Risk of Thromboembolic Events With COVID-19: A Sentinel System Investigation – Potential Aims/Methods

Vincent Lo Re, MD, MSCE, FIDSA, FISPE
Division of Infectious Diseases
Center for Clinical Epidemiology and Biostatistics
University of Pennsylvania

On Behalf of the FDA Sentinel COVID-19 Coagulopathy Workgroup

Penn Infectious Diseases

Sentinel Initiative

CENTER FOR CLINICAL EPIDEMIOLOGY AND BIOSTATISTICS

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

Reports of Coagulopathy, Thromboembolic Events Associated With COVID-19

- Laboratory findings of **coagulopathy**:
  - ↑ D-dimer, fibrinogen levels
  - Disseminated intravascular coagulation (DIC)
- **Thromboembolic events**:
  - Venous thromboembolism (DVT/PE, microthrombi on autopsy)
  - Arterial occlusion (acute MI, stroke), even at younger ages

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

Incidence of Thromboembolic Events Still Unknown

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

Specific Aims of the Sentinel Workgroup Under Consideration

Aim 1: Determine incidence and consequences of thromboembolic events (venous, arterial) with COVID-19.

- Describe anticoagulant, anti-platelet drug use at diagnosis

Aim 2: Identify risk factors for the events in COVID-19.

- Demographics, pre-existing comorbidities, disease severity

Aim 3: Compare risk of thromboembolic events after COVID-19 diagnosis with that after influenza diagnosis.

Significance of Study Aims

Biological

- Gain insights in risk factors for thromboembolism in COVID-19.
- Determine if risk of events is higher for COVID-19 vs. influenza.

Clinical

- Identify interventions to ↓ thromboembolism risk in COVID-19.
- Identify subgroups to monitor closely for clots in COVID-19.

Public Health

- Modifying risk factors for thromboembolic events could help to prevent their development and prolong survival.

Study Design / Data Source

- **Design**: Retrospective cohort study
- **Data Source**: FDA's Sentinel Distributed Data Network
  - Proposed Data Partners: Integrated health systems (EHR+claims)
    - Lab data available → COVID-19 PCR+, influenza, coagulation labs
    - Outpatient/hospital diagnoses → thrombotic events
    - Pre-existing comorbidity diagnoses
    - Medication exposure at COVID-19 diagnosis
    - Integrated systems minimize missed events

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

Study Patients

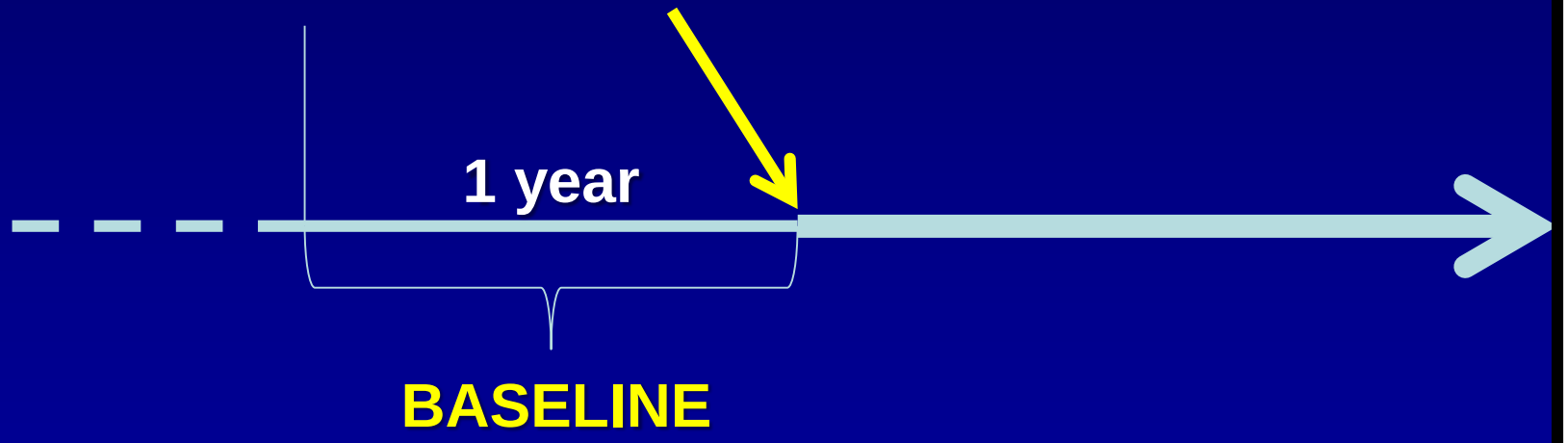
- **Aims 1, 2**
  - COVID-19 diagnosis (Feb. 1, 2020 – June 30, 2020)
- **Aim 3**
  - Inpatient COVID-19 diagnosis (Feb. 1, 2020 – June 30, 2020)
  - Inpatient influenza A or B diagnosis (Oct. 1, 2019 – Dec 31, 2019)
  - Non-overlapping periods to minimize missing coinfections
  - Exclude if diagnosed with both

Patient Follow-up

Index Date

Aims 1,2: Date COVID-19 diagnosed

Aim 3: Date COVID-19, influenza diagnosed



Thrombotic event

Death

90 days after index date*

June 30, 2020

* To enhance likelihood that outcomes are due to infection.

Proposed Study Outcomes

Primary

Thrombotic Complications (composite)

ICD-10 Diagnoses

Secondary

Venous Thromboses

DVT

Pulmonary embolism

Other venous clots (CRRT, ECMO clots)

DIC?

Secondary

Arterial Thromboses

Acute MI, angina

Acute stroke, TIA

Peripheral vascular dz

DIC?

Variables to Collect

Demographic	Clinical	Laboratory	Medications*
Age	Hospitalization	D-dimer	Heparin
Sex	ICU admission, ventilation	Fibrinogen	Anticoagulants
Race	Diabetes	PT/INR	Anti-platelet drugs
Body mass index	Hypertension	PTT	Oral contraceptives
Location of care	Cardiovascular disease	Hemoglobin	
Tobacco use	Peripheral arterial disease	Platelet count	
Alcohol use	COPD / asthma	Ferritin	
	Liver disease	CRP / ESR	
	Chronic kidney disease	Procalcitonin	
	Malignancy	Factor VIII	
	DVT/PE	Antiphospholipid Ab	
	Thrombophilia history		

*Based on fills between 90 and 3 days prior to index date; can explore different exposure windows to minimize protopathic bias.

Potential Study Limitations to Consider

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 • Evaluate outpatients and hospitalized persons
Misclassification	Lack of validation of ICD-10 diagnoses for COVID-19, thrombotic events in some data sources	Evaluate validated diagnoses
Uncontrolled Confounding	Incomplete data on tobacco, alcohol in some data sources	Sensitivity analyses: • Assess effects of unmeasured confounders on results

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