Risk of Arterial/Venous Thrombotic Events with COVID-19: A Sentinel System Investigation – Focus on Endpoints

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Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Sentinel Coagulopathy Workgroup: Specific Aims

- **Aim 1**: Determine 90-day incidence of arterial and venous thrombotic events (evaluated separately) with COVID-19 and its consequences.
  - Hypothesis: Events will occur within 90 days of COVID-19 diagnosis and may result in death.

- **Aim 2**: Evaluate patient characteristics present at COVID-19 diagnosis as risk factors for arterial and venous thrombotic events (evaluated separately).
  - Hypothesis: Characteristics that promote endothelial injury, stasis of circulation, and hypercoagulability will be risk factors for thrombosis.

- **Aim 3**: Compare 90-day risk of arterial and venous thrombotic events (evaluated separately) between health plan members with COVID-19 and those with influenza.
  - Hypothesis: Risk of thrombotic events will be higher with COVID-19 than influenza.

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Primary Outcomes for Aims 1-3: Thrombotic Events

Primary

Arterial Thrombosis

Acute myocardial infarction

Acute ischemic or embolic stroke

Primary

Venous Thromboembolism

Acute upper/lower deep venous thrombosis (DVT)

Acute pulmonary embolism (PE)

Primary or Secondary Hospital Discharge ICD-10-CM Diagnosis (Mapped from ICD-9-CM Diagnoses Validated in Sentinel Data)

Rationale for Focus on Validated Diagnostic Coding Algorithms

- **Minimize misclassification of study outcomes**
  - Reduce likelihood of biased estimates of associations between exposures and outcomes
  - Have confidence that ascertained outcomes = true events

- **Validated algorithm → majority of events confirmed via medical record review**
  - Preliminary evaluation indicates similar numbers of events with ICD-10-CM diagnoses

- **Algorithm's accuracy may differ by database**
  - Due to differences in setting, practice approaches, patients, disease incidence
  - Algorithms may not be transportable

Ehrentstein V. *Clin Epidemiol* 2017;9:245-50.

Validation of Acute MI Algorithms in Sentinel

Setting	ICD-9-CM	Algorithm	Positive Predictive Value % (95% CI)
Mini-Sentinel Distributed Database[1] • HealthCore • HMO Research Network • Humana • Kaiser	410.x0 410.x1	Hospital Discharge Dx: Primary	86% (79 – 91%)
Sentinel Distributed Database[2] • 13 Data Partners	410.x0 410.x1	Hospital Discharge Dx: Primary	93% (78 – 99%)
		Hospital Discharge Dx: Secondary	88% (72 – 97%)

[1] Cutrona SL. *Pharmacoepidemiol Drug Saf* 2013;22:40-54. Validation performed in random sample of members from specified Data Partners.
[2] Ammann EM. *Pharmacoepidemiol Drug Saf* 2018;27:398-404. Validation performed among members administered immunoglobulin therapy.

Validation of Acute Stroke Algorithms in Sentinel

Setting	ICD-9-CM	Algorithm	Positive Predictive Value % (95% CI)
HealthCore[1]	433.x1 434.x1 436.x4 437.1x, 437.9x	Hospital Discharge Dx: Primary	86% (79 – 91%)
TennCare[2]	433.x1 434 436	Hospital Discharge Dx: Primary	80% (74 – 85%)
Sentinel Distributed Database[3] • 13 Data Partners	433.x1 434.xx 436	Hospital Discharge Dx: Primary	60% (37 – 84%)
		Hospital Discharge Dx: Secondary	42% (28 – 57%)

[1] Wahl PM. *Pharmacoepidemiol Drug Saf* 2010;19:596-603. Validation performed in members administered selective COX-2 inhibitors or non-OTC NSAIDs.
[1] Roumie CL. *Pharmacoepidemiol Drug Saf* 2008;17:20-26. Validation performed in random sample of TennCare members.
[3] Ammann EM. *Medicine* 2018;97:8(e9960). Validation performed among members administered immunoglobulin therapy.

Validation of Acute DVT/PE Algorithms in Sentinel

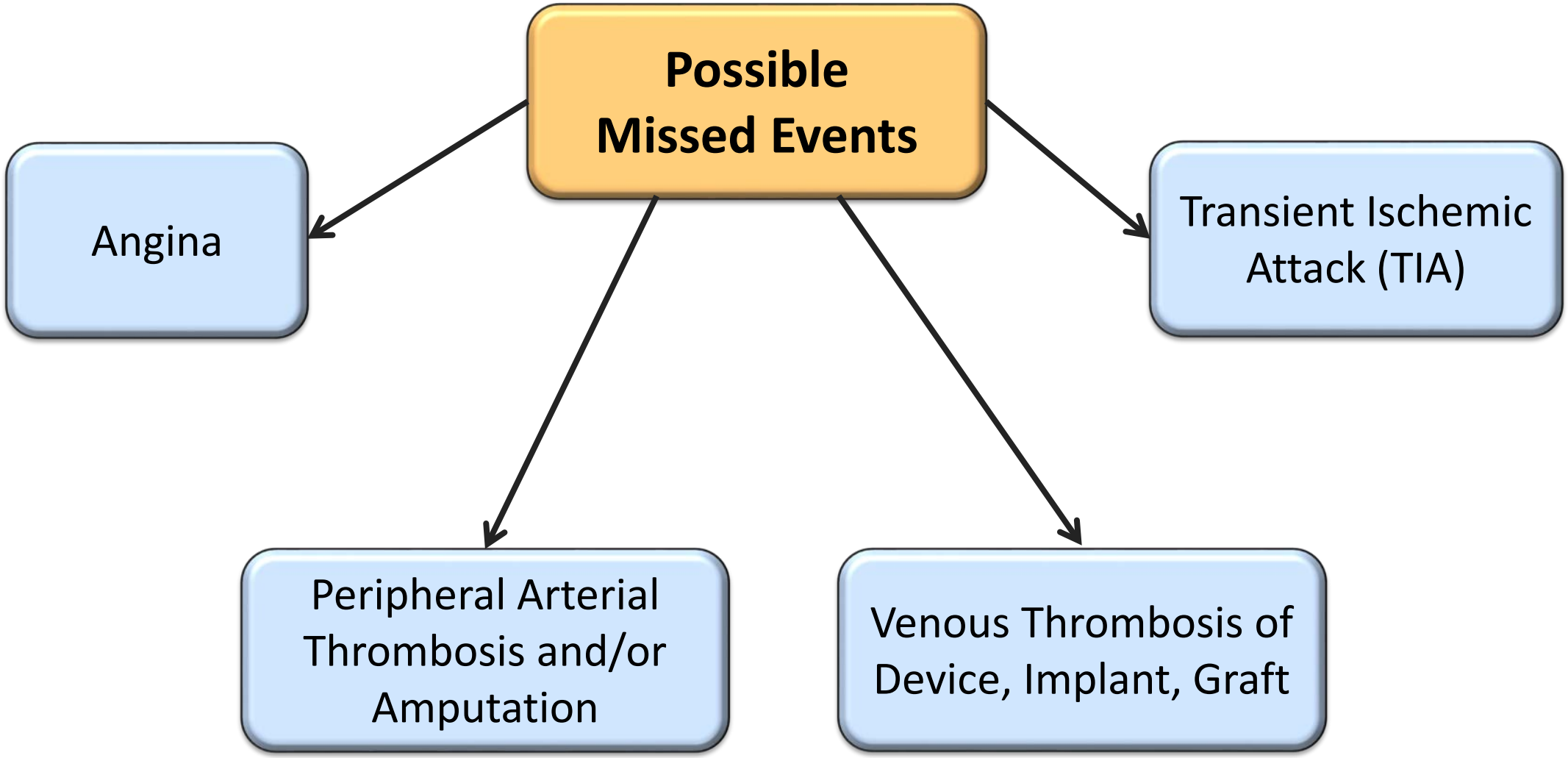
Setting	ICD-9-CM	Algorithm	Positive Predictive Value % (95% CI)
Mini-Sentinel Distributed Database[1] • Aetna • HealthCore • Humana • Optum • TennCare	415.1x 453.x	Hospital Discharge Dx: Primary or Secondary	65% (95% CI not reported)
Sentinel Distributed Database[2] • 13 Data Partners	415.1x 451.1x 453.1, 453.2, 453.4x, 453.9	Hospital Discharge Dx: Primary	90% (73 – 98%)
		Hospital Discharge Dx: Secondary	80% (28 – 99%)

[1] Yih Wk. *Vaccine* 2016;34:172-178. Validation performed among female members aged 9-26 years administered quadrivalent HPV vaccine.
[2] Ammann EM. *Medicine* 2018;97:8(e9960). Validation performed among members administered immunoglobulin therapy.

Additional Study Outcome Considerations - 1: No Validated Thrombosis Algorithms in COVID-19

- **Performance of ICD-10-CM thrombosis algorithms unknown in COVID-19**
- **Thrombotic events may not be primary hospital discharge diagnosis in COVID-19**
  - COVID-19 may be principal hospital discharge diagnosis
  - Arterial, venous thrombotic events may be secondary diagnoses
  - Will need to consider primary or secondary hospital discharge diagnoses
- **Clinicians may empirically treat venous thromboembolism with anticoagulation therapy but no confirmatory diagnosis**
  - COVID-19 precautions, need for prone positioning limit access to diagnostic imaging

Additional Study Outcome Considerations - 2: Possible Missed Events with Existing Algorithms



Secondary Endpoints Under Consideration

- **Primary outcome OR outpatient, ED, or hospital discharge (any position) ICD-10-CM for angina, TIA, peripheral arterial thrombosis, or limb ischemia/amputation**
- **Primary outcome OR dispensed anticoagulant therapy during follow-up (challenging)**
- **Bleeding**
  - Primary/secondary hospital discharge ICD-10-CM for GI bleed, intracranial bleed, epistaxis
- **Death (any cause)**
  - Death occurring outside the hospital may be incompletely captured

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