL, United States

10Mercy Health, Chesterfield, MO, United States

11Department of Biostatistics, Harvard School of Public Health, Cambridge, Boston, United States

Twitter Arjun Majithia @arjmajmd and Joseph Drozda @jpdrozda

Contributors AM, FSR, DM-D, S-LN, and MEM designed the study. All data were collected via the NCDR CathPCI Registry database. AP and KH were responsible for the upload of the deidentified “limited” CathPCI dataset onto the secure DELTA server. Data analysis was conducted by FSR, MEM, HS, and SR. The manuscript was drafted by AM, MEM, FSR, and SD and critical edits were performed by AP, S-LN, DM-D, NL-B, KH, AP, IM, and JD.

Funding This research was primarily supported through research grants from the US Food and Drug Administration (HHSF Contract 22320083005SC) and the William M. Wood Foundation. In addition, Drs Resnic and Normand’s efforts were funded, in part, by Contract HHSF223201110172C (MDEpiNet Methodology Center) and grant 1U01 FD004493-01 (MDEpiNet Medical Counter Measures Study), both from the US Food and Drug Administration. Dr Matheny’s efforts were funded, in part, by VA HS&RD CDA 08-020, VA HS&RD IIR 11-292, and 1U01 FD004493-01.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Prior to initiation of the CathPCI DELTA study, an oversight committee was established, and a written protocol was developed prespecifying the clinical end points, analytic methods, sensitivity analyses, and plans for interim data reviews. The Institutional review boards of the NCDR and the Lahey Hospital and Medical Center reviewed the study protocol, and the final study protocol was approved prior to the review of any study data.

Provenance and peer review Commissioned; externally peer reviewed.

Data availability statement No data are available. All analyses were conducted using deidentified patient case data from the National Cardiovascular Data Registry (NCDR) CathPCI registry. Individual case data are not publicly available for review. A detailed study protocol and statistical analysis plan is available for review.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs

Arjun Majithia http://orcid.org/0000-0002-8607-534X
Joseph Drozda http://orcid.org/0000-0001-9181-8534

REFERENCES

1 Hauser RG, Kallinen LM, Almqvist AK, et al. Early failure of a small-diameter high-voltage implantable cardioverter-defibrillator lead. Heart Rhythm 2007;4:892–6.

2 Maisel WH. Unanswered questions—drug-eluting stents and the risk of late thrombosis. N Engl J Med 2007;356:981–4.
3 Rosen CJ. The rosiglitazone story--lessons from an FDA Advisory Committee meeting. *N Engl J Med* 2007;357:844–6.
4 Mehran R, Leon MB, Feigal DA, et al. Post-market approval surveillance: a call for a more integrated and comprehensive approach. *Circulation* 2004;109:3073–7.
5 Kessler DA. Introducing MEDWatch. A new approach to reporting medication and device adverse effects and product problems. *Gen Hosp Psychiatry* 1994;16:96–101. discussion 102.
6 O’Shea JC, Kramer JM, Califf RM, et al. Part I: identifying holes in the safety net. *Am Heart J* 2004;147:977–84.
7 Vidi VD, Matheny ME, Resnic FS. Post-marketing device safety surveillance. *Contemp Clin Trials* 2011;32:307–8.
8 Resnic FS, Majithia A. Postmarket medical device safety: moving beyond voluntary reporting. *BMJ Qual Saf* 2018;27:174–5.
9 Normand S-LT, Hatfield L, Drozda J, et al. Postmarket surveillance for medical devices: America’s new strategy. *BMJ* 2012;345:e6848.
10 Resnic FS, Normand S-LT. Postmarketing surveillance of medical devices--filling in the gaps. *N Engl J Med* 2012;366:875–7.
11 Matheny ME, Morrow DA, Ohno-Machado L, et al. Validation of an automated safety surveillance system with prospective, randomized trial data. *Med Decis Making* 2009;29:247–56.
12 Matheny ME, Normand S-LT, Gross TP, et al. Evaluation of an automated safety surveillance system using risk adjusted sequential probability ratio testing. *BMC Med Inform Decis Mak* 2011;11:75.
13 Kumar A, Matheny ME, Ho KKL, et al. The data extraction and longitudinal trend analysis network study of distributed automated postmarket cardiovascular device safety surveillance. *Circ Cardiovasc Qual Outcomes* 2015;8:38–46.
14 Resnic FS, Gross TP, Marinac-Dabic D, et al. Automated surveillance to detect postprocedure safety signals of Approved cardiovascular devices. *JAMA* 2010;304:2019-27.
15 Resnic FS, Majithia A, Marinac-Dabic D, et al. Registry-Based prospective, active surveillance of medical-device safety. *N Engl J Med* 2017;376:526–35.
16 Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011;10:150–61.
17 Austin PC. The relative ability of different propensity score methods to balance measured covariates between treated and untreated subjects in observational studies. *Med Decis Making* 2008;29:661–77.
18 Bernaards CA, Belin TR, Schafer JL. Robustness of a multivariate normal approximation for imputation of incomplete binary data. *Stat Med* 2007;26:1368–82.
19 Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med* 1998;17:873–90.
20 O’Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549–56.
21 Tavris DR, Wang Y, Jacobs S, et al. Bleeding and vascular complications at the femoral access site following percutaneous coronary intervention (PCI): an evaluation of hemostasis strategies. *J Invasive Cardiol* 2012;24:328–34.