



# Thrombotic events and death in inpatient-identified COVID-19

An Analysis in TriNetX Live™



**U.S. FOOD & DRUG  
ADMINISTRATION**

# Background

- NIH-funded RCT investigating anti-thrombotic strategies to increase the number of days free of organ support, reduce death, and reduce arterial and venous thrombotic events
  - ACTIV-4a: “A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19”
  - Stratified by d-dimer level and intensive care status
    - Limited information on background event rates

# Current Study Aims

- Among hospitalized non-pregnant adults aged 18+ years with COVID-19, describe the **proportion of patients**:
  - **With thrombotic events or death** through 28 days
- Provide estimates overall and stratified by d-dimer values and early intensive care indicators

# Data Source

- TriNetX Live™ USA network: De-identified electronic health record (**EHR**) data from 65 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, with an average 2-4 week lag from present

# Study Design

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# Inclusion criteria

Criteria	ACTIV-4a inpatient trial	TriNetX analyses
<b>Age</b>	18+ years	18+ years
<b>Hospitalization</b>	Hospitalized <b>for</b> COVID-19	Hospitalized <b>with</b> COVID-19 <sup>1</sup>
<b>COVID-19 identification</b>	Positive SARS-CoV-2 laboratory test ( <i>OK if high clinical suspicion and confirmation expected ≤ 24 hours</i> )	<ul style="list-style-type: none"> <li>COVID-19 ICD-10 diagnosis (B97.29, U07.1, B34.2, B97.2, J12.81) <b>OR</b></li> <li>SARS-CoV-2-positive lab: PCR or antigen</li> </ul>
<b>Enrollment or cohort entry</b>	Within 72 hours of hospitalization or COVID-19 test	COVID-19 identification ± 72 hours of hospitalization code
<b>Duration of hospitalization</b>	Expected to require hospitalization for > 72 hours	Not assessed in these analyses

<sup>1</sup>No information on primary or admitting diagnoses

# Exclusion criteria

Criteria	ACTIV-4a inpatient trial	TriNetX analyses
<b>Life expectancy</b>	Imminent death	Death on days [-1, 0]*
<b>Tracheostomy</b>	Requirement for chronic mechanical ventilation via tracheostomy prior to hospitalization	Evidence of tracheostomy on days [-30, 0]*
<b>Pregnancy</b>	Pregnant	No evidence of pregnancy on days [-84, 0]*
<b>Bleeding risk</b>	Known bleeding within the last 30 days requiring ER or hospitalization; inherited/active acquired bleeding disorder; history of HIT	Major bleeding event, hemophilia, von Willebrand disease, or HIT on days [-30, 0]*
<b>Anticoagulation</b>	Indication for therapeutic anticoagulation or indication for single or dual antiplatelet therapy	Anticoagulant, antiplatelet or thrombolytic use on days [-183, -2]* or thrombosis (PE, DVT, MI, IS) on days [-1, 0]*
<b>Platelets</b>	Platelet count < 50x10 <sup>9</sup> /L	Platelet count < 50x10 <sup>9</sup> /L on days [0, 3]*
<b>Hemoglobin</b>	Hemoglobin < 8 g/dL	Hemoglobin < 8 g/dL on days [0, 3]*

\* Timeframe relative to index : first date a patient was both hospitalized and had evidence of COVID-19 while meeting all exclusion criteria

DVT: deep vein thrombosis; ER: emergency room; HIT: heparin-induced thrombocytopenia; IS: ischemic stroke, MI: myocardial infarction; PE: pulmonary embolism

# Outcomes

Outcome	ACTIV-4a inpatient trial	TriNetX analyses
<b>An ACTIV-4a Secondary Outcome</b>	Composite at earlier of discharge or 28 days <sup>1</sup> <ul style="list-style-type: none"> <li>• Death, DVT, PE, systemic arterial thromboembolism, MI, or IS</li> </ul>	Composite at 28 days of: <ul style="list-style-type: none"> <li>• Death or (hospitalized DVT, PE, MI, or IS)<sup>2,3</sup></li> </ul>

<sup>1</sup> Other secondary endpoints with individual and combination outcomes; <sup>2</sup> DVT, PE, MI, or IS defined using ICD-10 codes

<sup>3</sup> Systemic arterial thromboembolism not included

DVT: deep vein thrombosis; ER: emergency room; HIT: heparin-induced thrombocytopenia; IS: ischemic stroke, MI: myocardial infarction; PE: pulmonary embolism



# Subgroup Analyses

- **D-dimer**<sup>1</sup> on days [0, 3] around the index date<sup>2</sup>
  - Elevated (> 500 ng/mL for FEU; > 250 ng/mL for DDU)
  - Normal ( $\leq$  500ng/mL for FEU;  $\leq$  250ng/mL for DDU)
  - Ambiguous (D-dimer values were recorded but no units were specified)
- **Intensive care** indicators on days [0, 3] around the index date<sup>2</sup>
  - Yes: Record of invasive mechanical ventilation, ECMO, or vasopressors; evaluation/management CPT codes for critical care
  - No: None of above

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

<sup>2</sup> Index date: first date a patient was both hospitalized and had evidence of COVID-19 while meeting all exclusion criteria

CPT: Current Procedural Terminology; DDU: d-dimer units; ECMO: extracorporeal membrane oxygenation; FEU: fibrinogen equivalent units

# Design Diagram

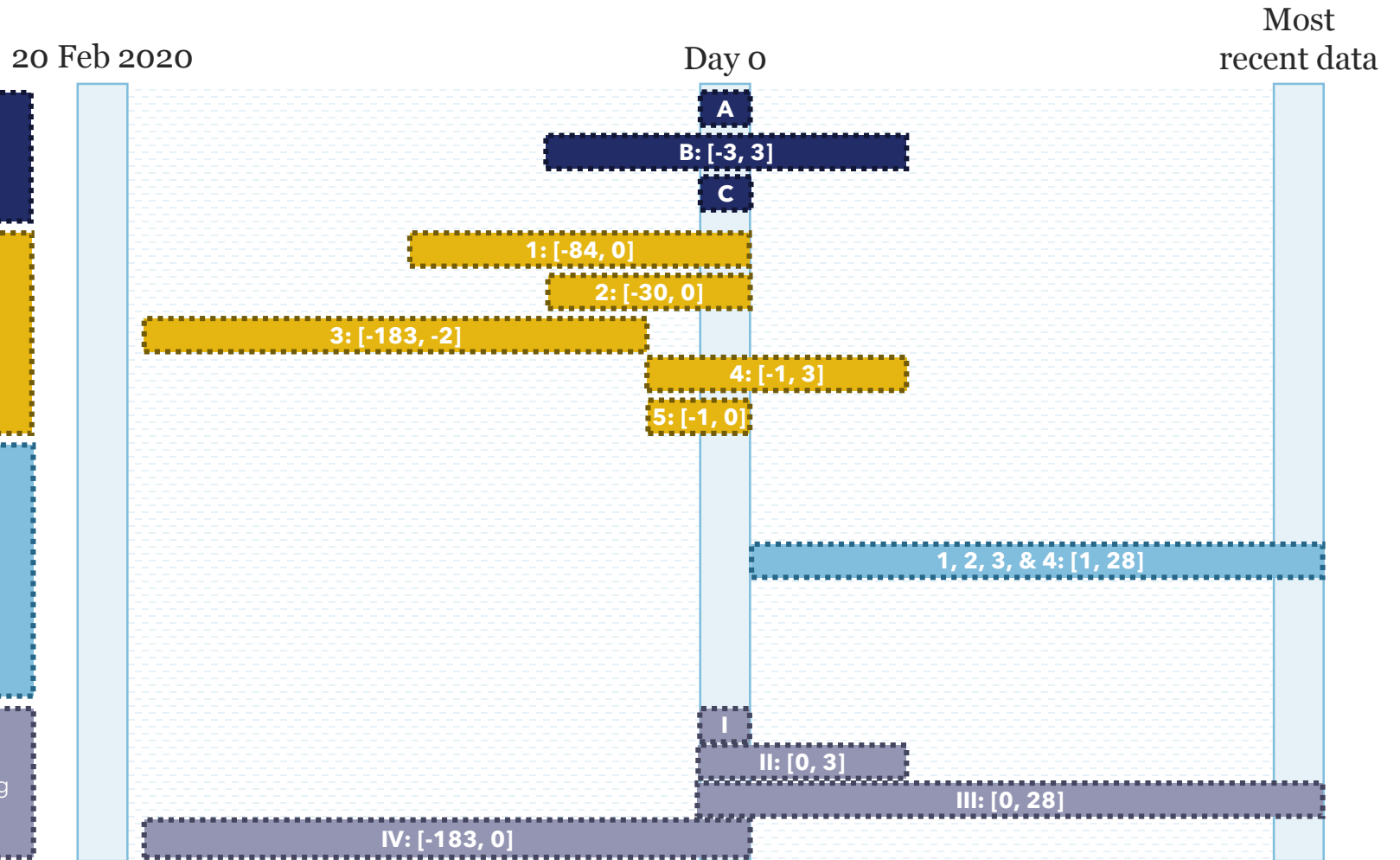
**Cohort Entry: 20 Feb – 16 Oct 2020**  
*Hospitalized with COVID-19*

**Cohort Identification Criteria Assessment**  
 Criteria A: Inpatient visit  
 Criteria B: COVID-19 positive (diagnosis, PCR, or antigen)  
 Criteria C: ≥ 18 years old

**Exclusion Criteria Assessment**  
 Exclusion 1: Pregnancy  
 Exclusion 2: Prior bleeding risk or tracheostomy  
 Exclusion 3: Prior anticoagulant, antiplatelet, or antithrombotic use  
 Exclusion 4: Low platelet and/or hemoglobin  
 Exclusion 5: DVT, PE, MI, IS, or death prior to entry or at index date

**Outcome Assessment**  
 Outcome 1: Hospitalized DVT, PE, MI, IS, or all-setting mortality  
 Outcome 2: Hospitalized DVT, PE  
 Outcome 3: Hospitalized MI, IS  
 Outcome 4: Any DVT, PE, MI, IS, or all-setting mortality

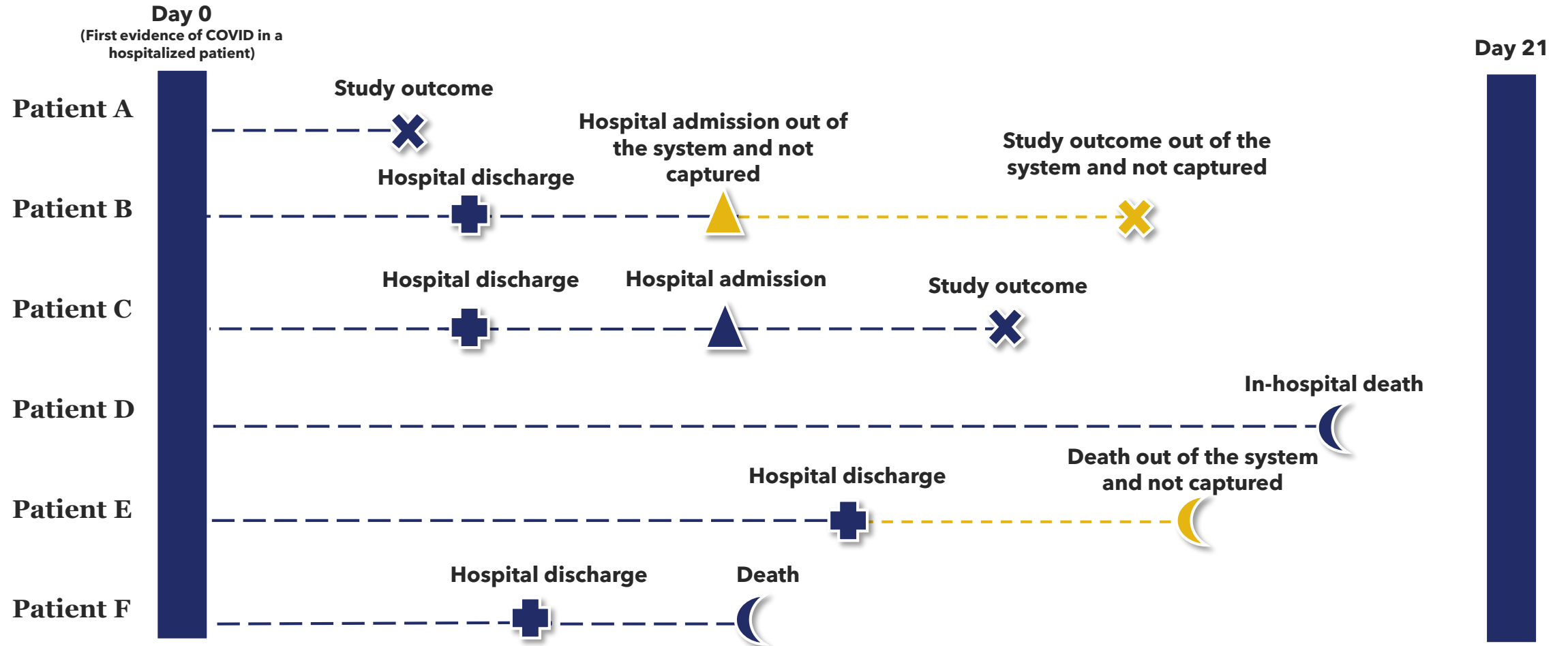
**Cohort Characteristics Assessment**  
 I: Age, sex, race, COVID-19 identification  
 II: Baseline labs; anticoagulant/antiplatelet/antithrombotic; care setting  
 III: Other concurrent medications  
 IV: BMI measurement



BMI: body mass index; DVT: deep vein thrombosis; ECMO: extracorporeal membrane oxygenation; IH: intracerebral hemorrhage; IS: ischemic stroke; MI: myocardial infarction; PCR: polymerase chain reaction; PE: pulmonary embolism

# Outcome Capture

- Captured in TriNetX
- Not captured in TriNetX (and not reported to the system)



# Results

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# Attrition

**Figure 1. Base Cohort Attrition**

	Patients		HCOs <sup>†</sup>
Network <sup>*</sup>	97,728,960		65
Base Population <sup>‡</sup> <a href="#">See All</a>	50,040	(-100%)	55
Population ≥ 18 years, Any sex	50,040	(0%)	55
✓ Event 3A: prior medications The terms in this event occurred between Feb 17, 2020 and Oct 19, 2020 Must Have: 94307-6 Sars coronavirus 2 n gene [presence] in unspecified ...	30,980	(-38%)	55
✓ Event 6A: Exclude Major Bleed/PE/DVT/MI/... The terms in this event occurred between Feb 17, 2020 and Oct 19, 2020 Must Have: Visit: inpatient encounter ≥ 18 years OR ...	27,800	(-10%)	55
✓ Event 4A: Pregnancy The terms in this event occurred between Feb 17, 2020 and Oct 19, 2020 Must Have: 94307-6 Sars coronavirus 2 n gene [presence] in unspecified ...	25,920	(-7%)	55
✓ Event 2A: pre-existing diagnoses The terms in this event occurred between Feb 17, 2020 and Oct 19, 2020 Must Have: 94308-4 Sars coronavirus 2 n gene [presence] in ...	24,580	(-5%)	55
✓ Event 5A: PLT /Hgb The terms in this event occurred between Feb 17, 2020 and Oct 19, 2020 Must Have: 94307-6 Sars coronavirus 2 n gene [presence] in unspecified ...	23,580	(-4%)	55
	<b>23,580<sup>§</sup></b>		<b>55</b>
	Patients		HCOs

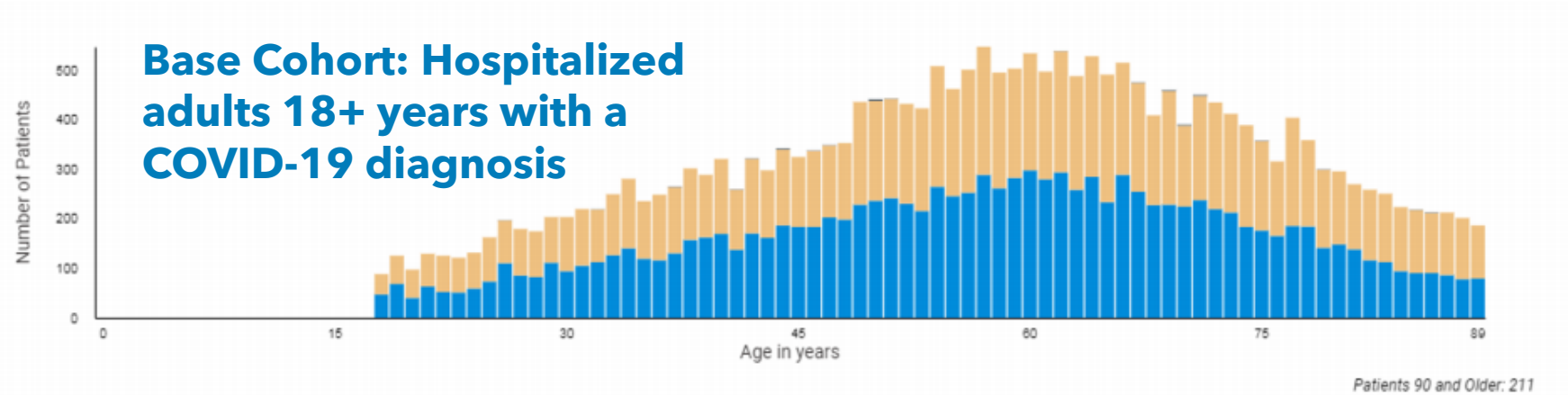
\* Network refers to the TriNetX™ USA Network

† HCOs refers to the number of HCOs who contributed at least one patient to the cohort

‡ Base population refers to the number of patients with inpatient records from 20 February – 16 October 2020 AND a COVID-19 record (positive laboratory test or ICD-10-CM code) from 3 days before to 3 days after the inpatient record

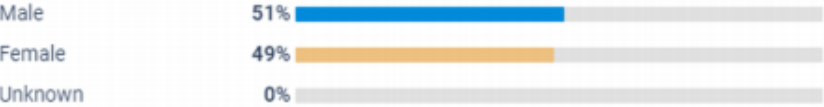
§ All counts on the TriNetX Live™ USA Network are rounded up to the nearest 10 to protect patient privacy (i.e. a count of 110 represents from 101-110 patients, etc.)

# Baseline Demographics

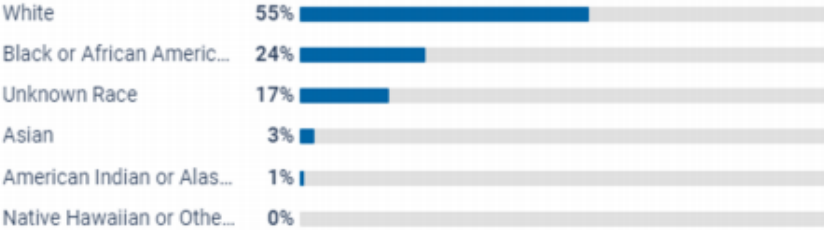


Total Patients	Minimum Age	Maximum Age	Mean Age	Standard Deviation
23,580	18	90	57	17

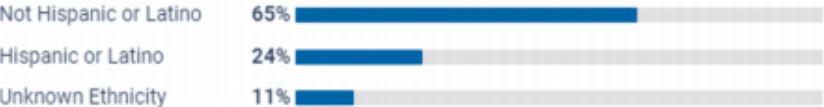
**Sex**



**Race**



**Ethnicity**



**NOTE:** Figure represents to the number of patients with inpatient records from 20 February – 16 October 2020 AND a COVID-19 record (positive laboratory test or ICD-10-CM code) from 3 days before to 3 days after the inpatient record who met all inclusion and exclusion criteria.

All counts on the TriNetX Live™ USA Network are rounded up to the nearest 10 to protect patient privacy (i.e. a count of 110 represents from 101-110 patients, etc.)

# Selected Patient Characteristics

	n	%
<b>Total Patients</b>	<b>23,580</b>	
<b>Method of COVID-19 Diagnosis (not mutually exclusive)</b>		
PCR	9,920	42.1
Antigen Test	70	0.3
ICD-10 code	14,680	62.3
<b>Laboratory tests [0, 3]</b>		
D-dimer (any)	10,900	46.2
Elevated (> 500 ng/mL for FEU; > 250 ng/mL for DDU)	3,380	14.3
Normal (≤ 500ng/mL for FEU; ≤ 250ng/mL for DDU)	7,470	31.7
Ambiguous (Evidence of lab drawn, but no units provided)	250	1.1
<b>Indicator for intensive care [0, 3]*</b>		
Yes	3,090	13.1
No	20,490	86.9

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

\* Includes record of invasive mechanical ventilation, extracorporeal membrane oxygenation, or vasopressors; evaluation/management CPT codes for critical care

# Selected Patient Characteristics

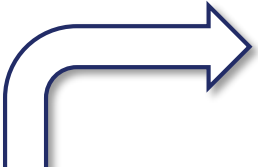
	n	%
<b>Total Patients</b>	<b>23,580</b>	
<b>Anticoagulants, antiplatelets, and/or thrombolytics [0, 3]</b>		
Anticoagulants, antiplatelets, and/or thrombolytics	12,510	53.1
<b>Anticoagulants*</b>	11,900	50.5
Heparin (excluding heparin flushes)	2,610	11.1
LMWH (enoxaparin, dalteparin)	9,640	40.9
Other anticoagulants	1,190	5.0
<b>Anti-platelet agents</b>	3,680	15.6
<b>Thrombolytics</b>	60	0.3
<b>Therapeutics used for COVID-19 [0, 28]</b>		
Anticoagulants, antiplatelets, and/or thrombolytics	13,180	55.9
Systemic corticosteroids	9,650	40.9
Convalescent plasma <sup>†</sup>	410	-
Remdesivir <sup>†</sup>	2,600	-
Tocilizumab	190	0.8

\* Include dabigatran, rivaroxaban, warfarin, desirudin, defibrotide, apixaban, argatroban, edoxaban, betrixaban, lepirudin, fondaparinux, heparin, bivalrudin, enoxaparin, dalteparin, tirofiban, and eptifibatide; <sup>†</sup> ICD-10-PCS codes not available until 01 Aug 2020; no percentages displayed  
All values are rounded up to the highest 10 to protect patient privacy



# Outcomes

<b>Total patients</b>		<b>N=23,580</b>	
<b>Outcomes</b>	<b>Window (days)</b>	<b>n</b>	<b>%</b>
Hospitalized DVT, PE, MI, IS, or all-setting death	1-28	1,290	5.5
Hospitalized MI, ischemic stroke	1-28	100	0.4
Hospitalized DVT, PE	1-28	110	0.5
Any DVT, PE, MI, IS, or all-setting death	1-28	1,570	6.7



**5.5% of patients experienced hospitalized DVT, PE, MI, IS, or died in the 28 days following hospitalization with COVID-19**

All values are rounded up to the nearest 10 to protect patient privacy  
DVT: deep vein thrombosis; IS: ischemic stroke; MI: myocardial infarction; PE: pulmonary embolism

# Outcomes by d-dimer

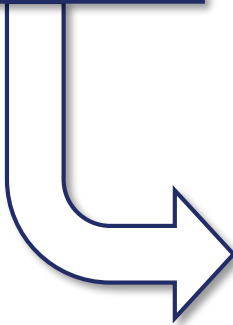
<b>Total Patients</b>		<b>10,900</b>		<b>3,380</b>		<b>7,470</b>	
		<b>Any<sup>1</sup></b>		<b>Elevated</b>		<b>Normal</b>	
<b>Outcomes</b>	<b>Window (days)</b>	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>
Death or hospitalized DVT, PE, MI, or IS	1-28	700	6.4	190	5.6	480	6.4
Hospitalized MI, ischemic stroke	1-28	60	0.6	20	0.6	40	0.5
Hospitalized DVT, PE	1-28	60	0.6	20	0.6	50	0.7
Death or any DVT, PE, MI, or IS	1-28	880	8.1	280	8.3	560	7.5

**~6% of patients experienced hospitalized DVT, PE, MI, IS, or died in the 28 days following hospitalization regardless of d-dimer**

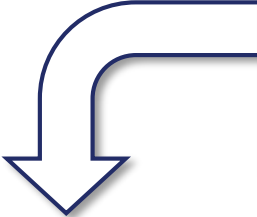
All values are rounded up to the nearest 10 to protect patient privacy; Results for 250 patients with ambiguous d-dimer results are not separately reported.

# Selected outcomes by early intensive care (IC)

17.8% of patients with early IC experienced hospitalized DVT, PE, MI, IS or death



~3.7% of patients with no early IC required organ support or died through 21 days



Total patients		N = 3,090		N = 20,490	
		Early IC		No Early IC	
Outcomes	Window (days)	n	%	n	%
Death or hospitalized DVT, PE, MI, or IS	1-28	550	17.8	750	3.7

All values are rounded up to the nearest 10 to protect patient privacy  
 Intensive care (IC) includes invasive mechanical ventilation, ECMO, vasopressors, and evaluation/management CPT codes for critical care on days [0, 3] around index  
 DVT: deep vein thrombosis; IS: ischemic stroke; MI: myocardial infarction; PE: pulmonary embolism

# Conclusions

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# Study population

- Identified **~24,000** adults hospitalized with COVID-19 who might have been eligible for the ACTIV-4a trial
  - Average age **57±17 years**, majority white and non-Hispanic
- Use of **anticoagulant, antiplatelet, or thrombolytic** was ~50% and **systemic corticosteroids** was ~40%
  - May have modified the disease course → fewer adverse outcomes?
- **D-dimer** results were **elevated** in **14.3%** but were **missing** in **~50%**
  - If missingness not at random, may impact interpretation

# Thrombotic events and death

- Overall, **5.5% died or experienced hospitalized DVT, PE, MI, or IS** in the 28 days following index
  - **~5 times as likely among those with IC indicators in first 3 days** compared to those without (~18 vs ~4%)
- Lower than published estimates, possibly due to:
  - Study population (age differences)
  - Exclusion of patients with thrombotic events or death on index date (not eligible for randomization in the RCT)
  - Outcome ascertainment and definitions (ICD-10 codes vs. imaging)
  - No capture of out-of-HCO events or death

## Literature Suggests:

- Mortality among hospitalized patients ~20%
- Venous events alone in intensive care ~16-69%

# Contextualizing death in COVID-19

Reference	Study period (2020)	Setting	Hospitalized COVID-19 patients (age)	Outcome	%
<a href="#">Atkins, et al., J. of Gerontology, 2020</a>	Mar. - Apr.	UK	607 ( $\bar{x}$ 73 years)	Death	27.8
<a href="#">Hewit, et al. Lancet, 2020</a>	Feb.-Apr.	UK & Italy	1,564 ( $\tilde{x}$ 74 years)	Death	27.2
<a href="#">Richardson, et al. JAMA, 2020</a>	Mar. - Apr.	NYC, USA	5,700 ( $\tilde{x}$ 63 years)	Death	21
<a href="#">Zhou, et al. Lancet, 2020</a>	Dec. 2019- Jan. 2020	China	191 ( $\tilde{x}$ 56 years)	Death	28.2
<a href="#">Docherty AB et al. BMJ, 2020</a>	Feb.-Apr.	UK	20,133 ( $\tilde{x}$ 73 years)	Death	26
<a href="#">Piazza et al, JACC, 2020</a>	Mar. - Apr.	USA	<ul style="list-style-type: none"> <li>• 229 non-ICU</li> <li>• 170 ICU</li> </ul> ( $\tilde{x}$ 50.6 years)	Death	<ul style="list-style-type: none"> <li>• 6.7</li> <li>• 23.5</li> </ul>

Clicking on the references will link to the Pubmed abstract  
 Derived from: Izcovich A, et al. PLoS One. 2020;15(11):e0241955.  
 $\tilde{x}$ : median;  $\bar{x}$ : mean

# Contextualizing thrombotic events in COVID-19

Reference (2020)	Setting	COVID-19 patients	Outcome	Incidence
<a href="#">Klok et al., Thromb Res*</a>	Netherlands	184 in ICU	Arterial/venous clots	31 (16.8%)
<a href="#">Lodigiani et al., Thromb Res*</a>	Italy	48 in ICU	VTE	8 (16.7%)
<a href="#">Llitjos et al., J Thromb Haemost*</a>	France	26 in ICU	DVT	18 (69.0%)
<a href="#">Cui et al., Thromb Haemost</a>	China	81 in ICU	VTE	20 (24.7%)
<a href="#">Poissy et al., Circulation*</a>	France	107 in ICU	PE	22 (20.6%)
<a href="#">Goyal et al., N Engl J Med</a>	USA	393 hospitalized	VTE	13 (3.3%)
<a href="#">Cattaneo et al., Thromb Haemost*</a>	Italy	388 hospitalized	DVT	0 (0.0%)
<a href="#">Al-Samkari at al., Blood*</a>	USA	400 hospitalized	VTE	19 (4.8%)
			Arterial thrombosis	11 (2.8%)

\* Manuscript suggests all or most participants received anti-coagulation Clicking on the references will link to the Pubmed abstract  
DVT: deep vein thrombosis; ICU: intensive care unit; PE: pulmonary embolism; VTE: venous thromboembolism



# Limitations

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# Data Source

- Can only capture events **recorded in medical chart**
  - Unable to capture events occurring outside of the HCOs providing data<sup>1</sup>
- **Non-random** sample of HCOs
  - USA Network in TriNetX Live™ primarily academic medical centers
- Code-based algorithms used in study have not been validated in an EHR data source
  - Only validated in administrative claims data
- Cannot assess **temporality** within single healthcare encounter (i.e. no admission/discharge dates)
- Privacy concerns limit causal inference
  - Counts rounded up to nearest 10 to protect patient privacy

<sup>1</sup>Some outcomes may have occurred in a subsequent hospitalization or out of the system

# Study Design/Analysis

- Included patients hospitalized **with** rather than **for** COVID-19
  - Cannot capture primary diagnosis in platform
- Potential **confounding by indication**
  - Higher risk for thrombotic events (esp. ↑ d-dimer) → higher probability of anticoagulant treatment shortly after COVID-19
- Differing **outcome definitions** from RCT
  - Arterial thromboembolic events (other than MI and ischemic stroke) not included

# Acknowledgements

## Sentinel Operations Center

- Meg Her
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- Ashley Martinez
- Mayura Shinde

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- Sarah Dutcher
- Brian Kit
- Silvia Perez-Vilar

## TriNetX

- Sierra Luciano

**We would like to thank the Health Care Organizations that provided data for this analysis.**

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

"This project was supported by Master Agreement 75F40119D10037 from the US Food and Drug Administration (FDA). The FDA approved the study protocol including statistical analysis plan, and reviewed and approved this presentation. Coauthors from the FDA participated in the results interpretation and in the preparation. The FDA had no role in data collection, management, or analysis."



# Thank You

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# Extra Slides

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# 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

<b>90M</b> PATIENTS	<b>67</b> HCOs	<b>27</b> STATES
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### Real-World Evidence Generation

**89+** TRINETX CITATIONS IN GOOGLE SCHOLAR



# TriNetX Process Flow

## VARIOUS AND DISPARATE DATA

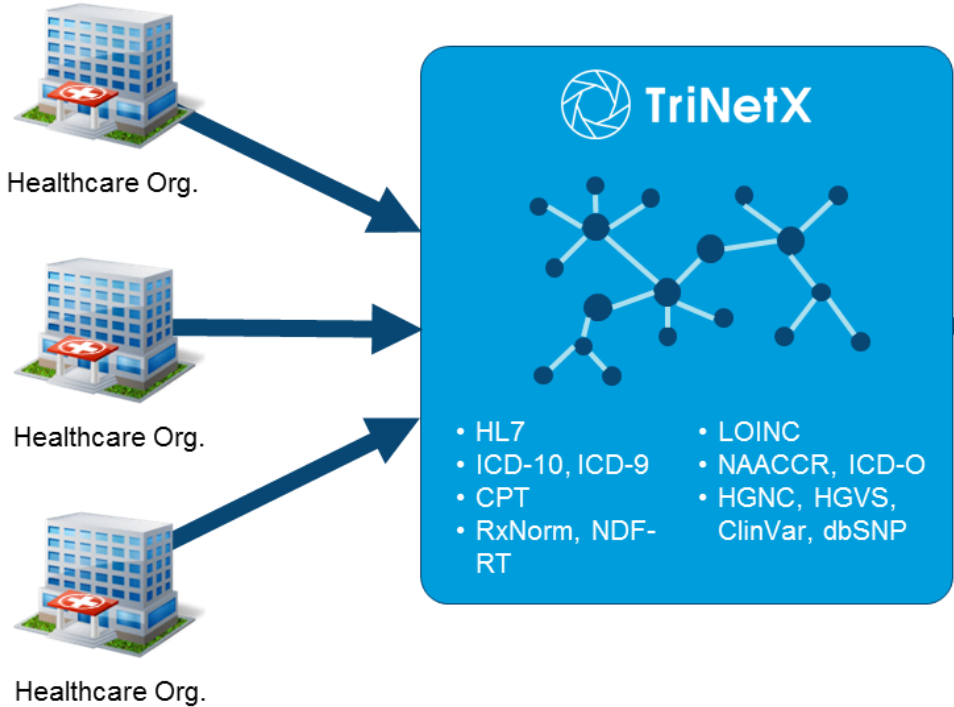
Demographics      Lab Results

Diagnoses      Oncology

Procedures      Genomics

Medications      NLP

## MAPPED TO CONTROLLED TERMINOLOGIES



## MASTER TERMINOLOGY BUILT FOR USABILITY

**MUST Have**      **CANNOT Have**

HbA1c      Search Term...

Code	Term Description	Patients
TXN:LAB:9037	L Hemoglobin a1c/hemoglobin.total in blood	3,294,500

**ADD TO QUERY**

D Demographics      Dx Diagnoses      L Labs

M Medications      P Procedures      G Genomics

# Claims vs EHR Data

## Administrative Claims

- 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

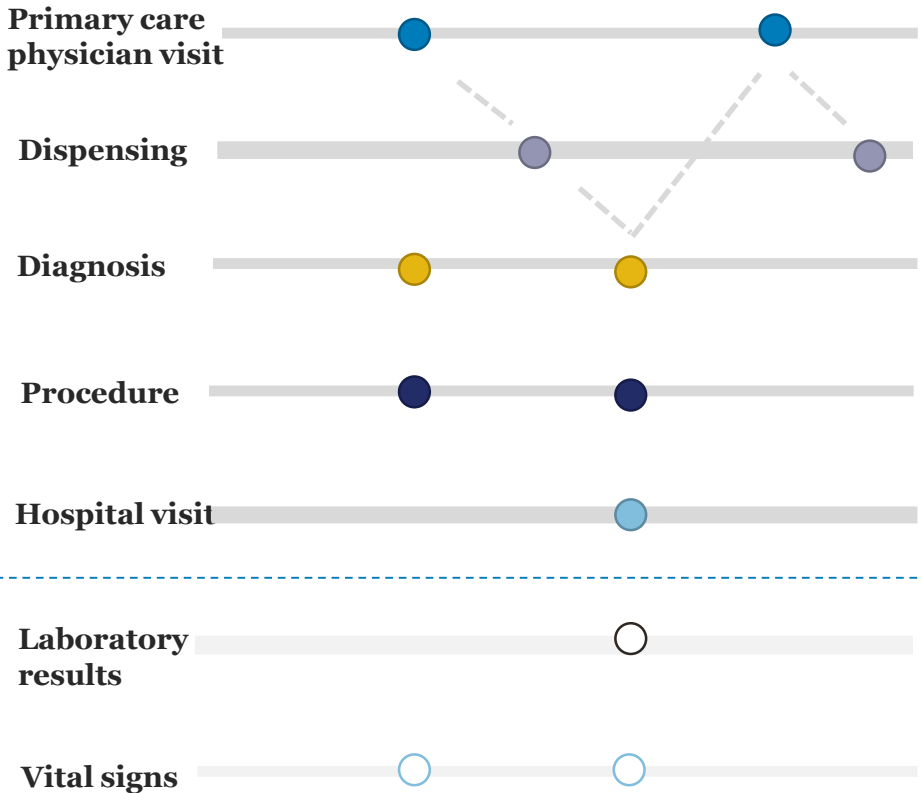
## Electronic Health Care Records

- 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

# Comparing Claims Data vs. EHR Data

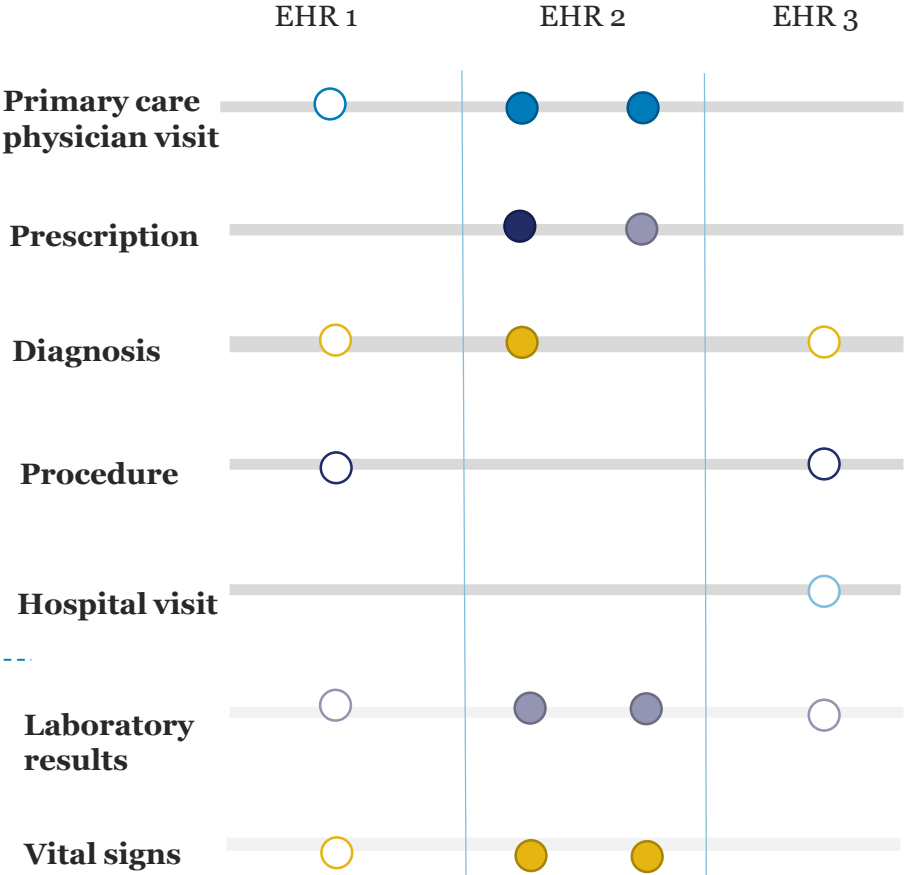
## Claims Data

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

# Select outcomes stratified by d-dimer and intensive care (IC) indicator

		Elevated d-dimer & IC		Elevated d-dimer & non-IC		Normal d-dimer & IC		Normal d-dimer & non-IC	
<b>Total Patients</b>		<b>N = 410</b>		<b>N = 2,970</b>		<b>N = 1,020</b>		<b>N = 6,450</b>	
<b>Outcomes</b>	<b>Window (days)</b>	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>
Hospitalized DVT, PE, MI, IS, or death	1-28	90	22.0	100	3.4	220	21.6	260	4.0

IC includes invasive mechanical ventilation, extracorporeal membrane oxygenation, vasopressors, and evaluation/management CPT codes for critical care

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

DVT: deep vein thrombosis; IS: ischemic stroke; MI: myocardial infarction; PE: pulmonary embolism

# Safety outcome

<b>Total patients</b>		<b>N=23,580</b>	
<b>Outcomes</b>	<b>Window (days)</b>	<b>n</b>	<b>%</b>
Hospitalized bleeding*	1-28	90	0.4

\* Major bleeding through 28 days post-index defined using a simplified algorithm as in: Cunningham A et al. Pharmacoepidemiol Drug Saf. 2011 Jun;20(6):560-6  
All values are rounded up to the nearest 10 to protect patient privacy