Sentinel

Thrombotic events in outpatient-identified COVID-19

An Analysis in TriNetX Live™

TriNetX

U.S. FOOD & DRUG ADMINISTRATION

November 10, 2020

Background and Study Aims

- NIH-funded RCT investigating whether anticoagulation reduces life-threatening cardiovascular or pulmonary complications in newly diagnosed COVID-19 patients who do not require hospital admission
  - ACTIV-4: *"A Multicenter Adaptive Randomized Double-Blind Placebo Controlled Platform Trial of the Efficacy and Safety of Antithrombotic Strategies in COVID-19 Adults not Requiring Hospitalization at Time of Diagnosis"*
- To inform future sample size calculations, we describe **occurrence of thrombotic events and death** among patients aged 40-79 years not hospitalized at the time of COVID-19 identification

Protocol available at: https://fnih.org/sites/default/files/final/activ-4b.pdf
https://www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ4

Data Source

- TriNetX Live™ USA network: De-identified electronic health record (EHR) data from 64 health care organizations (HCOs)
  - HCOs include hospitals, primary care clinics, and specialty clinics
  - Provide inpatient and/or outpatient information (including laboratory results and vitals)
  - Some HCOs validate death information
  - Individuals may seek care in multiple different HCOs, some of which may not be included in TriNetX
  - Constantly updating, at an average 2-4 week lag from present

Claims vs EHR Data

Administrative Claims	Electronic Health Care Records
• Provide information on medical events that are **billed** and **adjudicated** by a patient's **health insurance** company • Lack information that is not "billable" and paid by the insurance	• Provide information on medical events that are **recorded** in a patient's **medical record** by a **health care organization** • Lack information about events occurring outside of the organization

Study Population: Inclusion

Criteria	ACTIV-4 outpatient trial	Presented analyses
Age	40-79 years	40-79 years
COVID-19 identification	Polymerase chain reaction (PCR)-positive symptomatic COVID infection	• COVID-19 ICD-10 diagnosis (B97.29, U07.1, B34.2, B97.2, J12.81) • COVID-19-positive lab: PCR or antigen
Hospitalization	No hospitalization at time of diagnosis	No hospitalization [-2, 0 days] from COVID-19 record
COVID-19 identification care setting	Diagnosed in emergency department or other appropriate outpatient urgent care setting with on-site physician and blood draw capability	Not factored into these analyses
Pregnancy	Not pregnant or lactating	No evidence of pregnancy [-84, 0 days]
Inflammatory labs	• D-dimer > than the upper limit of normal (ULN) • High-sensitivity C-reactive protein (hs-CRP) > 10mg/L	• Included patients regardless of laboratory values • Subgroup analysis restricted to individuals with d-dimer > ULN and hs-CRP or CRP > 10 mg/L

Study Population: Exclusion

Criteria	ACTIV-4 outpatient trial	Presented analyses
Anticoagulation	Indication for therapeutic anticoagulation or indication for single or dual antiplatelet therapy	Anticoagulant, antiplatelet or thrombolytic use [-183, -2 days] from COVID-19 record
Concomitant medications	Concomitant need for p-gp or CYP3A4 strong inducers/inhibitors	Record of p-gp or CYP3A4 strong inducers/inhibitors [0, 45 days] from COVID-19 record
Bleeding risk	Bronchiectasis/pulmonary cavitation, gastroduodenal ulcer, recent major surgery, recent ischemic stroke, recent intracranial hemorrhage	Bronchiectasis, ischemic stroke, intracranial hemorrhage [-30, 0 days] from COVID-19 record
Cancer	Active cancer	Evidence of cancer [-30, 0 days] from COVID-19 record
Platelets	Platelet count < 100,000 per microliter	N/A
Kidney function	Calculated creatine clearance < 30 ml/min	N/A

Study Outcomes

- Composite of thrombotic events (DVT, PE, MI, ischemic stroke), ascertained in the "hospital" and in "any setting," and all-cause mortality at 45 days
  - Defined using ICD-10 algorithms validated in previous Sentinel analyses
- Other combinations of thrombotic events
- Safety outcome: Major bleeding (including gastrointestinal bleeding, hemoptysis, hemarthrosis, and intracranial hemorrhage) at 75 days using a modified/simplified case-definition[1]
- **Additional endpoint components included in ACTIV-4 but not included in this analysis:**
  - Arterial thromboembolic events other than MI and stroke (no known validated ICD-10 algorithm)
  - Hospitalization for non-thrombotic pulmonary events (i.e. hypoxemia, hypoxemic respiratory failure, ARDS) not analyzed because of the focus on thrombotic events

[1] Cunningham A et al. Pharmacoepidemiol Drug Saf. 2011 Jun;20(6):560-6.
DVT: deep venous thrombosis; MI: myocardial infarction; PE: pulmonary embolism

Subgroup Analyses

- **CRP/hs-CRP**
  - Elevated (> 10 mg/L)
  - Normal (≤ 10 mg/L)
- **D-dimer[1]**
  - Elevated (> 500 ng/mL for FEU; > 250 ng/mL for DDU)
  - Normal (≤ 500ng/mL for FEU; ≤ 250ng/mL for DDU)
- **D-dimer & CRP/hs-CRP**
  - Elevated d-dimer (>500 ng/mL [FEU] or >250 ng/mL [DDU]) and elevated CRP/hs-CRP (>10mg/L)

DDU: d-dimer units; FEU: fibrinogen equivalent units

[1] Bilaloglu S, et al. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. JAMA. 2020;324(8):799

Study Design

Cohort Identification Criteria

COVID-19 Diagnosis (ICD-10 or PCR or antigen +ve test)

Exclusions

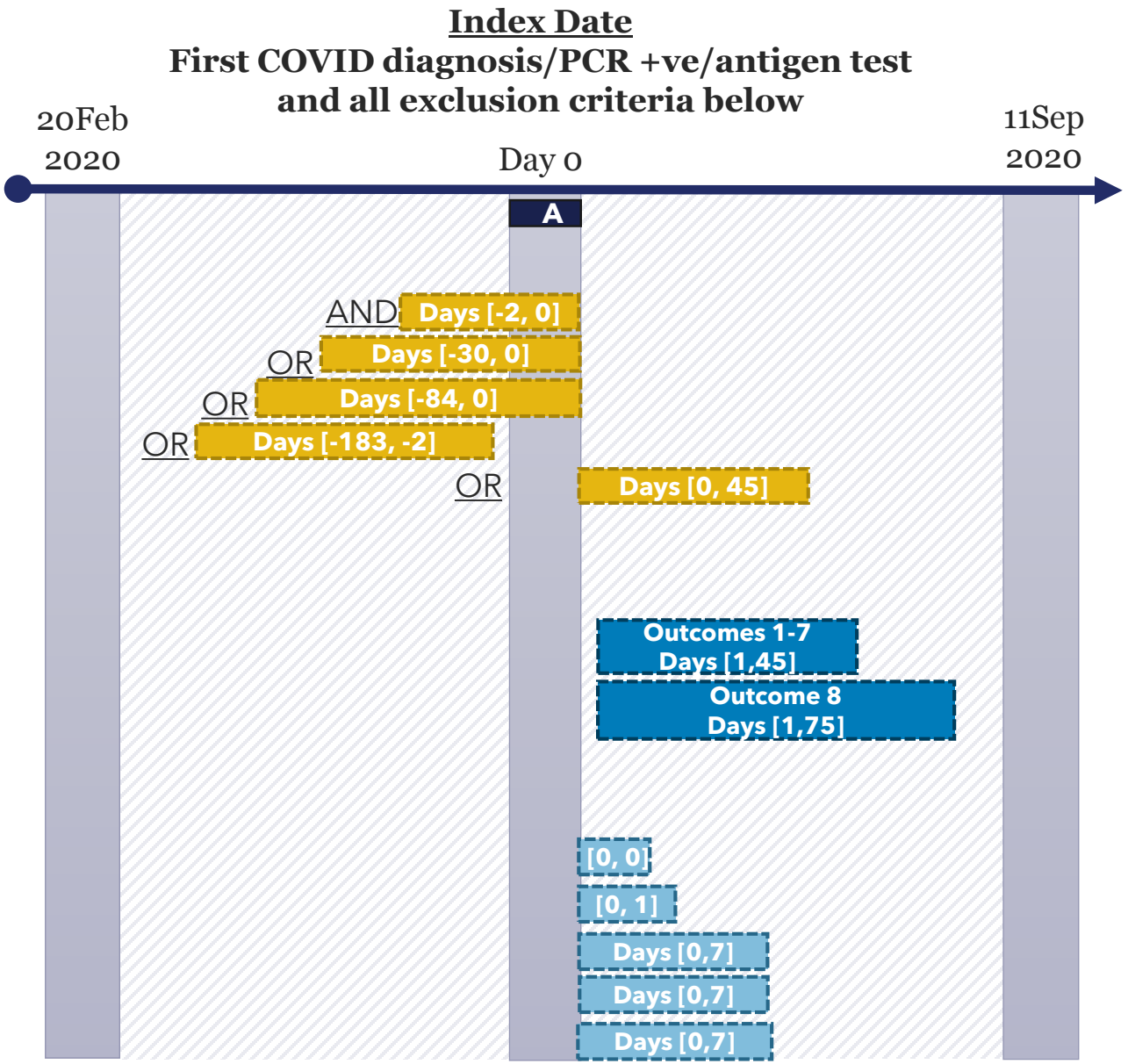
Exclusion 1: No hospitalization [-2,0]
Exclusion 2: Prior conditions (IH, bronchiectasis, IS, and cancer) [-30,0]
Exclusion 3: Pregnancy indicators [-84,0]
Exclusion 4: Anticoagulants/anti-platelet/thrombolytic agents [-183,-2]
Exclusion 5: inhibitors or inducers of p-gp and CYP3A4 [0,45]

Outcomes

Outcome 1: Hospitalized [1,45] + DVT/PE [1,45]
Outcome 2: Hospitalized [1,45] + MI/IS [1,45]
Outcome 3: Hospitalized [1,45] + DVT/PE/MI/IS [1,45]
Outcome 4: Hospitalized [1,45] + Death [1,45]
Outcome 5: Death [1,45]
Outcome 6: Hospitalized [1,45] + DVT/PE/MI/IS/Death [1,45]
Outcome 7: DVT/PE/MI/IS/Death
Outcome 8: Hospitalized [1,75] + Major bleeding [1,75]

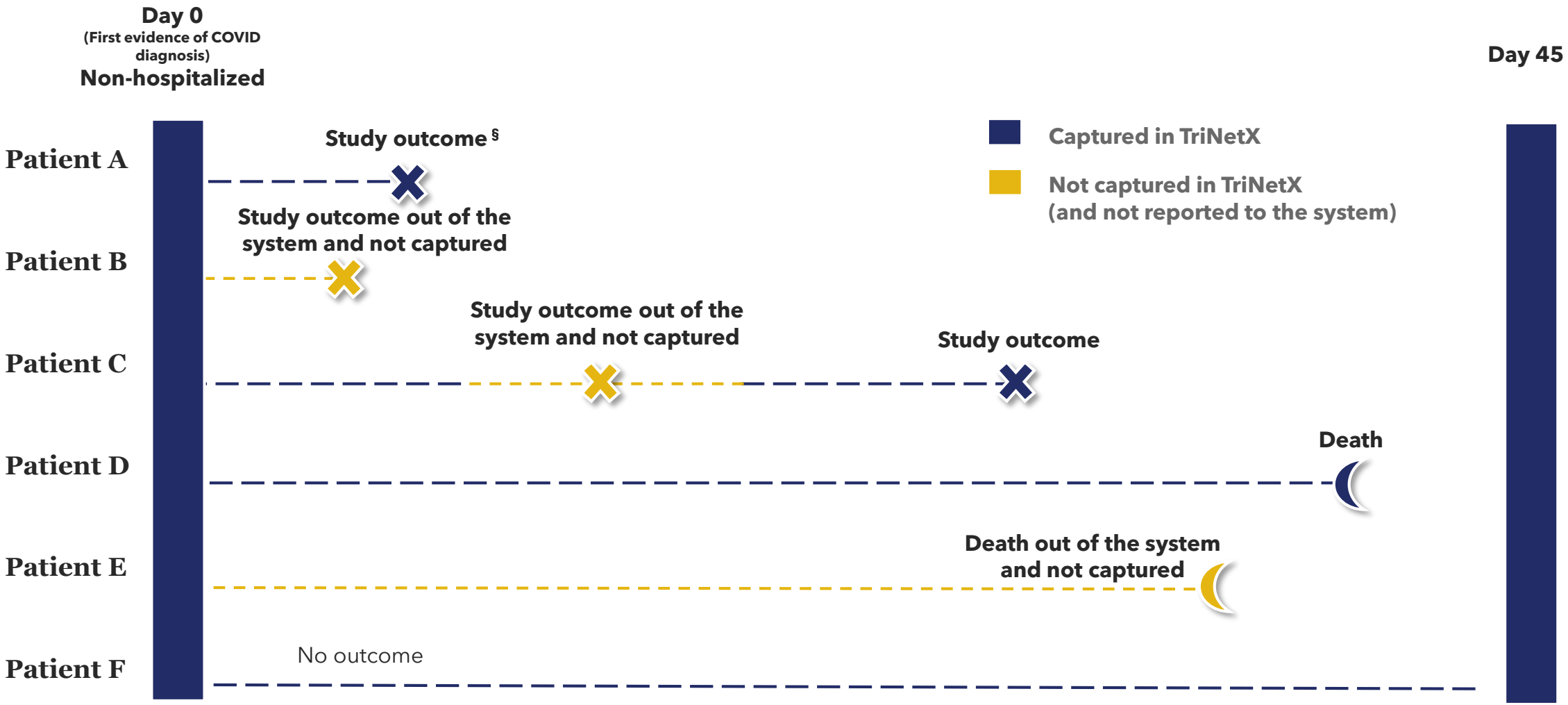
Cohort Characterization (CC) and Stratification (S)

CC1. Method of COVID diagnosis
CC2. S1. Treatment with anticoagulants/antiplatelets/thrombolytics
CC3. S2. D-dimer lab test: Missing, ≥ULN, <ILN
CC4. S3. CRP test: Missing, ≥10mg/L, <10mg/L
CC5. S4. D-dimer ≥ULN & CRP ≥10mg/L



CRP: C-reactive protein; DVT: deep vein thrombosis; IH: intracerebral hemorrhage; IS: ischemic stroke; MI: myocardial infarction; PCR: polymerase chain reaction; PE: pulmonary embolism

Outcome Capture



§All but one study outcome requires hospitalization

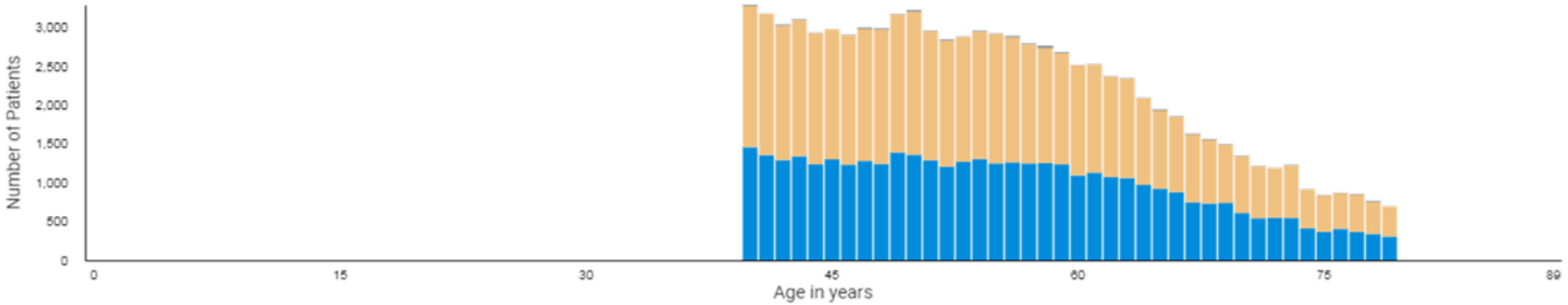
Attrition

	Patients		HCOs
Network	92,513,780		64
Base Population	262,900	(-100%)	61
Population 40 - 79 years, Any sex	135,240	(-49%)	60
Event 1A: Hospitalization [-2,0] The terms in this event occurred between Feb 20, 2020 and Sep 11, 2020 **Must Have:** 94308-4 Sars coronavirus 2 n gene [presence] in unspecified ···	106,910	(-20%)	60
Event 3A: Blood thinners [-183,-2] The terms in this event occurred between Feb 20, 2020 and Sep 11, 2020 **Must Have:** 94307-6 Sars coronavirus 2 n gene [presence] in unspecified ···	93,500	(-13%)	60
Event 2A: Comorbidities [-30,0] The terms in this event occurred between Feb 20, 2020 and Sep 11, 2020 **Must Have:** 94308-4 Sars coronavirus 2 n gene [presence] in unspecified ···	90,620	(-3%)	59
Event 4A: Enzyme inhibitors/enhancers [0... The terms in this event occurred between Feb 20, 2020 and Sep 11, 2020 **Must Have:** 94307-6 Sars coronavirus 2 n gene [presence] in ···	89,920	(-1%)	59
Event 5A: Pregnancy [-84,0] The terms in this event occurred between Feb 20, 2020 and Sep 11, 2020 **Must Have:** 94307-6 Sars coronavirus 2 n gene [presence] in unspecified ···	89,640	(0%)	59
	89,640 Patients		**59** HCOs

All values are rounded up to the highest 10 to protect patient privacy

Baseline Demographics

Base Cohort: Adults (aged 40-79) not hospitalized at the time of their COVID-19 diagnosis



Patients 90 and Older: 0

Total Patients	Minimum Age	Maximum Age	Mean Age	Standard Deviation
89,640	40	79	55	10

Sex

Female	56%
Male	44%
Unknown	0%

Ethnicity

Not Hispanic or Latino	54%
Unknown Ethnicity	30%
Hispanic or Latino	16%

Race

White	52%
Black or African American	23%
Unknown Race	22%
Asian	3%
American Indian or Alask...	0%
Native Hawaiian or Other ...	0%

All values are rounded up to the highest 10 to protect patient privacy

Selected Baseline Characteristics

	Base Cohort (non-hospitalized COVID-19 at diagnosis)	
	n	%
Total Patients	**89,640**	
Method of COVID-19 Diagnosis (not mutually exclusive)		
PCR	43,290	48.3%
Antigen Test	90	0.1%
ICD-10 code	54,210	60.5%
Medications initiated on the same day or the day after index date [0, 1 days]¥		
Any blood thinner	3,310	3.7%
Anticoagulants*	2,780	3.1%
Heparin (excluding heparin flushes)	570	0.6%
LMWH (enoxaparin, dalteparin)	2,140	2.4%
Anti-platelets	1,270	1.4%
Thrombolytics	10	0.0%
Inflammatory/coagulation lab results on the same day or after index date [0, 7 days]		
CRP/hs-CRP		
Elevated (>10 mg/L)	3,120	3.5%
Normal (≤ 10 mg/L)	1,370	1.5%
Not measured	85,150	95.0%
D-dimer		
Elevated (> 500 ng/mL for FEU; > 250 ng/mL for DDU)	770	0.9%
Normal (≤ 500ng/mL for FEU; ≤ 250ng/mL for DDU)	2,420	2.7%
Unknown§	1,070	1.2%
Not measured	85,380	95.2%
D-dimer and CRP/hs-CRP elevated	590	0.7%

¥ Some of these medications may have been initiated in the inpatient setting and/or following a thrombotic event diagnosed within 1 days post-COVID diagnosis;
* Dabigatran, rivaroxaban, warfarin, desirudin, defibrotide, apixaban, argatroban, edoxaban, betrixaban, lepirudin, fondaparinux, heparin, bivalrudin, enoxaparin, dalteparin, tirofiban, and eptifibatide; § There is evidence that there was a lab obtained but no result provided

Outcomes

Total patients	N=89,640	
Outcomes	**n**	**%**
Hospitalized*	2,440	2.7%
Hospitalized DVT or PE	60	0.1%
Hospitalized MI or ischemic stroke	60	0.1%
Hospitalized and death (in-hospital death)	100	0.1%
All-cause death (any setting)	420	0.5%
Hospitalized DVT, PE, MI, or ischemic stroke*	110	0.1%
Hospitalized DVT, PE, MI, ischemic stroke or death*	520	0.6%
Hospitalized or non-hospitalized (any setting) DVT, PE, MI, ischemic stroke, or death*	890	1.0%
Hospitalized major bleeding*	130	0.1%

* Outcomes presented in subsequent slides
All values are rounded up to the highest 10 to protect patient privacy

Outcomes stratified by d-dimer

5.0% of patients with normal d-dimer and 7.8% of patients with elevated d-dimer had DVT, PE, MI, ischemic stroke, or death in any setting

	D-dimer					
	≤ ULN		> ULN		Unknown	
Total patients	n=2420	100.0%	n=770	100.0%	n=1070	100.0%
Outcomes						
Hospitalized	350	14.5%	120	15.6%	90	8.4%
Hospitalized DVT, PE, MI, or ischemic stroke	20	0.8%	10	1.3%	10	0.9%
Hospitalized DVT, PE, MI, ischemic stroke or death	90	3.7%	20	2.6%	90	8.4%
Any setting DVT, PE, MI, ischemic stroke, or death	120	5.0%	60	7.8%	90	8.4%
Hospitalized major bleeding	20	0.8%	10	1.3%	10	0.9%

D-dimer values resulted [0, 7] days from COVID-19 identification
All values are rounded up to the highest 10 to protect patient privacy

Outcomes stratified by CRP/hs-CRP

2.9% of patients with normal CRP and 6.7% with an elevated CRP had DVT, PE, MI, ischemic stroke, or death in any setting

	CRP/hs-CRP			
	≤ 10mg/L		> 10mg/L	
Total patients	n=1370	100.0%	n=3120	100.0%
Outcomes				
Hospitalized	190	13.9%	380	12.2%
Hospitalized DVT, PE, MI, or ischemic stroke	10	0.7%	10	0.3%
Hospitalized DVT, PE, MI, ischemic stroke or death	30	2.2%	140	4.5%
Any setting DVT, PE, MI, ischemic stroke, or death	40	2.9%	210	6.7%
Hospitalized major bleeding	10	0.7%	20	0.6%

CRP values resulted [0, 7] days from COVID-19 identification
All values are rounded up to the highest 10 to protect patient privacy

Outcomes stratified by d-dimer and CRP/hs-CRP

Trial inclusion criteria

6.8% of patients with an elevated D-dimer and CRP/hs-CRP had had DVT, PE, MI, ischemic stroke, or death in any setting

	D-dimer > ULN and CRP/hs-CRP > 10mg/L	
Total patients	n=590	100.0%
Outcomes		
Hospitalized	100	16.9%
Hospitalized DVT, PE, MI, or ischemic stroke	10	1.7%
Hospitalized DVT, PE, MI, ischemic stroke or death	20	3.4%
Any setting DVT, PE, MI, ischemic stroke, or death	40	6.8%
Hospitalized major bleeding	10	1.7%

CRP values resulted [0, 7] days from COVID-19 identification
All values are rounded up to the highest 10 to protect patient privacy

Limitations, Part 1

- Unable to capture events occurring outside of the HCOs providing data → underestimation?
- Counts rounded up → overestimation?
- Date-stamps for data within a single healthcare encounter not visible in application, limiting the ability to assess temporality of events
- Confounding by indication?
  - Patients at higher risk for thrombotic events (esp. those with elevated D-dimer and/or CRP/hs-CRP) may have been treated with anticoagulant therapy shortly after COVID-diagnosis

Limitations, Part 2

- Sample was relatively young and more female → affects counts and limits generalizability
- Tested asymptomatic patients may have been included in this analysis → underestimation?
- Arterial thromboembolic events (other than MI and stroke) and hospitalization for non-thrombotic pulmonary events (i.e. hypoxemia, hypoxemic respiratory failure, ARDS) were not evaluated in this analysis

Limitations, Part 3

- Major bleeding definition simplified for this analysis → underestimation?
- Algorithms used in this analysis haven't been validated in EHR-only data sources (versus a claims-based source)
- Small sample sizes → no stratification by medication use for individuals with elevated D-dimer and/or CRP/hs-CRP

Conclusions, Part 1

- >95% of patients had **no data available** for D-dimer or CRP/hs-CRP
  - *Among those who had data,* ~70% had elevated CRP/hs-CRP
  - *Among those who had data,* ~18% had elevated d-dimer
  - *Among those who had data,* ~25% had a d-dimer value without units
  - We identified *~0.7% of COVID-19 patients with both elevated d-dimer and CRP/hs-CRP levels*
- Approximately **3.7%** of patients had record of an **anticoagulant, antiplatelet, or thrombolytic medication** on [0, 1 days] **after COVID-19** identification

CRP/hs-CRP > 10mg/L is elevated; d-dimer > 500 ng/mL FEU or > 250 ng/mL is elevated

Conclusions, Part 2

- Among COVID-19 patients with both elevated D-dimer and CRP/hs-CRP levels:
  - **3.4%** developed DVT, PE, MI, ischemic stroke or death in the **inpatient setting**
  - **6.8%** developed DVT, PE, MI, ischemic stroke or death in **any care setting**
- Comparable to the 4-12% estimation used to inform sample size calculations in the ACTIV-4 outpatient clinical trial
  - *The trial will include additional arterial thromboembolic events and non-thrombotic pulmonary events*
- Also similar to published estimates of ~3-5% for VTE and 2.8% in arterial thrombotic events in a non-ICU setting[1, 2]

[1] Goyal P at al. Clinical Characteristics of Covid-19 in New York City. *N Engl J Med*. 2020 Jun 11;382(24):2372-2374.; [2] Al-Samkari et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood*. 2020 Jul 23;136(4):489-500.
Primary outcome: Composite endpoint of deep venous thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, & mortality ≤ 45 days post-COVID-19

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- The views expressed in this presentation are those of the presenter and do not necessarily reflect those of the FDA

Sentinel

Thank You

Extra Slides

TRINETX: THE GLOBAL RESEARCH NETWORK

Largest network of healthcare organizations, biopharmaceutical companies and contract research organizations working together to improve clinical research

REAL-WORLD DATA

Real-time access to patient populations, driven and refreshed by electronic medical record (EMR) data, to determine protocol feasibility, cohort analysis and site identification

- Demographics
- Lab Results
- Genomics
- Medications
- Diagnoses
- Patient Location
- Provider Notes (NLP)
- Vitals
- Mortality
- Oncology
- Tumor Registry
- Procedures
- Longitudinal Patient History
- Data Linking

Federated Model Attracting Leading Healthcare Organizations (HCOs)

USA NETWORK

- Academic and community health systems
- Primary through tertiary care for adults and children
- Rounded patient counts

90M PATIENTS

67 HCOs

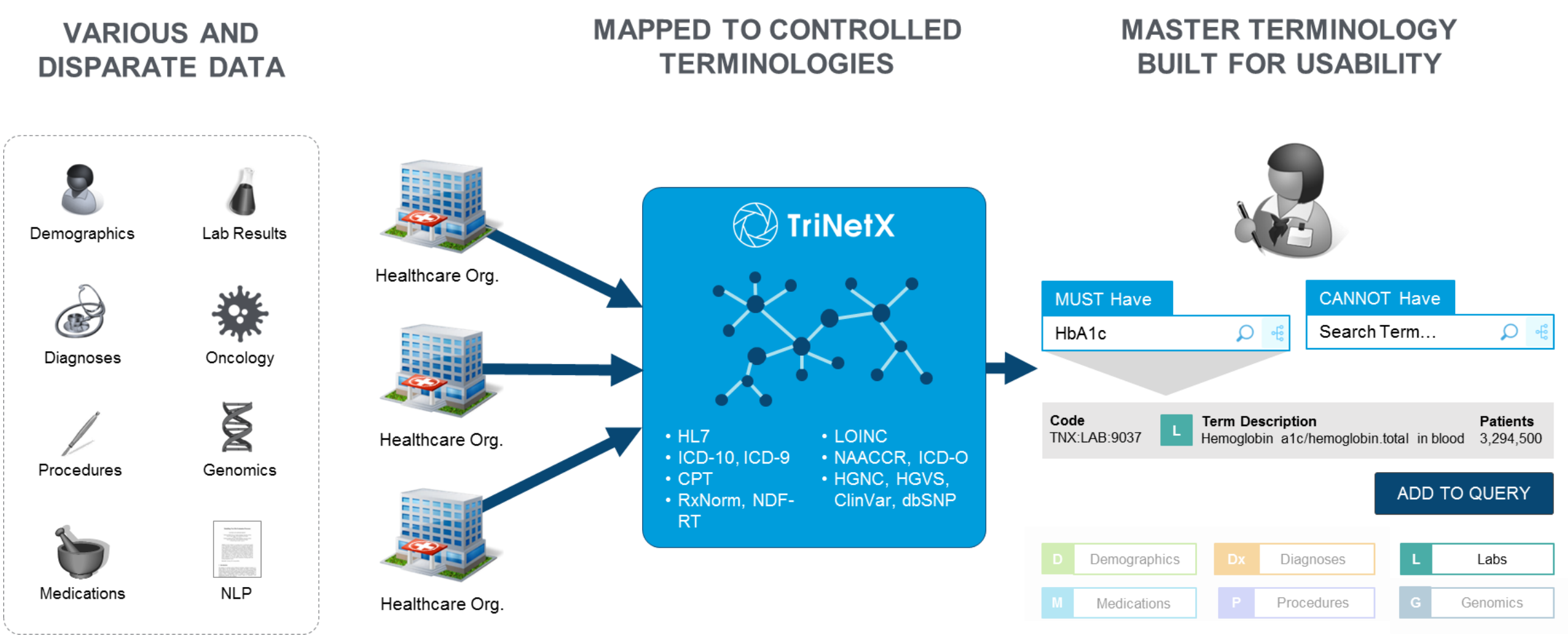
27 STATES

Real-World Evidence Generation

THE LANCET · Annals of the Rheumatic Diseases · PLOS MEDICINE · PREVENTING CHRONIC DISEASE PUBLIC HEALTH RESEARCH, PRACTICE, AND POLICY · International Journal of Stroke · WSO · The American Journal of Cardiology · JCO Clinical Cancer Informatics An American Society of Clinical Oncology Journal · Gastroenterology · aga American Gastroenterological Association · BRAIN, BEHAVIOR, and IMMUNITY · Disability and Health Journal · AIDS · MAYO CLINIC PROCEEDINGS

89+ TRINETX CITATIONS IN GOOGLE SCHOLAR

TriNetX Process Flow



Published estimates on the incidence of thrombotic events in COVID-19

Reference	Setting	No. COVID-19 Patients	Outcome Evaluated	Incidence Of Events
Klok et al., Thromb Res, 2020	Netherlands	184 in ICU	Arterial or venous clots	31 (16.8%)
Lodigiani et al., Thromb Res, 2020	Italy	48 in ICU	VTE events	8 (16.7%)
Ziehr et al., Am J Respir Crit Care Med, 2020	USA	66 in ICU	VTE events	15 (22.7%)
Llitjos et al., J Thromb Haemost, 2020	France	26 in ICU	DVT	18 (69.0%)
Cui et al., Thromb Haemost, 2020	China	81 in ICU	VTE events	20 (24.7%)
Poissy et al., Circulation, 2020	France	107 in ICU	PE	22 (20.6%)
Goyal et al., N Engl J Med, 2020	USA	393 hospitalized	VTE events	13 (3.3%)
Cattaneo et al., Thromb Haemost, 2020	Italy	388 hospitalized	DVT	0 (0.0%)
Al-Samkari at al., Blood, 2020	USA	400 hospitalized	VTE	19 (4.8%)
			Arterial thrombosis	11 (2.8%)

DVT=deep vein thrombosis; ICU=intensive care unit; PE=pulmonary embolism; VTE=venous thromboembolic
Clicking on the references will link to the Pubmed abstract

Note about d-dimer

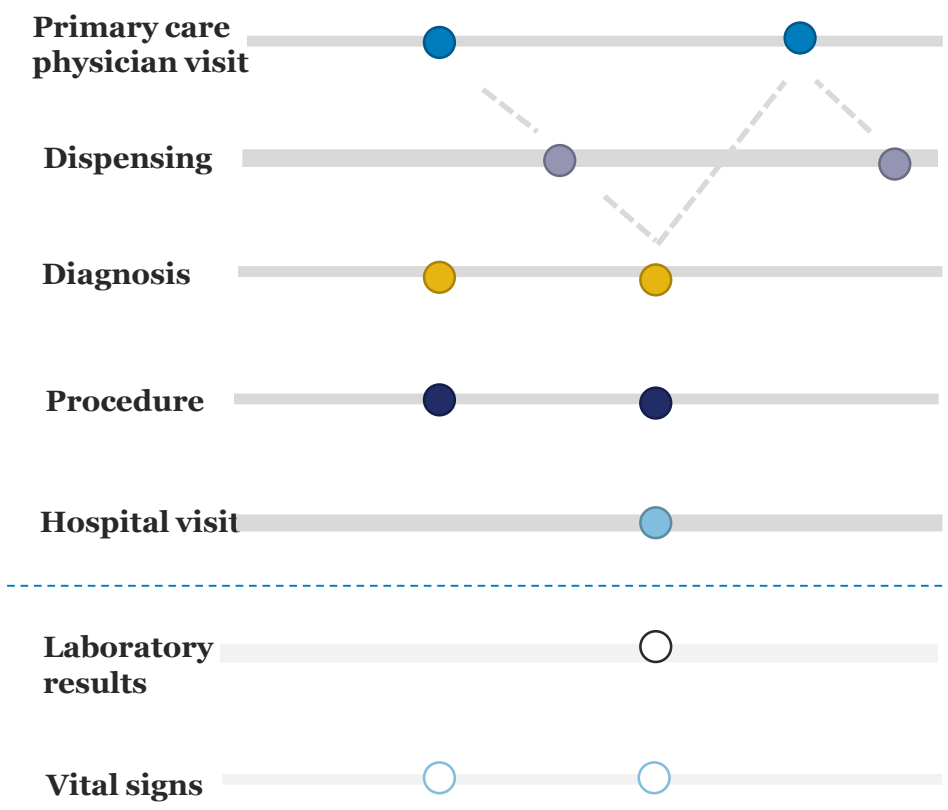
- 2.6% of patients with D-dimer>ULN experienced DVT, PE, MI, ischemic stroke or death in the inpatient setting, compared to 3.8% w/ normal d-dimer<ULN
- These estimates may not be different but potential explanations for the observation may include:
  - Sample sizes are small & error around these estimates may overlap
  - Estimates are crude/unadjusted (group differences may have contributed)
  - Patients w/elevated d-dimer may have been more likely to be treated w/anticoagulation, decreasing risk
    - Small sample size precluded investigation of anticoagulation
  - A relatively high number (n=1,040) of individuals with D-dimers had no units reported; unclear how these missing results may have contributed to the observed findings

Primary outcome: Composite endpoint of deep venous thrombosis [DVT], pulmonary embolism [PE], myocardial infarction [MI], ischemic stroke, and all-cause mortality for up to 45 days after index date

Comparing Claims Data vs. EHR Data

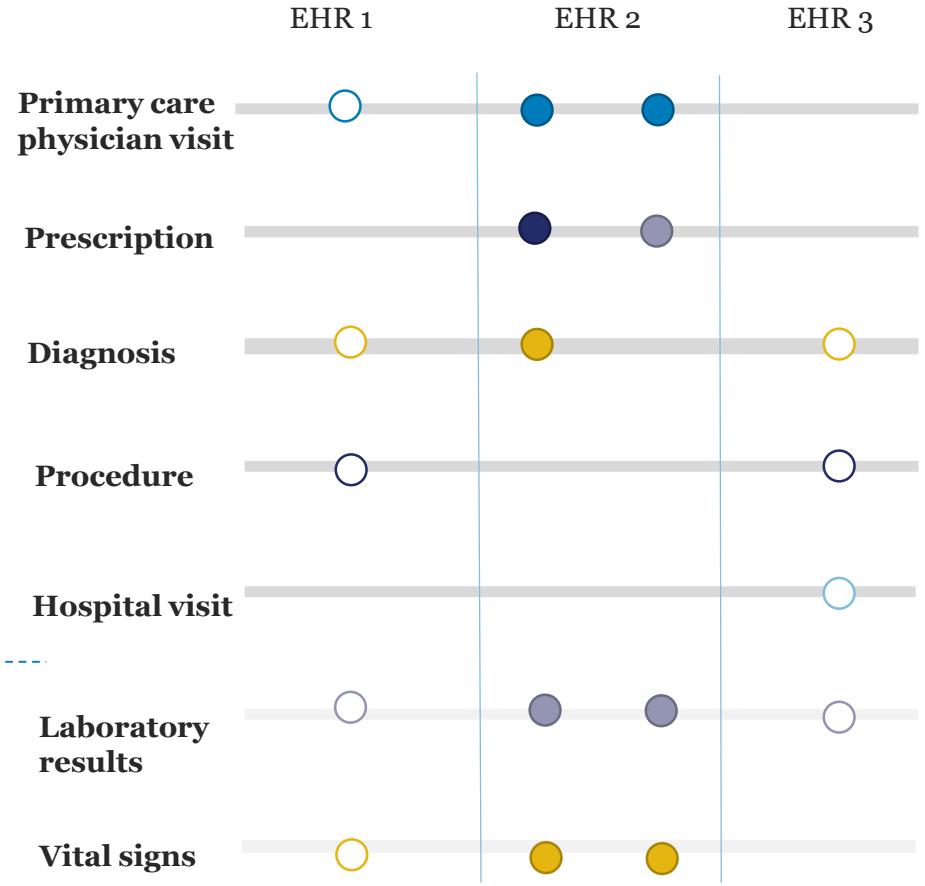
Claims Data

Comprehensive data across all encounters and settings
Miss some clinical detail



EHR Data

Detailed data within a single encounter that miss other encounters



Solid circles = captured data; Open circles = missing data