DELTA *to support Active Surveillance for Medical Devices*

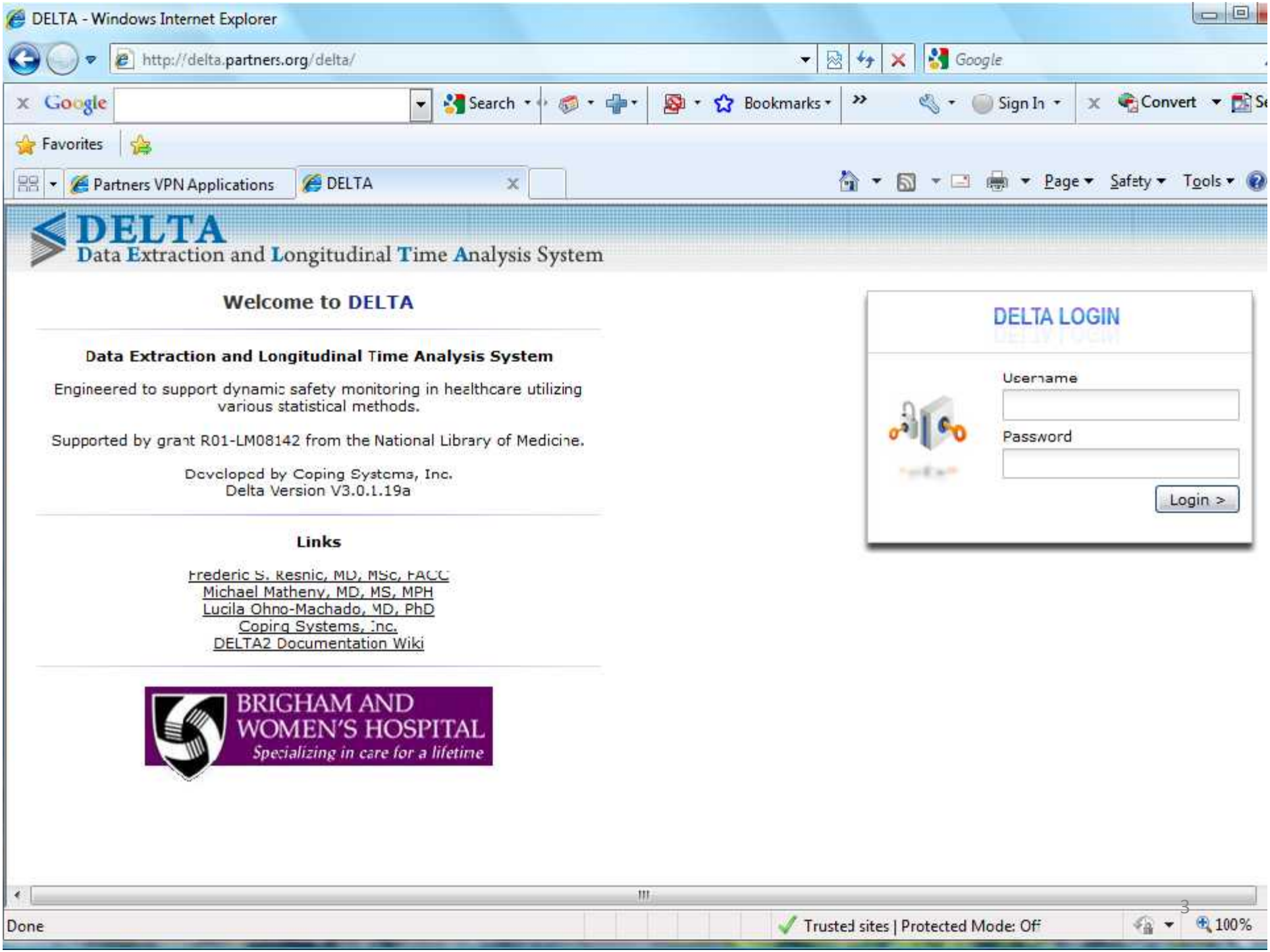
June, 2016

Frederic S. Resnic, MD MSc
Chairman, Department of Cardiovascular Medicine
Co-Director, Comparative Effectiveness Research Institute
Lahey Clinic Medical Center

Associate Professor of Medicine
Tufts University School of Medicine

What is DELTA?

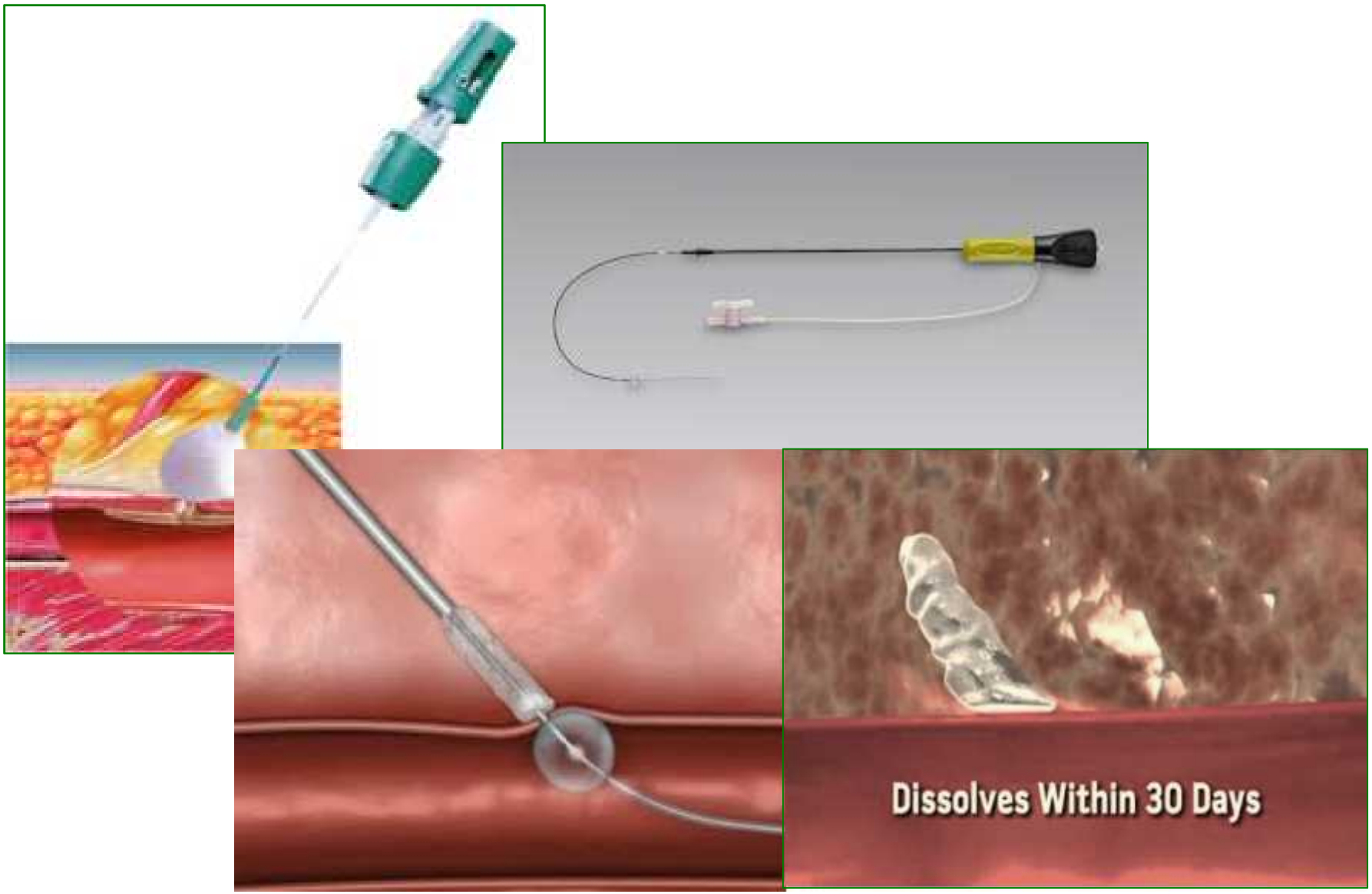
- ***D***ata ***E***xtraction and ***L***ongitudinal ***T***rend ***A***nalysis System
- Software suite designed to support multiple, simultaneous, prospective surveillance of clinical datasets for the purpose of low frequency signal detection.
  - Methods: Propensity matching, sequential methods, survival analysis, multivariate adjustment models and simple Bayesian inference.
  - Supports any relational data model, with specific translation interfaces for OMOP v4 and NCDR registries
- Validated using RCT datasets, regional and state mandated registries.
- ***Open source release*** anticipated on July 1, 2016.


DELTA - Windows Internet Explorer
http://delta.partners.org/delta/
Google
Search
Bookmarks
Sign In
Convert
Favorites
Partners VPN Applications
DELTA
Page
Safety
Tools
DELTA
Data Extraction and Longitudinal Time Analysis System
Welcome to DELTA
Data Extraction and Longitudinal Time Analysis System
Engineered to support dynamic safety monitoring in healthcare utilizing various statistical methods.
Supported by grant R01-LM08142 from the National Library of Medicine.
Developed by Coping Systems, Inc.
Delta Version V3.0.1.19a
Links
Frederic S. Resnic, MD, MSc, FACC
Michael Matheny, MD, MS, MPH
Lucila Ohno-Machado, MD, PhD
Coping Systems, Inc.
DELTA2 Documentation Wiki
BRIGHAM AND WOMEN'S HOSPITAL
Specializing in care for a lifetime
DELTA LOGIN
Username
Password
Login >
Done
Trusted sites | Protected Mode: Off
100%

CathPCI DELTA Pilot: Background

- Vascular Closure Devices (VCD) approved for use following cardiac catheterization procedures.
  - VCD use variety of mechanical/pharmacologic designs and delivery mechanisms to secure device and accelerate clotting.
  - PMA studies generally small and limited high quality post-market safety data regarding VCD.
- Mynx VCD suspected of having higher failure rates than alternative VCD.
  - Observations from 5-hospital prospective safety surveillance (Kumar et al - *Circ Card Qual Outcomes* 2014).
  - Post-publication analysis of national registry study (Tavris et al - *J Invasive Card* 2012).

CathPCI DELTA Pilot: Background



CathPCI DELTA Pilot: Hypothesis

1. Active, prospective surveillance of national cardiovascular registry will demonstrate:

   Mynx VCD is associated with increased rates of post-procedure vascular complications and/or bleeding compared with propensity matched patients receiving alternative VCD.

2. Additionally, Mynx safety signal will be heightened in high risk patient subgroups: women, age>70yrs, and diabetic patients.

CathPCI DELTA Pilot: Methods (1)

- **Study Oversight Committee:** representatives from NCDR, CDRH and DELTA team. Developed written *Statistical Analysis Plan (SAP)* with pre-specified methods, analytic approach, interim reviews (no stopping rules).
- **Data source**: NCDR CathPCI National Registry includes submissions from >1,460 participating U.S. PCI centers. CathPCI centers undergo random annual data audits.
- **Population**: All patients undergoing PCI via femoral access exposed to exactly 1 "active" VCD. Excluded non-femoral access, intra-aortic balloon pump, VAD.
- **Study Period**: 1/1/2011 through 9/30/2013

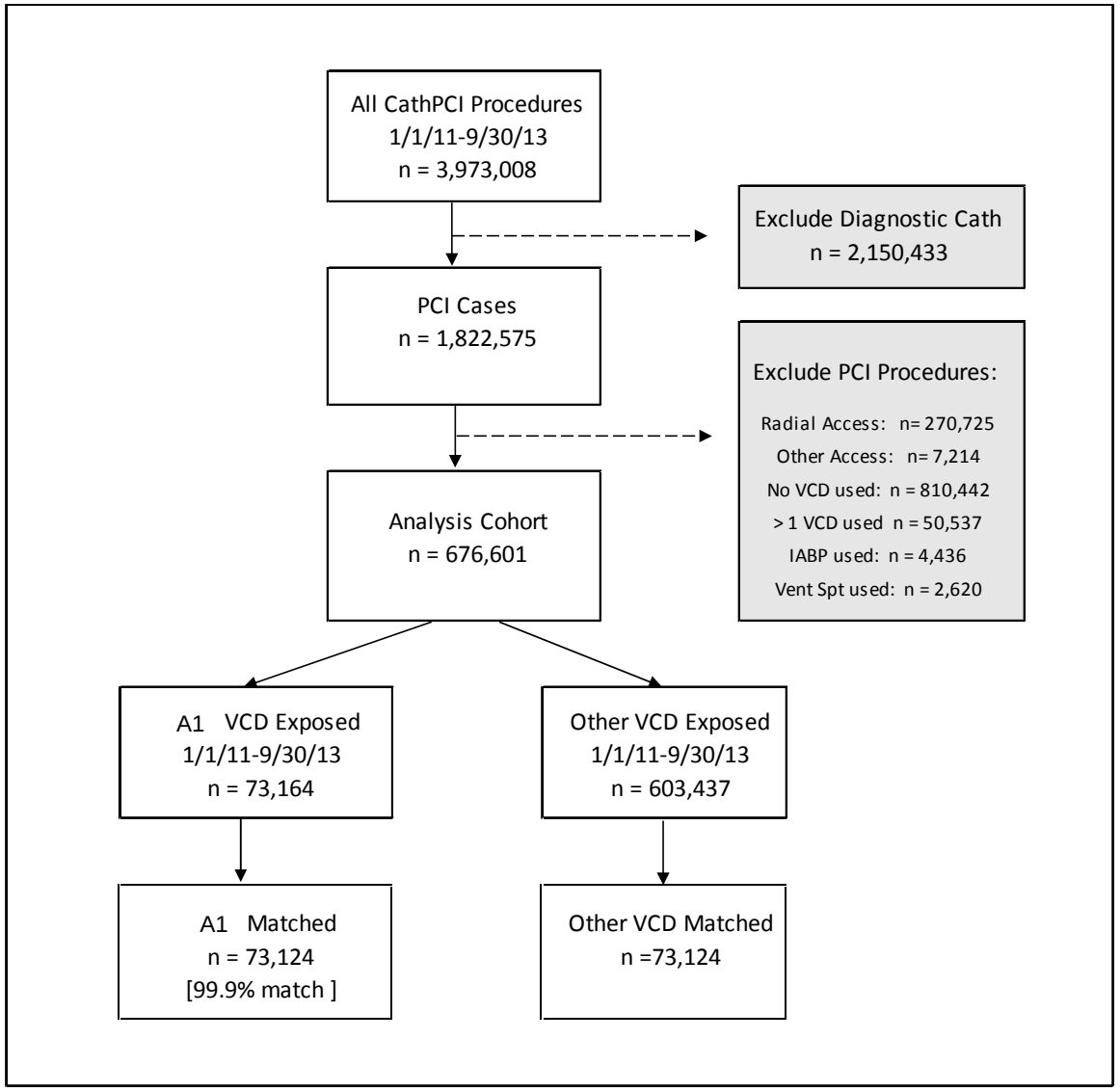
CathPCI DELTA Pilot: Methods (2)

- **Outcomes:** In-hospital significant vascular and bleeding:
  - **Primary** Safety: Any Vascular Complication – composite of access site bleeding requiring treatment, large hematoma (>6cm), retroperitoneal hemorrhage, vascular comp. requiring intervention.
  - **Secondary** Safety : Access site bleeding alone, requirement for post-procedural blood transfusion.
- **Pre-specified Analyses**: per written SAP
  - High risk populations: Women, diabetics, age≥70 years.
  - Alternative risk adjustment: Multivariate logistic risk adjustment
  - Falsification Hypothesis: Thrombectomy catheter adverse events (anticipated no difference expected between devices).
- **Interim Reviews:** pre-specified (SAP) for review by oversight committee after 12 months and at study completion.

CathPCI DELTA Pilot: Methods (3)

- **Propensity Match Analysis**: 1:1 match of patients treated with Mynx as compared to patients treated with alternative active VCD within 6 months of Mynx case.
  - Non-parsimonious propensity model (likelihood of receiving Mynx), fixed caliper width=0.01, greedy match.
  - Quarterly analysis with adjustment for multiple comparisons (O'Brien-Fleming) for each endpoint.
  - Alert if 95% CI of differences between proportions (Wilson method) do not cross zero.
- **Missing Data**: Simple imputation (unknown "missingness" in advance)
- **Post-Hoc Analyses**: On basis of interim and final reviews, SC recommended additional analyses: Sensitivity analyses based on matching rules, center experience, and missing data imputation. Also, analysis of *independent* validation dataset (10/1/13-9/20/15)

CathPCI DELTA Pilot Results (1): Patient Flow Diagram



Resnic FS and DELTA Research Team: CathPCI DELTA Pilot

CathPCI DELTA Pilot Results (2): Patient Characteristics and Match

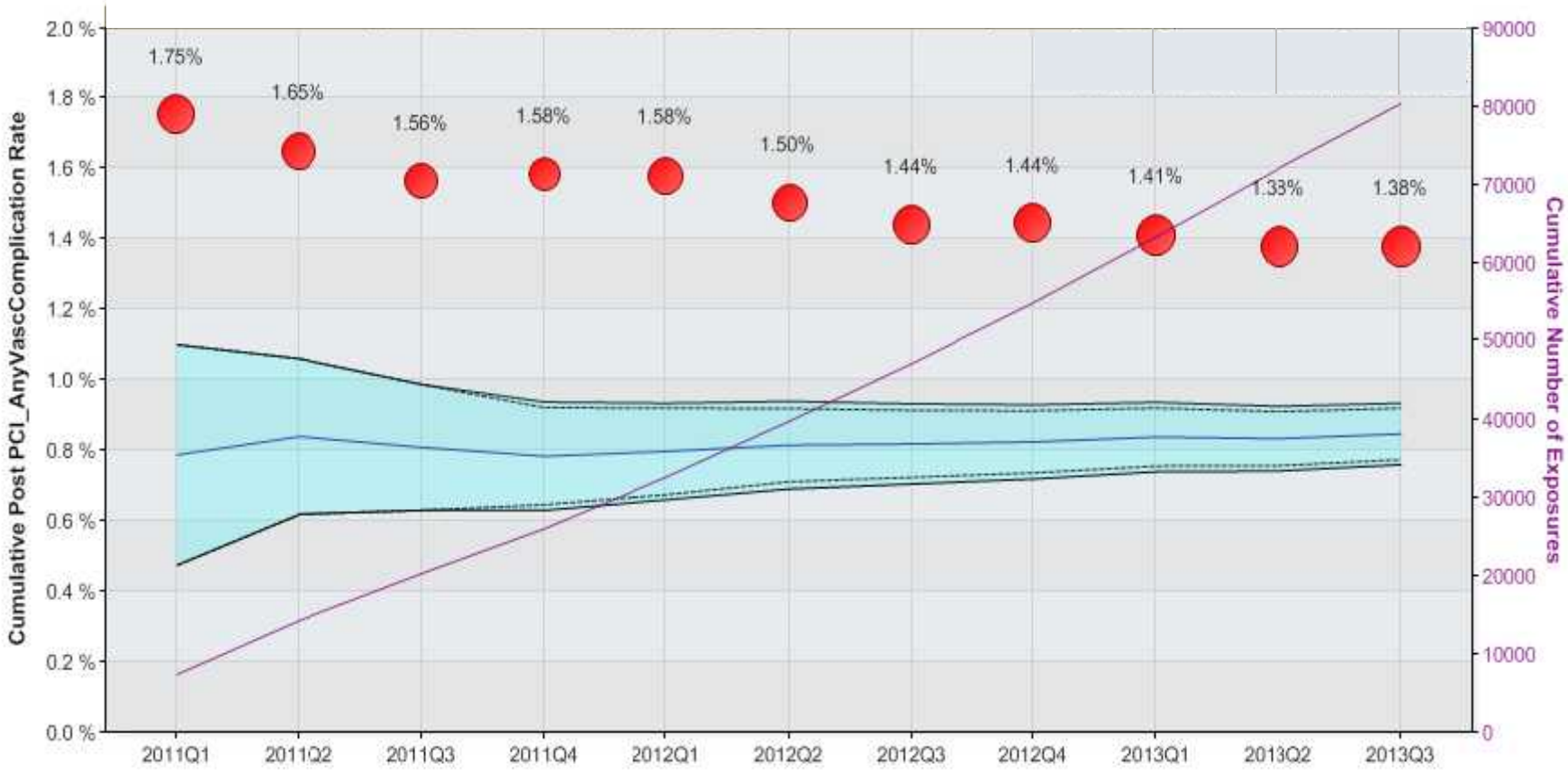
Propensity matching resulted in comparable distribution of key covariates as measured by standardized differences (all less than 10% target).

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
Age (yrs)	65.31 ± 11.91	65.11 ± 12.10	0.0166	65.31 ± 11.91	65.32 ± 11.98	0.0007	64.15 ± 11.99	0.098
Female Gender	34.30%	30.50%	0.0814	34.30%	34.27%	0.0008	30.00%	0.092
Body Mass Index (kg/m^2)								
<21	3.66%	3.69%	0.0018	3.66%	3.72%	0.0033	7.50%	0.168
≥25 and <30	35.4%	37.0%	0.0333	35.4%	35.4%	0.0009	35.0%	0.009
≥30	45.22%	43.19%	0.0410	45.23%	45.42%	0.0038	42.50%	0.055
Diabetes	39.8%	35.9%	0.0802	39.8%	40.2%	0.0081	45.0%	0.105
Chronic Lung Disease	16.5%	13.6%	0.0814	16.5%	16.7%	0.0058	35.0%	0.433
Hypertension	84.8%	81.1%	0.0992	84.8%	84.8%	0.0003	80.0%	0.128
Baseline Creatinine (mg/dL)	1.20 ± 1.08	1.17 ± 0.98	0.0341	1.20 ± 1.08	1.20 ± 1.10	0.0003	1.46 ± 1.37	0.240
Peripheral Arterial Disease	12.7%	9.8%	0.0918	12.6%	12.7%	0.0016	25.0%	0.320
Emergent Procedure Status	13.0%	18.7%	0.1575	13.0%	12.9%	0.0024	17.5%	0.126
NSTEMI on Presentation	18.90%	20.34%	0.0362	18.90%	18.91%	0.0003	27.50%	0.205
Bivalirudin exposure	67.9%	64.4%	0.0723	67.9%	68.6%	0.0157	67.5%	0.008
Left Main Coronary Artery PCI	2.09%	2.23%	0.0092	2.09%	2.14%	0.0031	2.50%	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	0.0033	1.75 ± 0.98	0.462
Fluoroscopy time (min)	12.54 ± 9.73	14.11 ± 11.22	0.1419	12.48 ± 9.24	12.58 ± 8.95	0.0107	122.72 ± 71.97	11.747
Total number of PCI during admission	1.05 ± 0.22	1.05 ± 0.22	0.0020	1.05 ± 0.22	1.05 ± 0.21	0.0008	1.03 ± 0.16	0.102

Resnic FS and DELTA Research Team: CathPCI DELTA Pilot

CathPCI DELTA Pilot Results (3): Mynx VCD Primary Endpoint

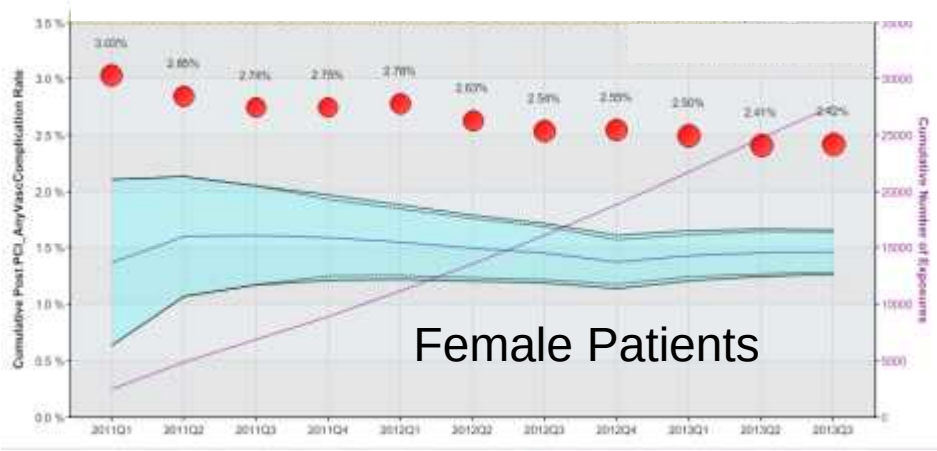
Propensity matched analysis of the incidence of Any Vascular Complication following use of Mynx VCD versus all other active VCD. Safety alert triggered during the first quarter and persisted throughout study period.

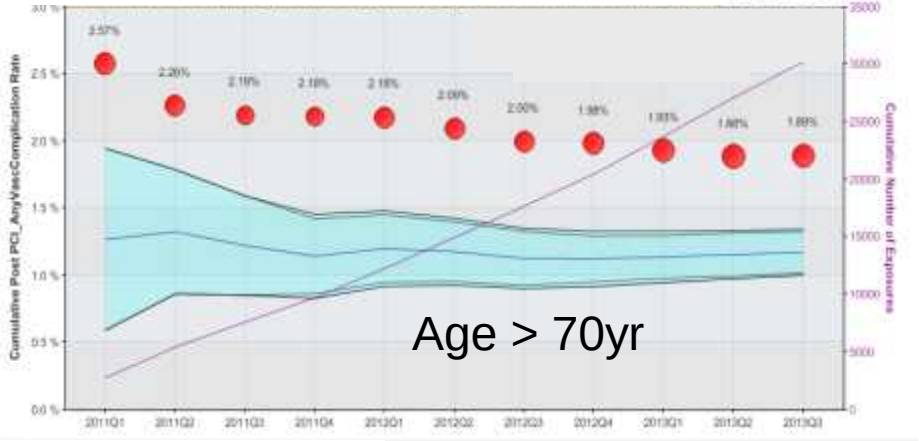


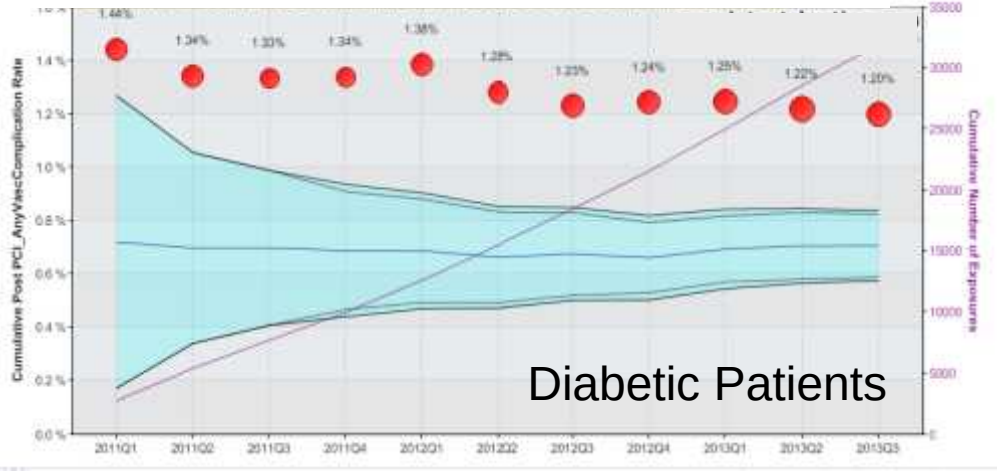
Resnic FS and DELTA Research Team: CathPCI DELTA Pilot

CathPCI DELTA Pilot Results (4): High Risk Populations

Pre-specified subgroup analysis was performed for high risk subgroups including: women, the age>70 and patients with diabetes.

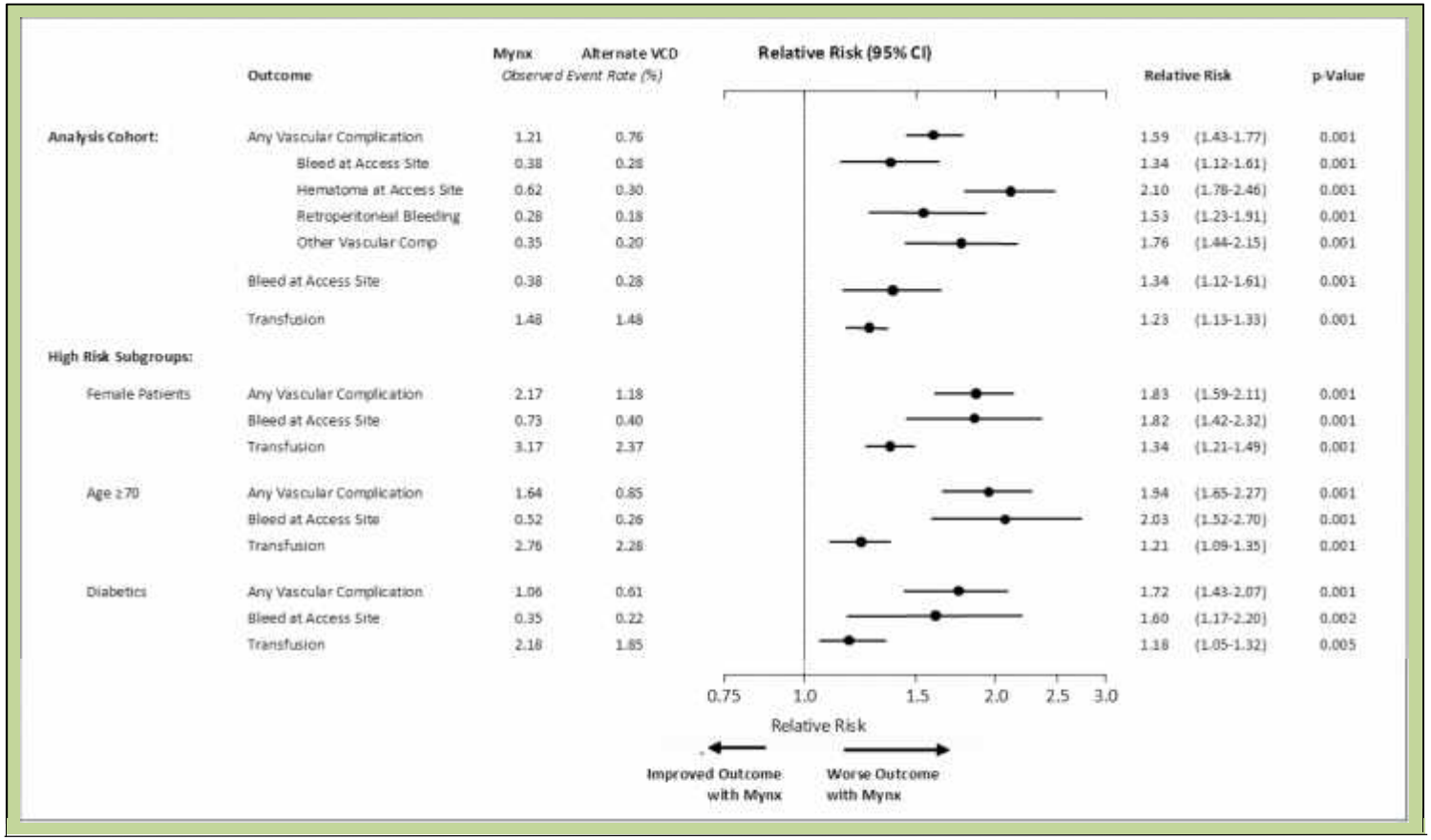






Preliminary Analysis: DELTA NCDR CathPCI Pilot Project

CathPCI DELTA Pilot Results (5): Summary of All Analyses



	Outcome	Mynx (Observed Event Rate %)	Alternate VCD (Observed Event Rate %)	Relative Risk		p-Value
Analysis Cohort:	Any Vascular Complication	1.21	0.76	1.59	(1.43-1.77)	0.001
	Bleed at Access Site	0.38	0.28	1.34	(1.12-1.61)	0.001
	Hematoma at Access Site	0.62	0.30	2.10	(1.78-2.46)	0.001
	Retroperitoneal Bleeding	0.28	0.18	1.53	(1.23-1.91)	0.001
	Other Vascular Comp	0.35	0.20	1.76	(1.44-2.15)	0.001
	Bleed at Access Site	0.38	0.28	1.34	(1.12-1.61)	0.001
	Transfusion	1.48	1.48	1.23	(1.13-1.33)	0.001
High Risk Subgroups:						
Female Patients	Any Vascular Complication	2.17	1.18	1.83	(1.59-2.11)	0.001
	Bleed at Access Site	0.73	0.40	1.82	(1.42-2.32)	0.001
	Transfusion	3.17	2.37	1.34	(1.21-1.49)	0.001
Age ≥70	Any Vascular Complication	1.64	0.85	1.94	(1.65-2.27)	0.001
	Bleed at Access Site	0.52	0.26	2.03	(1.52-2.70)	0.001
	Transfusion	2.76	2.28	1.21	(1.09-1.35)	0.001
Diabetics	Any Vascular Complication	1.06	0.61	1.72	(1.43-2.07)	0.001
	Bleed at Access Site	0.35	0.22	1.60	(1.17-2.20)	0.002
	Transfusion	2.18	1.85	1.18	(1.05-1.32)	0.005

Advantages of DELTA Approach

1. *Automated Continuous, Prospective, Active Surveillance:* suitable for monitoring of large clinical datasets using straightforward analytic methods.
2. Supports *multiple, simultaneous,* active surveillance analyses.
3. *Pre-specified analytic plan:* DELTA configured at outset of analysis to perform studies in accordance with SAP/protocol.
4. *Propensity matching* is uniquely suited to comparative safety analyses. Statistically robust, very easy to interpret and explain, and is conducive to post-hoc analysis for signal exploration.
5. *Pragmatic and Scalable Approach.* Validated in central data model and distributed models.

Limitations and Lessons Learned

1. *Dependence on Case Level Data Access:* provided exceptional access to case level data through data use agreement with NCDR.
2. *Signal Verification and Communication:* CRITICAL for active surveillance efforts; need for WRITTEN safety alert signal communication and action plan.
3. *Methodologic Challenges:* handling of missing data, center-level vs. global matching and appropriate adjustment for multiple comparisons.
4. *Sustainability:* Funded through FDA, NIH, VA and private foundation funding. Not sustainable for ongoing efforts.

CathPCI DELTA Pilot: Conclusions

1. DELTA surveillance of CathPCI registry identified a 1.6 fold increased risk of vascular and bleeding complications following use of Mynx VCD compared with other approved VCD .

2. This safety signal was identified in high risk populations and verified in an independent contemporary cohort.

3. DELTA can be applied to accruing national clinical registries, such as NCDR, with prompt analysis of medical device safety.

4. Further DELTA pilot projects currently underway within the NCDR ICD Registry and the TVT Registry.

Thank You

Lahey Clinic Medical Center

Susan Robbins, BS
Henry Ssemaganda, MD, MPH
Marek Mizracki, MSc

Vanderbilt University VAMC

Michael Matheny, MD MSc MPH
Dax Westerman, MSc

For more information please contact:

Frederic S. Resnic, MD MSc
Lahey Hospital and Medical Center
41 Mall Road
Burlington, MA 01805
781-744-2778
frederic.resnic@lahey.org

Prior Investigation: VCD and CathPCI

Exploration of CathPCI cases 2005-2009 found that VCD's had lower risk adjusted adverse event rates as compared with manual compression. However, there was a safety signal for increased risk with the Mynx device with estimated RR=1.33 - 1.69

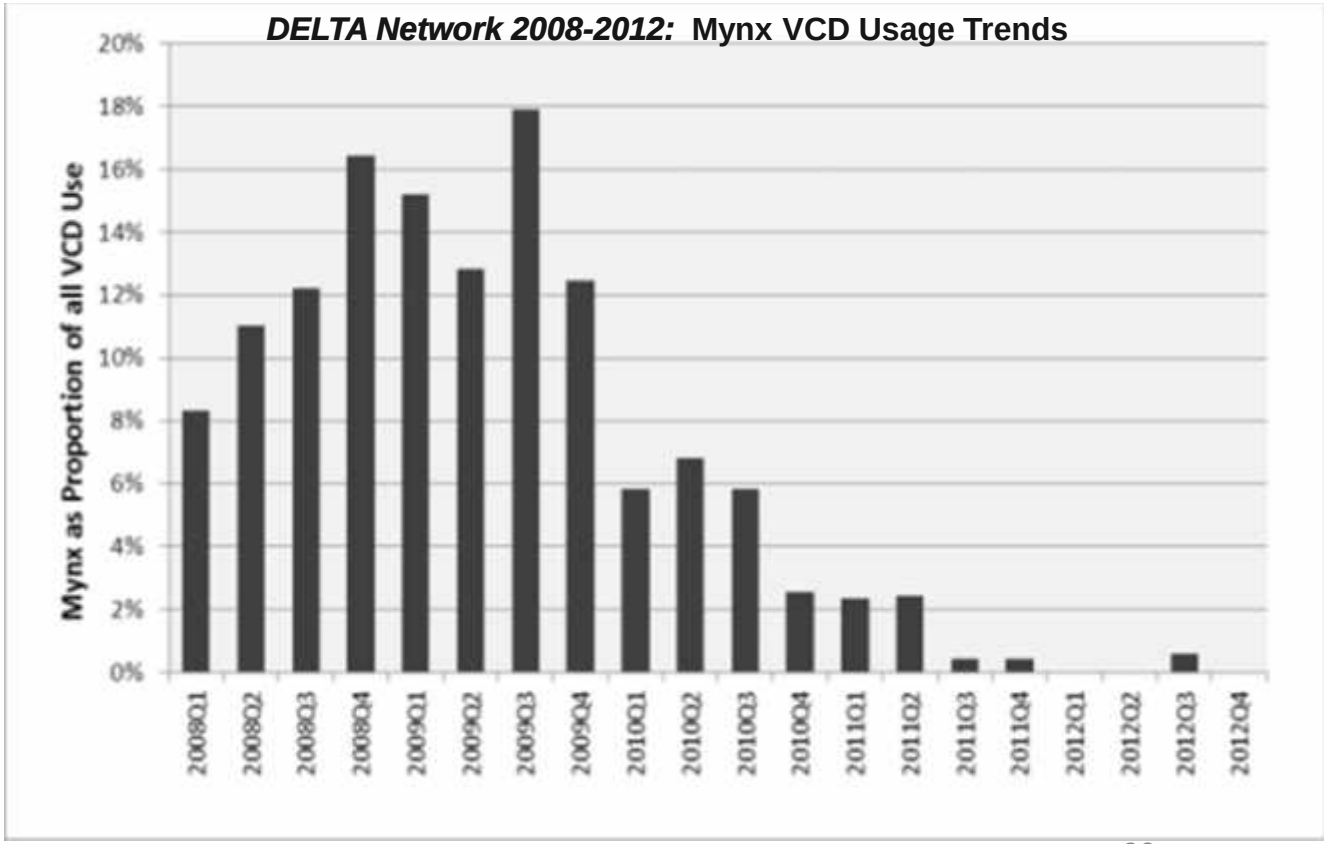
Table 3. Multivariate analysis of complication rates by device group for patients with femoral access sites.

Device group	Bleeding OR [LOR-UOR]	P-Value	Vascular OR [LOR-UOR]	P-Value	Either OR [LOR-UOR]	P-Value
Manual compression	—	—	—	—	—	—
Mechanical compression	1.09 [1.03-1.16]	.002	1.162 [1.09-1.24]	<.001	1.15 [1.10-1.20]	<.001
Angio-Seal	0.84 [0.80-0.87]	<.001	0.458 [0.43-0.48]	<.001	0.68 [0.65-0.70]	<.001
Perclose	0.69 [0.65-0.74]	<.001	0.343 [0.31-0.38]	<.001	0.54 [0.51-0.57]	<.001
StarClose	1.05 [0.98-1.13]	NS	0.385 [0.34-0.43]	<.001	0.77 [0.72-0.82]	<.001
Boomerang	0.98 [0.78-1.22]	NS	0.399 [0.31-0.51]	<.001	0.63 [0.53-0.75]	<.001
Mynx	1.32 [1.16-1.50]	<.001	0.478 [0.39-0.58]	<.001	0.91 [0.82-1.02]	NS
Patches	0.92 [0.86-0.98]	.013	0.527 [0.49-0.57]	<.001	0.70 [0.67-0.74]	<.001

Tavris et al. J Invas Card. July 2012

DELTA Automated Surveillance: Prospective Distributed Registry Analysis

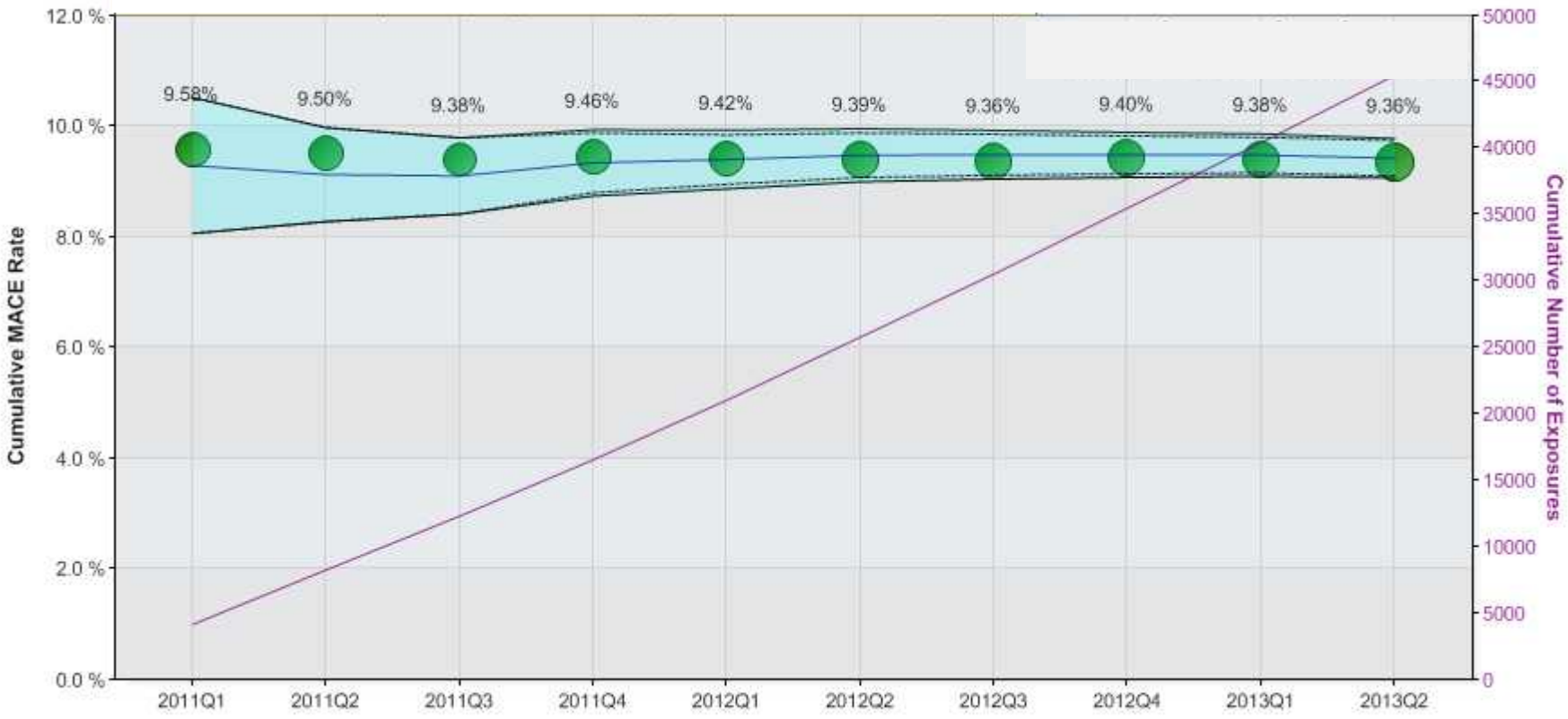
Mynx VCD was associated with a non-statistical trend toward increased vascular complications and transfusions following use with RR = 2.20 (95% CI: 0.71-6.3), the number of Mynx uses declined rapidly in the participating centers.



Kumar et al – Circ Cardiovasc Qual Outcomes - 2014

Falsification Hypothesis: Thrombectomy Catheter Safety

Pre-defined a study for devices for which there was no prior evidence or expectation of a safety signal: aspiration thrombectomy catheters. Propensity matched analysis of the incidence of MACE (Major Adverse Cardiac Event) following use of Device B1 versus Device B2



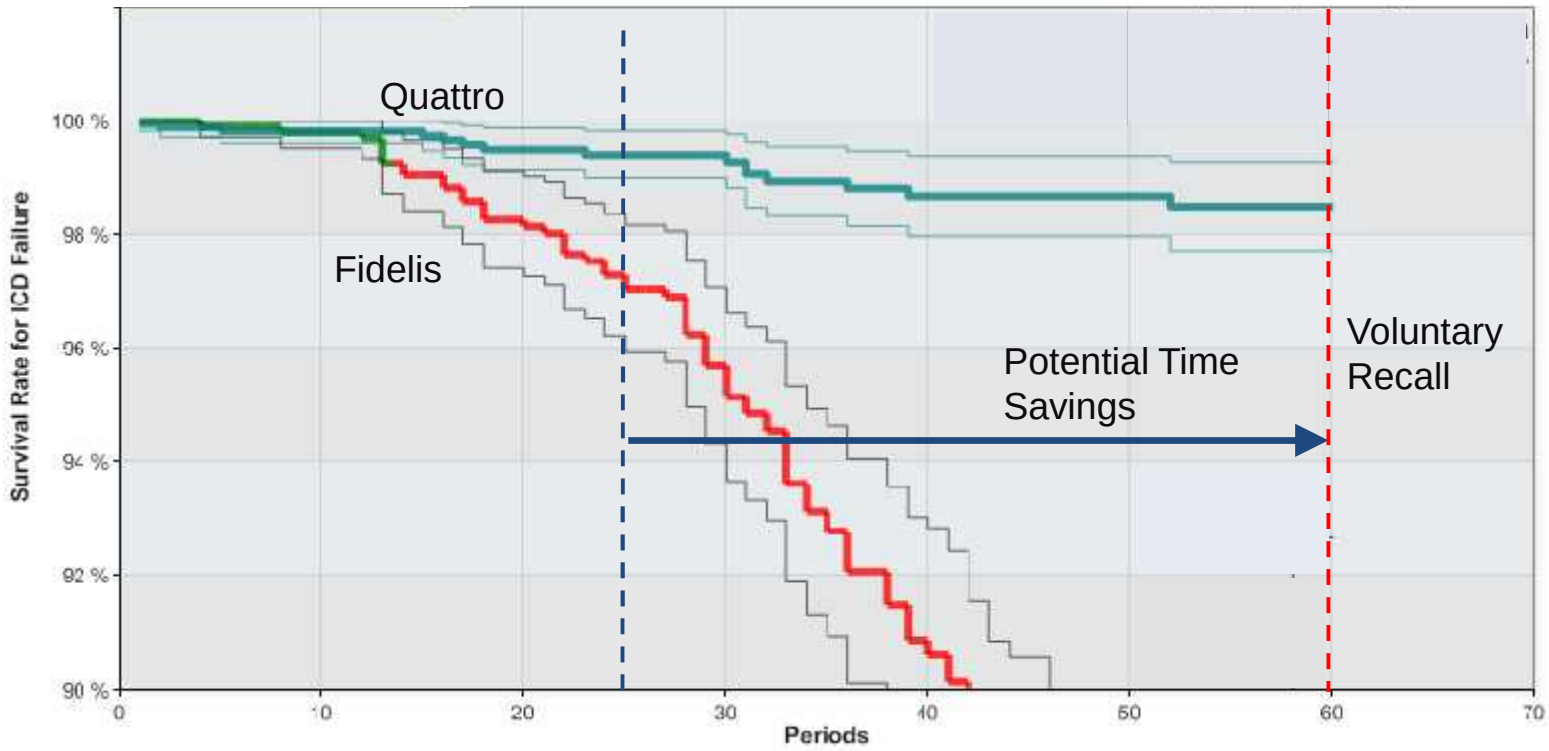
Preliminary Analysis: DELTA NCDR CathPCI Pilot Project

Alert Communication Proposal

- As part of written study protocol, establish formal communication and analytic protocol in the event safety alerts are triggered.
  - Specify study devices, outcomes of interest, populations, primary analyses, sensitivity analyses, and thresholds for alerting
  - Safety alerts categorized into three levels of severity: low, medium and high-risk alerts; with communication action plans assigned for each alert level.
- All alerts considered hypothesis generating; not definitive.
- Alert triggers written communication with details of analyses to steering committee (with manufacturer and FDA membership).
- Manufacturer has opportunity to examine and critique analyses and provide additional information to FDA within 30-90 days (depending on severity of safety risk).

DELTA Surveillance: Time Savings for Signal Identification

Using pooled data from *three* high volume centers, DELTA performed a propensity matched analysis 0f 859 Fidelis lead implants versus traditional leads. By 25 months of analysis (dashed line) 3% of Fidelis leads had fractured (red line) whereas only 0.1% (1 of 859) alternative ICD leads had fractured.



Source: Hauser et al. *Circ Cardiovasc Qual Outcomes*. 2012