Practical Lessons Learned for Identification of Thromboembolic Events and Intravenous Immunoglobulin Exposure in the Sentinel Distributed Database

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Background

- Sentinel is the US Food and Drug Administration (FDA)'s active safety surveillance system to monitor medical products
- Blood Safety Continuous Active Surveillance Network (BloodSCAN), initiated by the Center for Biologics Evaluation and Research (CBER), focuses on blood and blood product safety
  - A workgroup conducted a retrospective protocol-based assessment of thromboembolic events (TEE) after immunoglobulin (Ig) administration

Objective

To summarize lessons learned from medical record review for a Sentinel assessment of thromboembolic events (TEEs) after intravenous immune globulin (IVIg) that may be applicable to other project

Methods

- Medical records were retrieved for 299 of the 442 potential post-IVIg TEE cases identified at 13 Data Partners from the SDD
- Key elements for chart validation
  - IVIg exposure, brand
  - TEE outcomes
  - Timing of IVIg and TEE

Methods: Identification of potential IVIg TEE cases in administrative data

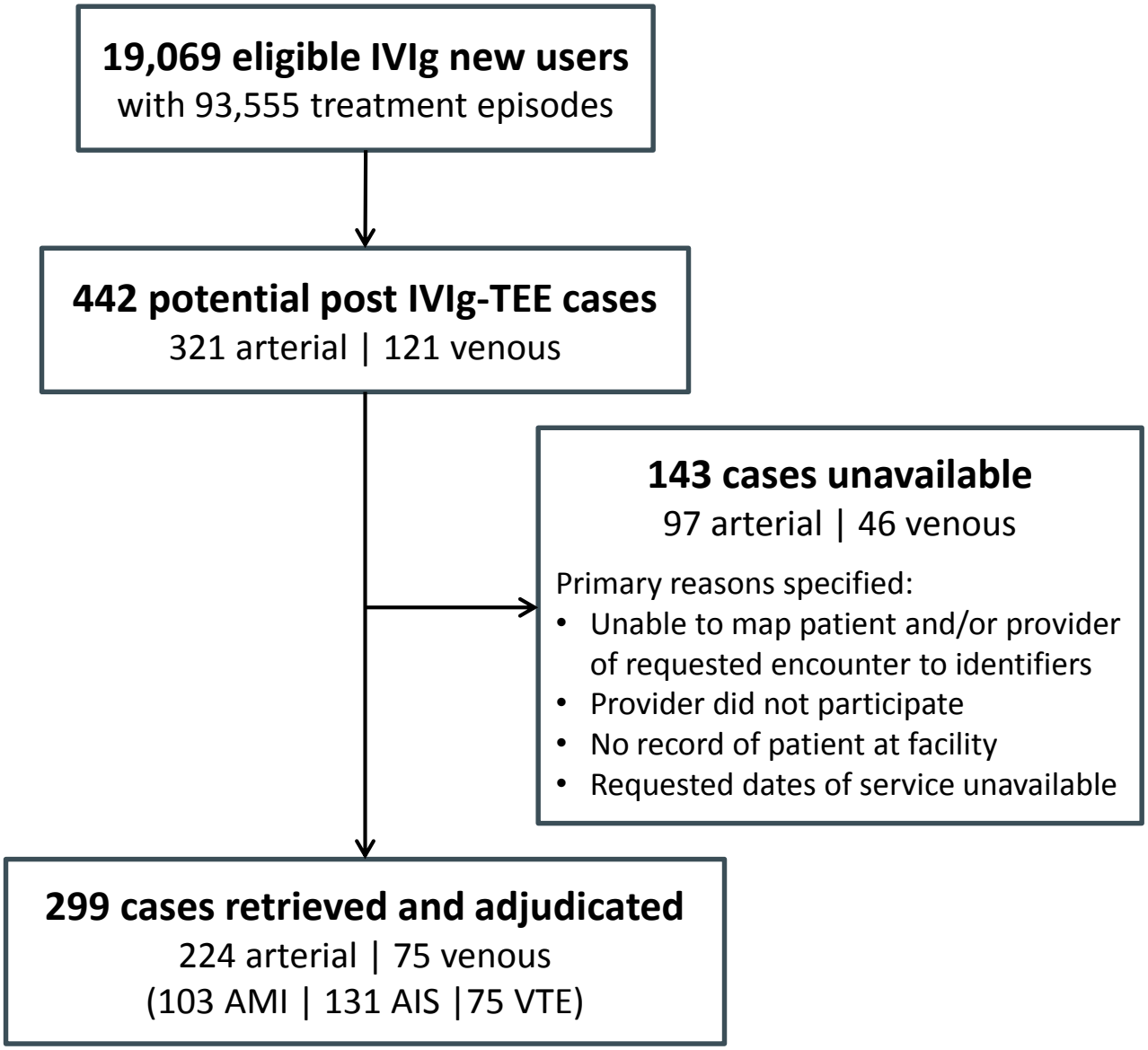
IVIg use

- Codes for IVIg (product specific and non-specific)
  - HCPCS
  - CPT-4
  - ICD-9-CM procedure
  - NDCs

TEE endpoints

- Inpatient ICD-9-CM diagnosis codes
  - Arterial TEE
    - Acute myocardial infarction (AMI)
    - Acute ischemic stroke (AIS)
  - Venous TEE
    - Deep vein thrombosis (DVT) (excluding upper extremity)
    - Pulmonary embolism (PE)

Methods



Results: TEE validation

Positive predictive values (PPVs) of ICD-9-CM diagnosis codes for acute TEE in SDD

TEE	All potential TEE cases identified in administrative data	Principal-position diagnosis	Secondary diagnosis	Position-unspecified diagnosis
AMI 410.x0, 410.x1	75% 67/89	93% 28/30	88% 29/33	38% 10/26
Stroke 433.x1, 434.x0, 434.x1, 436	27% 34/128	60% 9/15	42% 21/50	6% 4/63
VTE **DVT:** 451.11, 451.19, 451.2, 451.9, 453.1, 453.2, 453.40, 453.41, 453.42, 453.9 **PE:** 415.11, 415.12, 415.13, 415.19	61% 38/62	90% 27/30	80% 4/5	26% 7/27

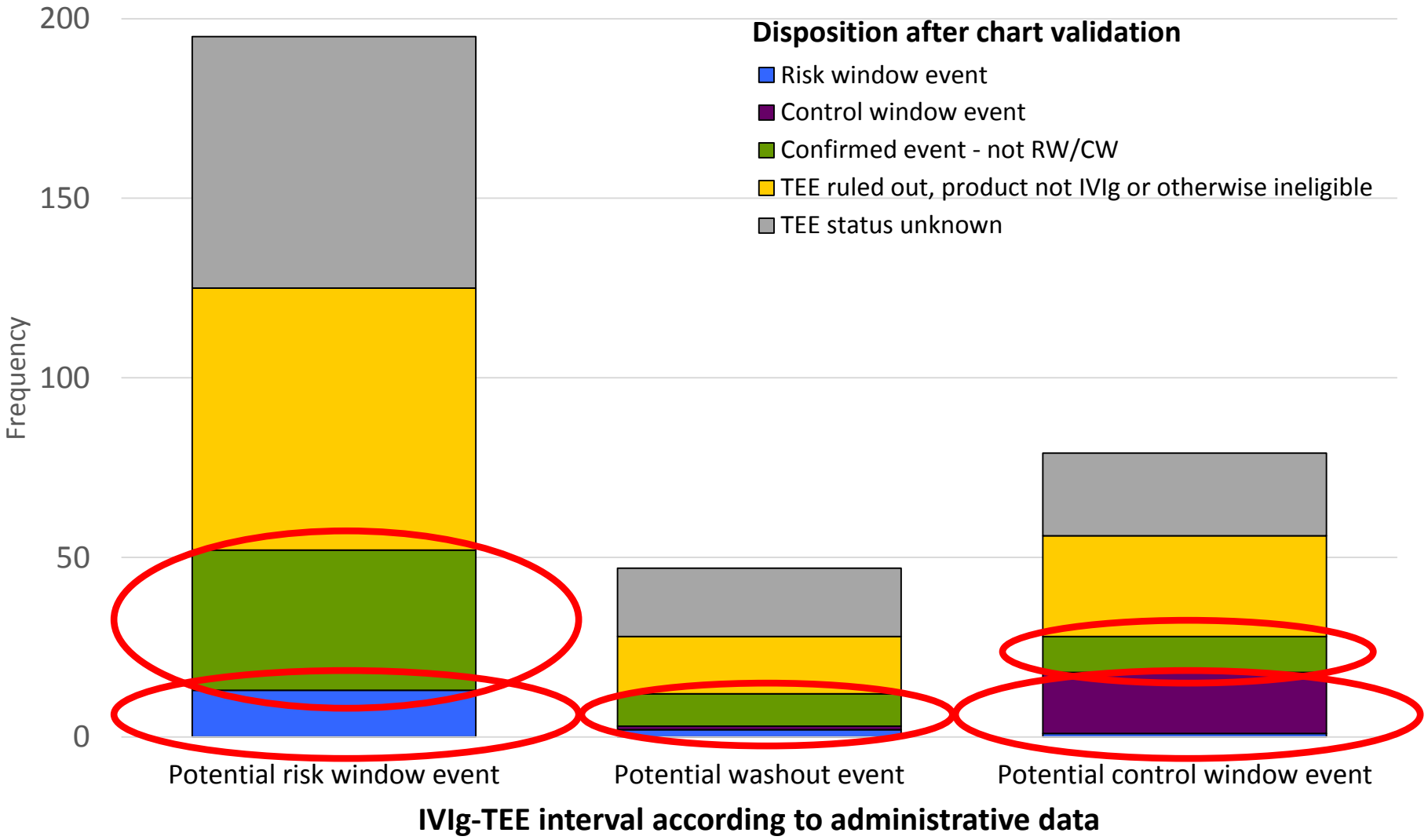
Results: Identification and validation of IVIg

- IVIg primarily identified from procedure codes
- IVIg brand was documented in the medical charts for 34% of cases reviewed
  - No discrepancies with brand recorded in administrative data

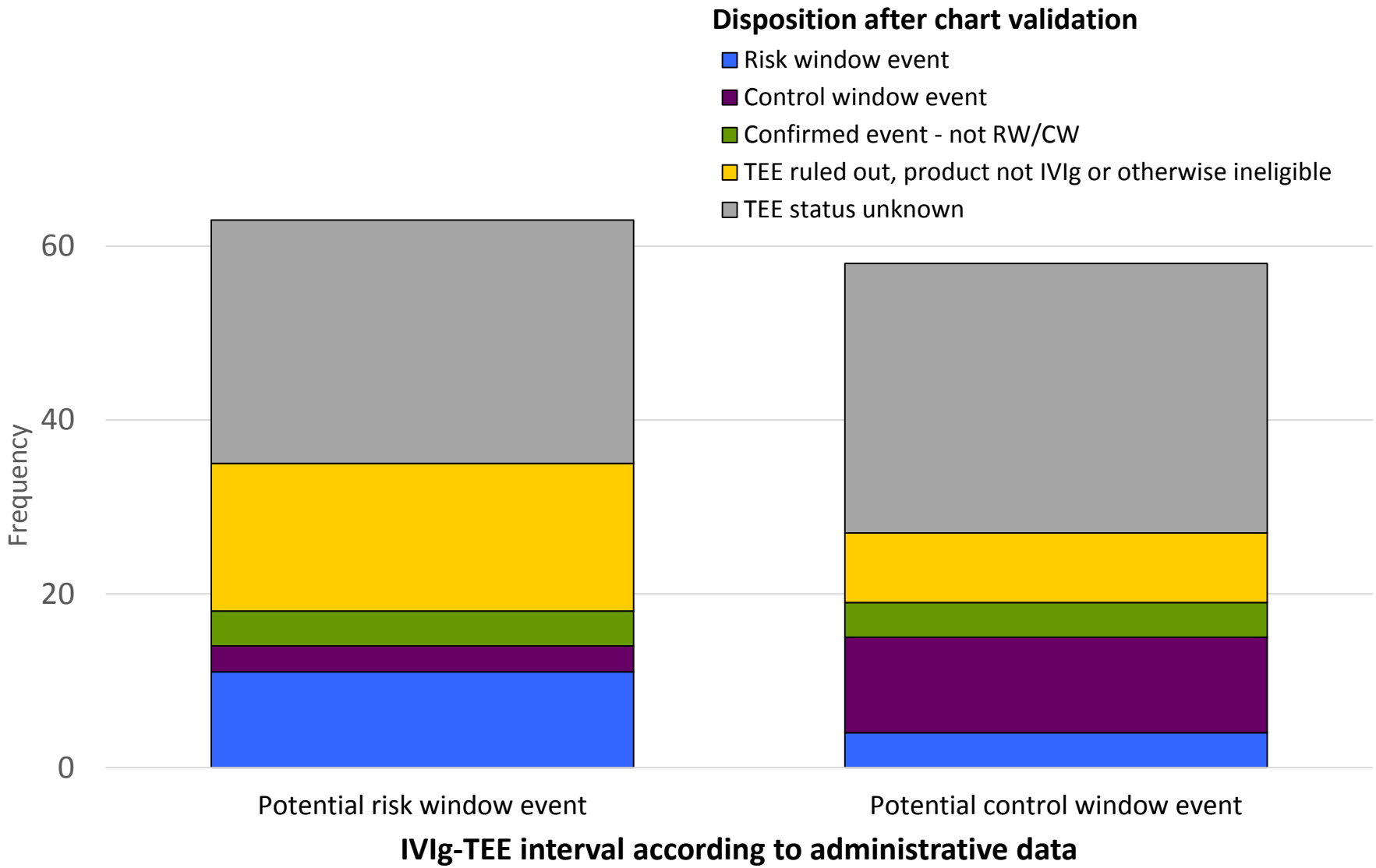
Results: Timing of IVIg and TEE

- Dates were corrected after medical record review for 88% of inpatient IVIg treatment records and 69% of inpatient TEE events

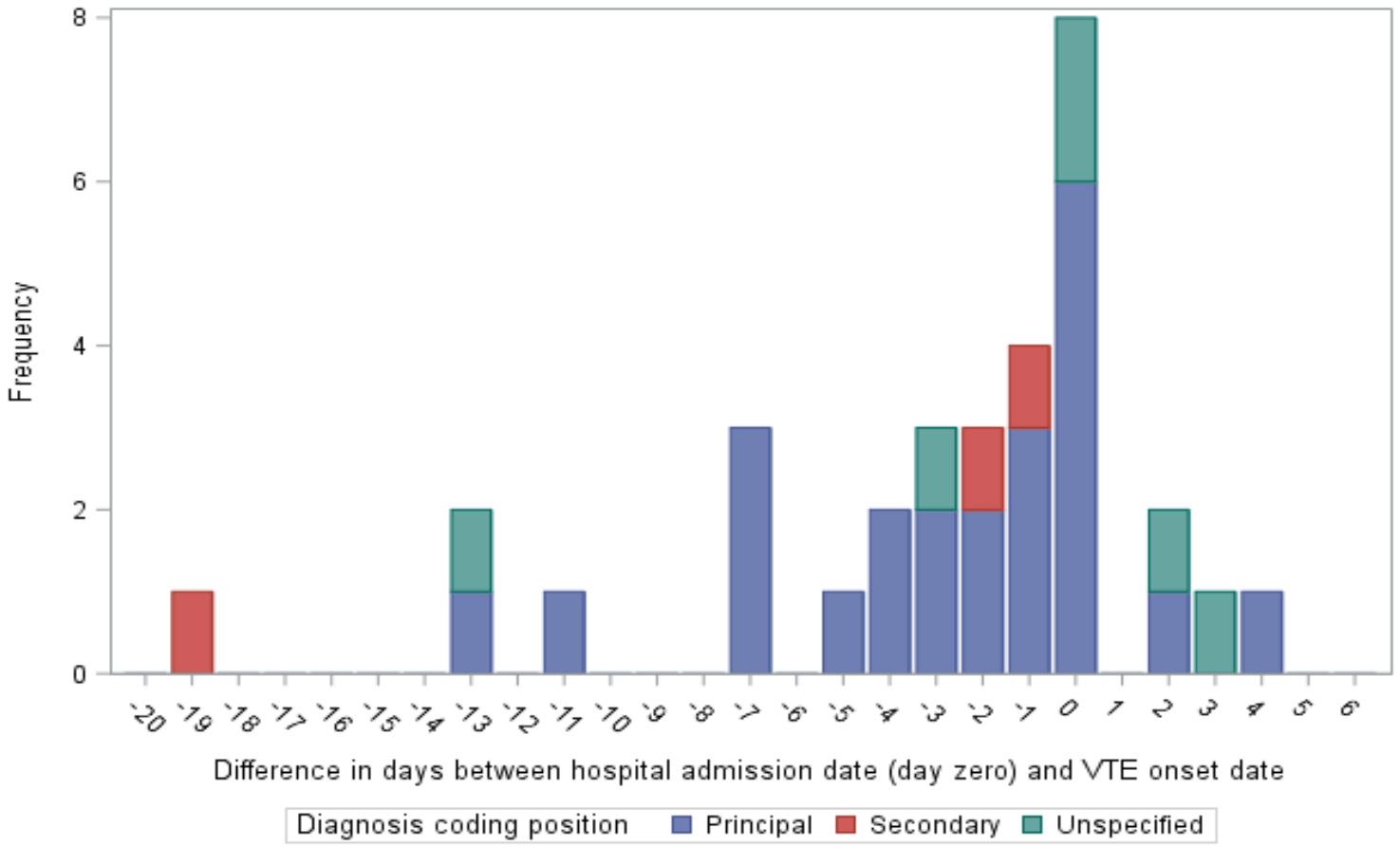
Results: Timing of IVIg and arterial TEE



Results: Timing of IVIg and venous TEE



Results: Timing of VTE onset relative to recorded diagnosis



Limitations

- High proportion of unavailable records
- Generalizability of findings

Conclusions

- Brand-specific administrative codes for IVIg were consistent with brand received by patient
- Charts were essential to accurately identify timing of **inpatient** treatments and diagnoses

Acknowledgements

- IVIg-TEE Workgroup
  - Leads: Betsy Chrischilles, Ryan Carnahan, Scott Winiecki
  - Members: Eric Ammann, Meghan Baker, Ryan Carnahan, Adam Cuker, Sudeepta Dandapat, Jayasheel Eshcol, Bruce Fireman, Candace Fuller, Crystal Garcia, Saket Girotra, Cole Haskins, Rami Kafa, Enrique Leira, Charlie Leonard, Nandakumar Nagaraja, Usha Perepu, Madelyn Pimentel, Jennifer Robinson, Nicholas Rudzianski, Marin Schweizer, Jim Torner
- Many thanks are due to Data Partners who provided data and medical records used in the analysis

Thank you!

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Extra slides

Results: TEE validation

PPVs of ICD-9-CM diagnosis codes for AIS in SDD

Code(s)	All potential AIS cases (N = 128)	Principal position AIS diagnoses (N = 15)	Secondary AIS diagnoses (N = 50)	Position-unspecified AIS diagnoses (N = 63)
All AIS codes	27% (34/128, 95% CI: 19-35%)	60% (9/15, 95% CI: 32-84%)	42% (21/50, 95% CI: 28-57%)	6% (4/63, 95% CI: 2-15%)
433.x1	50% (3/6, 95% CI: 12-88%)	50% (1/2, 95% CI: 1-99%)	100% (1/1, 95% CI: 3-100%)	33% (1/3, 95% CI: 1-91%)
434.x0	0% (0/9, 95% CI: 0-34%)	0% (0/2, 95% CI: 0-84%)	--	0% (0/7, 95% CI: 0-41%)
434.x1	33% (31/95, 95% CI: 23-43%)	73% (8/11, 95% CI: 39-94%)	43% (20/47, 95% CI: 28-58%)	8% (3/37, 95% CI: 2-22%)
436	0% (0/18, 95% CI: 0-19%)	--	0% (0/2, 95% CI: 0-84%)	0% (0/16, 95% CI: 0-21%)

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Results: TEE validation

PPVs of ICD-9-CM diagnosis codes for VTE in SDD

Code(s)	All potential VTE cases (N = 62)	Principal position VTE diagnoses (N = 30)	Secondary VTE diagnoses (N = 5)†	Position-unspecified VTE diagnoses (N = 27)†
All DVT codes	54% (15/28, 95% CI: 34-72%)	90% (9/10, 95% CI: 55-100%)	100% (1/1, 95% CI: 3-100%)	29% (5/17, 95% CI: 10-56%)
451.11	0% (0/1, 95% CI: 0-98%)	--	--	0% (0/1, 95% CI: 0-98%)
451.19	25% (1/4, 95% CI: 1-81%)	--	--	25% (1/4, 95% CI: 1-81%)
451.2	0% (0/1, 95% CI: 0-98%)	--	--	0% (0/1, 95% CI: 0-98%)
451.9	--	--	--	--
453.1	--	--	--	--
453.2	--	--	--	--
453.40	44% (4/9, 95% CI: 14-79%)	50% (1/2, 95% CI: 1-99%)	--	43% (3/7, 95% CI: 10-82%)
453.41	88% (7/8, 95% CI: 47-100%)	100% (5/5, 95% CI: 48-100%)	100% (1/1, 95% CI: 3-100%)	50% (1/2, 95% CI: 1-99%)
453.42	100% (3/3, 95% CI: 29-100%)	100% (3/3, 95% CI: 29-100%)	--	--
453.9	0% (0/2, 95% CI: 0-84%)	--	--	0% (0/2, 95% CI: 0-84%)
All PE codes	68% (23/34, 95% CI: 49-83%)	90% (18/20, 95% CI: 68-99%)	75% (3/4, 95% CI: 19-99%)	20% (2/10, 95% CI: 3-56%)
415.11	--	--	--	--
415.12	0% (0/1, 95% CI: 0-98%)	--	--	0% (0/1, 95% CI: 0-98%)
415.13	--	--	--	--
415.19	70% (23/33, 95% CI: 51-84%)	90% (18/20, 95% CI: 68-99%)	75% (3/4, 95% CI: 19-99%)	22% (2/9, 95% CI: 3-60%)

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Arterial TEE risk overstated in administrative data due to spurious day zero events

Scenario	Rate ratio	Absolute risk
All chart-confirmed risk window (RW) or control window (CW) cases	3.72 (95% CI: 1.75, 7.84)	9.45 (95% CI: 3.64, 15.6) per 10,000 patients
All RW or CW as determined from SDD	16.1 (95% CI: 12.1, 21.7)	93.7 (95% CI: 85.1, 102.1) per 10,000 patients