Natural History of Coagulopathy in COVID-19

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On behalf of the FDA Sentinel COVID-19 Coagulopathy Workgroup

Need for Real-World Evidence on COVID-19

- **Numerous limitations of existing data:**
  - Bulk of evidence from case reports, series
  - Limited sample sizes from single centers
  - Inherent biases (selection, misclassification), lack of control of confounders
- **Sentinel offers unique opportunity for real-world evidence on COVID-19**
  - Epidemiology, natural history of COVID-19
  - Effects of chronic medications taken in ambulatory setting on course of COVID-19
  - Safety, effectiveness of COVID-19 therapies

Reports of Abnormalities in Blood Coagulation

- **Arterial, venous thrombotic events**
  - Arterial occlusion (acute MI, ischemic stroke), even at younger ages
  - Venous thromboembolism (DVT/PE, microthrombi on autopsy)
- **Coagulopathy**
  - ↑ D-dimer, fibrinogen levels
  - Disseminated intravascular coagulation

Thachil J. *J Thromb Haemost* 2020:18:1023-6.

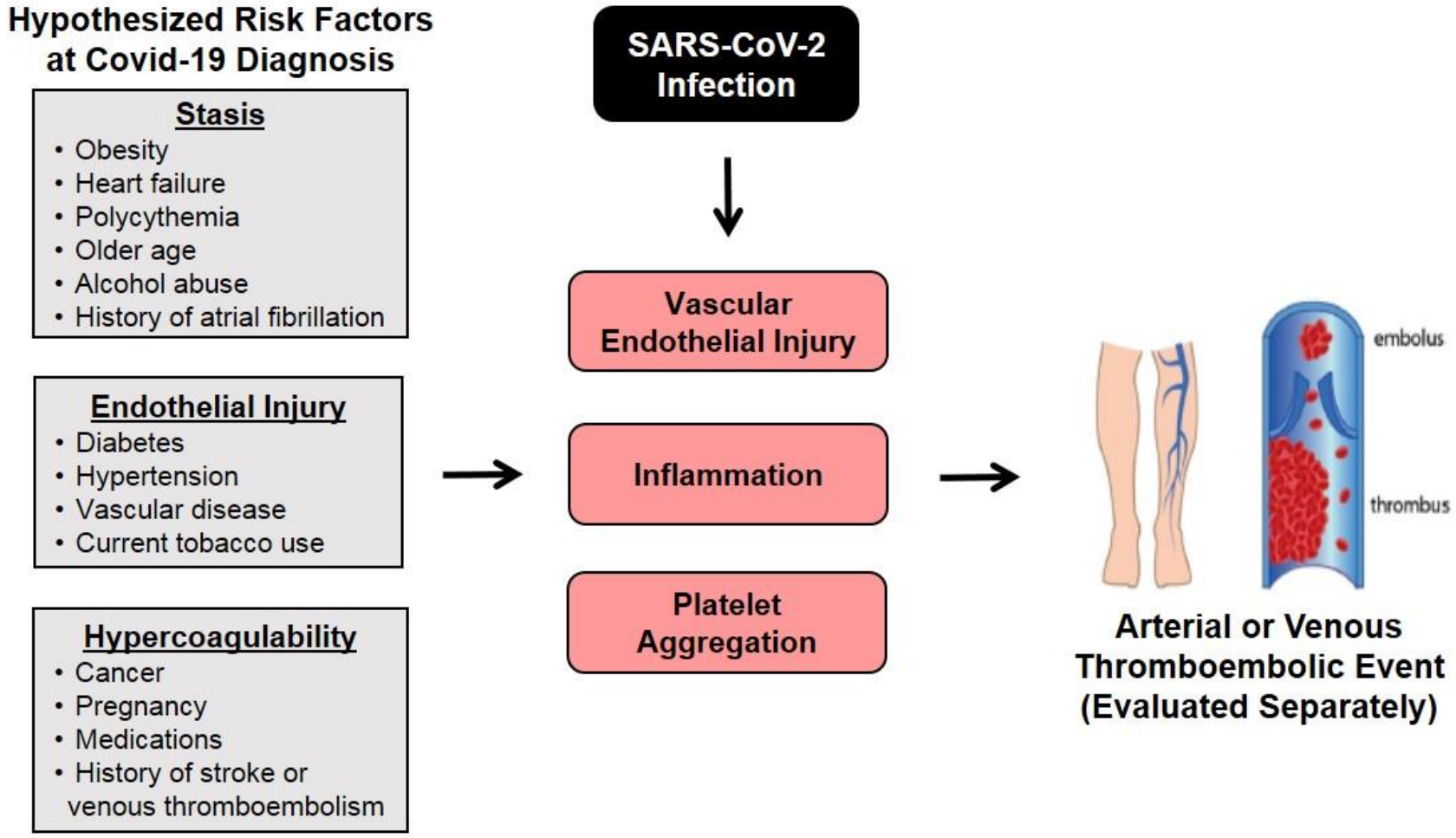
Specific Aims

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

Specific Aims

- **Aim 1**: Determine 90-day incidence of arterial and venous thrombotic events (evaluated separately) with COVID-19 and risk of death within 90 days of an event.
  - Hypothesis: Events will occur within 90 days of COVID-19 diagnosis and may result in death.
- **Aim 2**: Evaluate patient characteristics present prior to 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.

Potential Risk Factors for Thromboembolic Events in COVID-19 (Aim 2)



Kovačič A. *Eur J Clin Pharmacol* 2019;75:751-67; Thachil J. *J Thromb Haemost* 2020;18:1023-6; Moores LK. *Chest* 2020. In Press.

Specific Aims

- **Aim 1**: Determine 90-day incidence of arterial and venous thrombotic events (evaluated separately) with COVID-19 and risk of death within 90 days of an event.
  - Hypothesis: Events will occur within 90 days of COVID-19 diagnosis and may result in death.
- **Aim 2**: Evaluate patient characteristics present prior to 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.

Significance of Study Aims

Biological

- Gain insights into risk factors for thrombotic events with COVID-19
- Determine if risk of events is higher for COVID-19 vs. influenza

Clinical

- Identify interventions to ↓ risk of thrombotic events with COVID-19
- Identify high-risk subgroups to inform decisions, enroll in future trials

Public Health

- Modifying risk factors for thrombotic events could prevent their development and prolong survival

Study Design & Data Source

- **Study design: retrospective cohort study**
- **Data source: Data Partners from FDA's Sentinel Distributed Data Network**
  - Priority data sources: integrated health systems (EHR + claims)
    - Lab data available: COVID-19, influenza, coagulation labs
    - Can identify thrombotic events via outpatient/hospital diagnoses
    - Can determine pre-existing comorbidities, medication exposures at diagnoses
    - Integrated systems minimize missed events
  - Large national insurers (claims)
  - Working with Data Partners to determine feasibility

Platt R. *N Engl J Med* 2018;379:2019-3.

Study Patients (Aims 1 & 2)

	Criteria
Inclusion Criteria	1) COVID-19 ICD-10-CM diagnosis code or positive nucleic acid test between April 1, 2020 and 90 days before study end date* 2) ≥365 days of continuous enrollment at time of diagnosis
Exclusion criteria	Initial COVID-19 test result pending or inconclusive at dataset creation
Selection	All eligible health plan members will be selected

* Study end date to be determined by logistical considerations

Study Patients (Aims 1 & 2)

Inclusion Criteria	1) COVID-19 IC… between April 1, 20… …days before study end date* 2) ≥365 days … …inuous enrollment at time of diagnosis
Exclusion criteria	Initial COVID-19 test result pending or inconclusive at dataset creation
Selection	All eligible health plan members will be selected

Prior thromboembolism increases risk for subsequent event, so will <u>not</u> be an exclusion criterion

* Study end date to be determined by logistical considerations

Study Patients (Aim 3)

	COVID-19 Cohort	Influenza Cohort
Inclusion Criteria	COVID-19 ICD-10-CM diagnosis code or positive nucleic acid test between April 1, 2020 and 90 days before study end date*	Influenza A or B ICD-10-CM diagnosis OR positive nucleic acid test between October 1, 2018 and April 30, 2019
	≥365 days of continuous enrollment at time of diagnosis	
Exclusion criteria	Initial COVID-19 test result pending or inconclusive at dataset creation	Initial influenza result pending or inconclusive at dataset creation
	Coinfection with other respiratory virus	
Selection	All eligible members will be selected	

* Study end date to be determined by logistical considerations

Study Patients (Aim 3)

Ensure that influenza patients do not have COVID-19

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Primary Outcomes: Thromboembolic Events (All Aims)

Arterial Thrombosis

Acute myocardial infarction

Acute ischemic or embolic stroke

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.

Study Outcome Considerations: No Validated Thrombotic 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

Secondary Outcomes (All Aims)

1. Ambulatory, ED, or hospital discharge ICD-10-CM of arterial thrombosis (AMI or stroke) or venous thromboembolism (DVT or PE)

2a. **Arterial**: Meet primary outcome or have ambulatory, ED, or hospital discharge ICD-10-CM of angina, TIA, PAD, or amputation

2b. **Venous**: Meet primary outcome or have ambulatory, ED or hospital discharge ICD-10-CM of venous thrombosis of device, implant, or graft

3. Meet primary outcome or dispensed thrombolytic therapy and/or therapeutic anticoagulation therapy during follow-up

4. Intracranial, upper/lower GI tract, or retroperitoneal bleeding

5. Death (any cause)

Definitions of Risk Factors for Thromboembolic Events (Aim 2)

Category	Risk Factor	Definition
Stasis of Circulation	Obesity	Body mass index >30 kg/m^2
	Heart failure	ICD-10-CM diagnosis codes
	Polycythemia	Hemoglobin >16 gm/dL
	Older age	Will explore different age thresholds
	Alcohol abuse	ICD-10-CM diagnosis codes
Endothelial Injury	Diabetes	ICD-10-CM diagnosis codes or registry
	Hypertension	ICD-10-CM diagnosis codes
	Vascular disease	ICD-10-CM diagnosis codes
	Current tobacco use	Health factors data
Hypercoagulability	Cancer	ICD-10-CM diagnosis codes
	Pregnancy	ICD-10-CM diagnosis codes

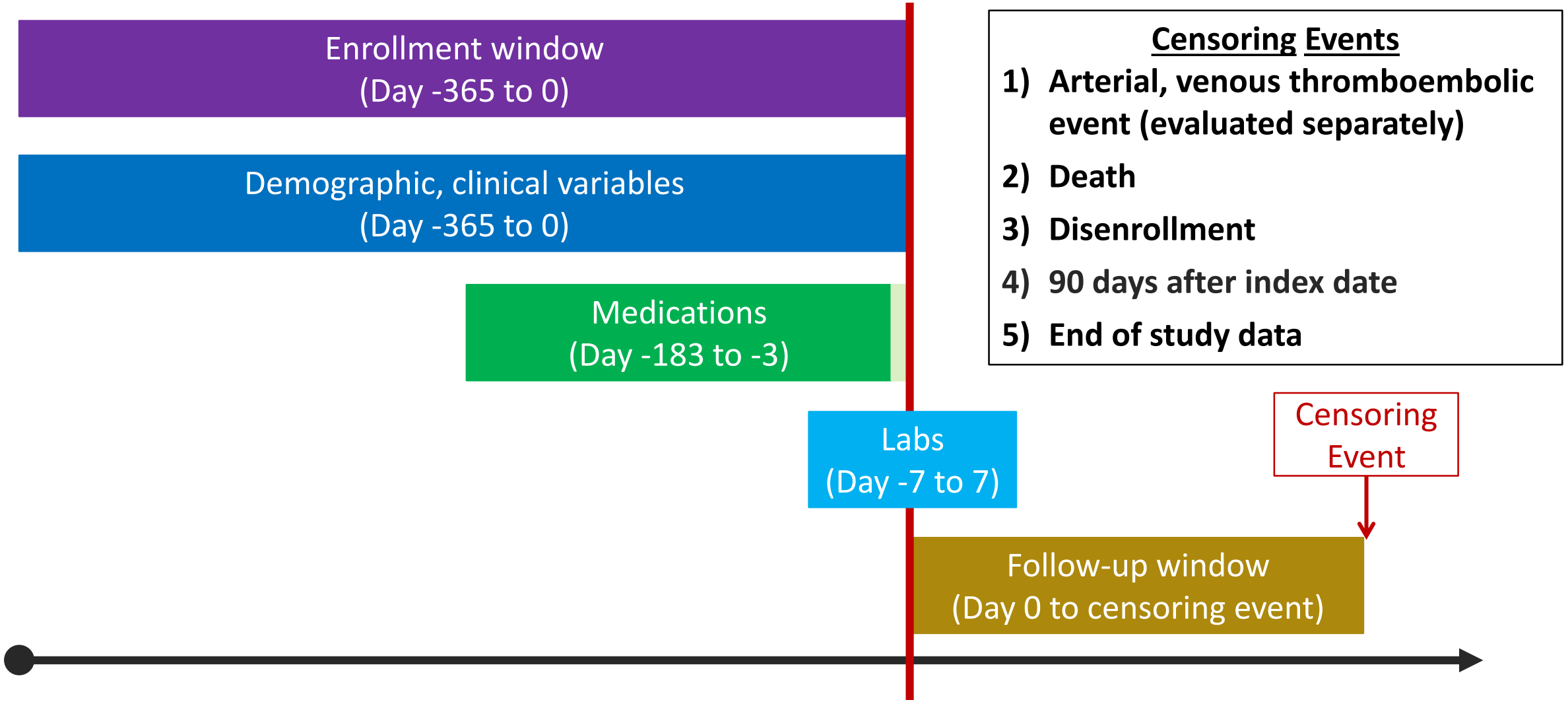
Data Elements (All Aims)

Demographic	Clinical	Laboratory*	Medication/Transfusions†
Enrollment status	Hospitalization	Hemoglobin	Anticoagulants
Age	ICU admission, ventilation	Platelet count	Anti-platelet drugs
Sex	Diabetes	PT/INR/PTT	Oral contraceptives
Race	Hypertension	D-dimer	Estrogen replacement
Body mass index	Vascular disease	Fibrinogen	Testosterone replacement
Location of care	COPD / asthma	Ferritin	Furosemide
Tobacco use	Liver disease	CRP / ESR	Morphine
Alcohol use	Chronic kidney disease	Procalcitonin	Thrombolytic agents
	Malignancy	Factor V Leiden	Blood transfusion
	Prior thromboembolism	Factor VIII	Immunoglobulin transfusion
	Severity of illness at diagnosis	Antiphospholipid Ab	
	Thrombophilia history	ABO blood type	

* On or within +/- 7 days around index date; if multiple results available, will collect closest to index date

† Based on outpatient medication fills between 90 and 3 days prior to index date

Data Analysis: Follow-up



Data Analysis

Aim	Planned Statistical Analyses
Aim 1	Characteristics of COVID-19 cohort Calculate incidence rates (events/1000 persons-years) of thromboembolic events: • Overall, by arterial and venous events • Stratify by age, sex, race, setting of diagnosis (ambulatory, hospital, nursing home) • Stratify by disease severity at diagnosis, prior thromboembolism history • Stratify by baseline anticoagulant use, anti-platelet use Calculate incidence rate of death within 90 days of thromboembolism event
Aim 2	Poisson regression: adjusted RRs (95% CIs) of events for risk factors
Aim 3	Compare characteristics between COVID-19 and influenza cohorts Poisson regression: adjusted RRs (95% CIs) of events in persons with COVID-19 vs. influenza • Stratify by disease severity, setting of diagnosis, prior thromboembolism history

Potential Study Limitations

Limitation	Reasons Limitation May Occur	Methods to Address
Selection Bias	Variations in COVID-19 testing by: • Geography • Calendar time • Disease severity	Sensitivity analyses: • Condition on geography • Restrict to time when testing more available • Stratify on severity, setting at diagnosis (e.g., hospital)
Misclassification	Lack of validation of ICD-10 diagnoses for thromboembolic events	Potentially evaluate the PPV of diagnosis code-based outcome algorithms via chart review in small samples
Uncontrolled Confounding	Incomplete data on race, tobacco, alcohol in some data sources	Sensitivity analyses: • Assess effects of unmeasured confounders on results

Project Status

- **Protocol is complete**
- **Establishing collaborations with multiple Sentinel Data Partners**
  - Integrated delivery system, claims partners
  - Increase sample size, enhance generalizability, permits evaluation of lab data
  - Allows for limited chart review to confirm PPVs of ICD-10-based outcomes
- **Working with Reagan-Udall Foundation**
  - Promote parallel analyses, enhance scientific validity

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Sentinel

Extra Slides

Sentinel COVID-19 Natural History Master Protocol

- **Provides approaches to identify COVID-19 patients in the Sentinel System**
- **Delineates variables relevant to such analyses**
  - Feasibility of collection of these variables within Sentinel's Data Partners
  - Proposed code lists for variables
- **Considers potential limitations of methods, approaches to address**
  - Biases (selection, misclassification, protopathic)
  - Unmeasured confounding variables
  - Generalizability

https://www.sentinelinitiative.org/methods-data-tools/methods/master-protocol-development-covid-19-natural-history

Published Estimates on the Incidence of Thromboembolic Events

Reference	Setting	No. COVID-19 Patients	% Administered DVT Prophylaxis at Admission	Outcome Evaluated	Incidence Of Events
Klok	Netherlands	184 in ICU	100%	Arterial or venous clots	31 (16.8%)
Lodigiani	Italy	48 in ICU	100%	VTE events	8 (16.7%)
Ziehr	USA	66 in ICU (all on ventilator)	Not Reported	VTE events	11 (16.7%)
Llitjos	France	26 in ICU	100%	DVT	13 (50.0%)
Cui	China	81 in ICU	0%	VTE events	20 (24.7%)
Poissy	France	107 in ICU	Not Reported	PE	22 (20.6%)
Goyal	USA	393 hospitalized	Not Reported	VTE events	13 (3.3%)
Cattaneo	Italy	388 hospitalized	100% (enoxaparin 40 mg QD)	DVT	0 (0.0%)
Al-Samkari	USA	400 hospitalized	97.3%	VTE	19 (4.8%)
				Arterial thrombosis	11 (2.8%)

DVT=deep vein thrombosis; ICU=intensive care unit; PE=pulmonary embolism; VTE=venous thromboembolic

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.