Natural History of Coagulopathy in COVID-19

Vincent Lo Re, MD, MSCE, FISPE

Division of Infectious Diseases
Center for Clinical Epidemiology and Biostatistics
Perelman School of Medicine, University of Pennsylvania

Noelle M. Cocoros, DSc, MPH

Department of Population Medicine
Harvard Pilgrim Health Care Institute
Harvard Medical School

On behalf of the FDA Sentinel COVID-19 Coagulopathy Workgroup

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.

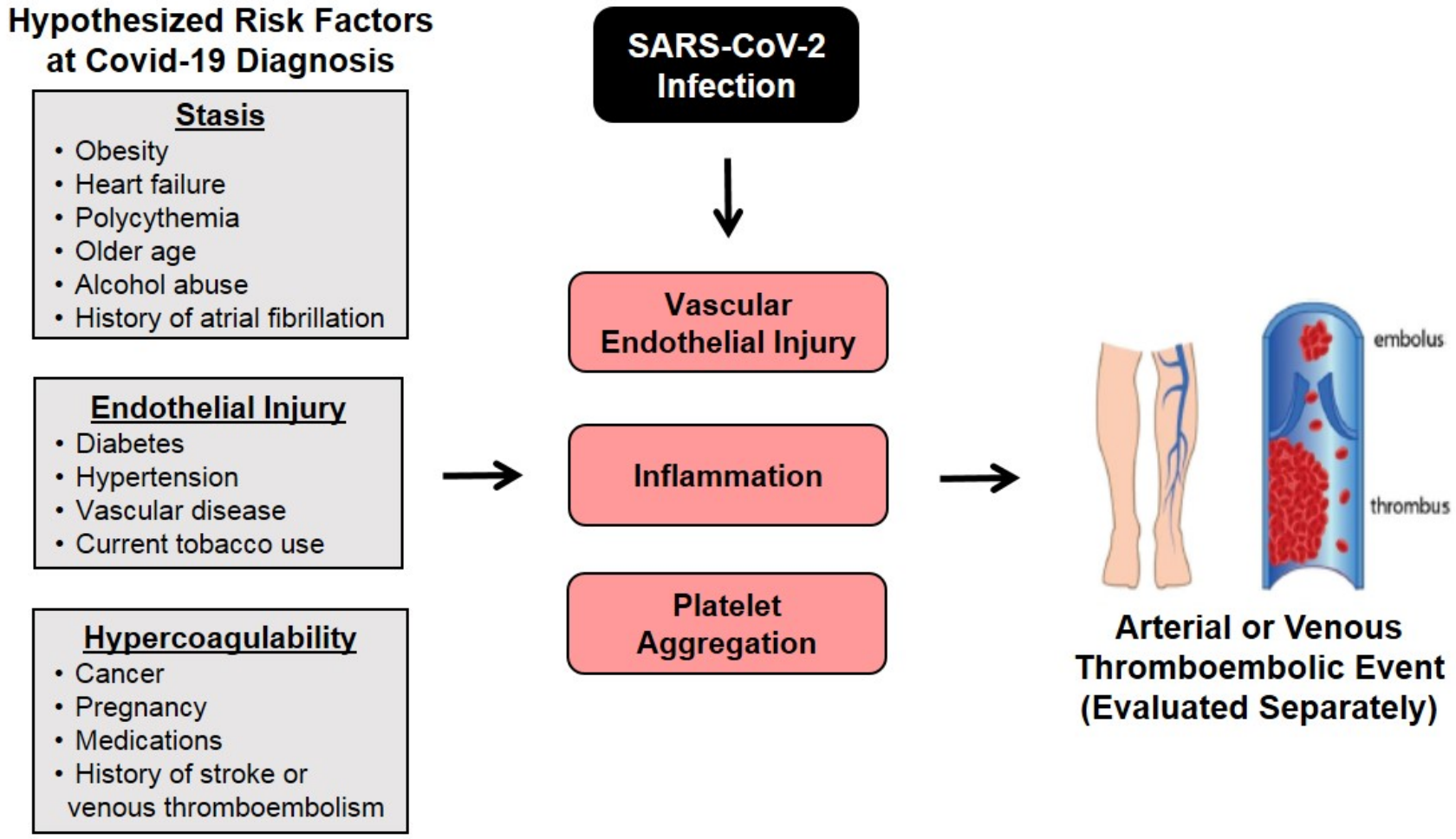
Specific Aims

- **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: Subset of Data Partners from FDA's Rapid Sentinel Distributed Database**
  - Priority data sources:
    - 4 integrated health systems (EHR + claims)
    - 2 large national insurers (claims only)
  - Lab data available: COVID-19, influenza, clinical labs
    - Availability of labs varies by partner and care setting
  - Can identify thrombotic events via outpatient/hospital diagnoses
  - Can determine pre-existing comorbidities, outpatient dispensed medications

Study Patients (Aims 1 & 2)

	Criteria
Inclusion Criteria	1) COVID-19 ICD-10-CM diagnosis code or positive nucleic acid test (NAAT) between April 1, 2020 and 90 days before October 31, 2020 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 pla… …bers selected

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

Study Patients (Aim 3)

Ensure that influenza patients do not have COVID-19

	COVID-19 Cohort	Influenza Cohort
Inclusion Criteria	COVID-19 ICD-10-CM diagnosis code or positive NAAT between April 1, 2020 and 90 days before October 31, 2020	Influenza A or B ICD-10-CM diagnosis OR positive NAAT between October 1, 2018 and April 30, 2019
	≥365 days of continuous enrollment at time of diagnosis	
Exclusion Criteria	Coinfection with another respiratory virus	
Selection	All eligible membe ected	

Included: adenovirus, parainfluenza, metapneumovirus, rhinovirus, respiratory syncytial virus, enterovirus, non-COVID-19 coronavirus

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)

Based on Hospital Discharge ICD-10-CM Diagnosis (from any position)

- **Mapped from ICD-9-CM Diagnoses Validated in Sentinel Data**
- **Mapped ICD-10-CM diagnoses underwent clinical review**

Study Outcome Considerations

- **Focused on validated endpoints to minimize outcome misclassification**
  - Reduce likelihood of biased estimates of associations between exposures, outcomes
  - Have confidence that ascertained outcomes = true events
  - Performing limited chart validation of arterial, venous thrombotic events
- **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

Secondary Outcomes (All Aims)

1a. **Arterial**: ICD-10-CM diagnosis for primary outcome, angina, TIA, PAD, amputation, or other cerebrovascular disease in ED, institutional stay, or inpatient setting

1b. **Venous**: ICD-10-CM diagnosis for primary outcome or thrombosis of device, implant, or graft in ED, institutional stay, or inpatient setting

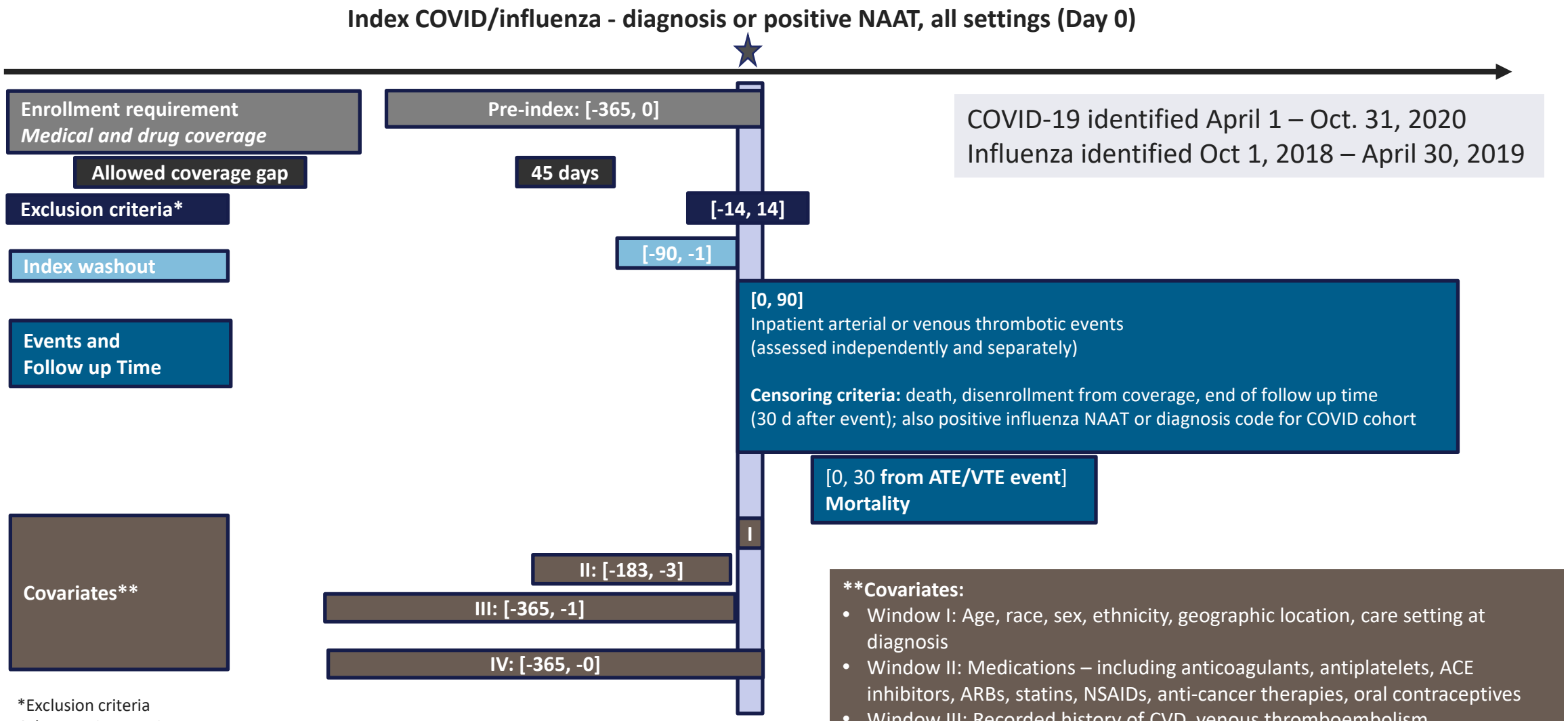
2. Death (any cause) among those with an ATE or VTE (evaluated separately)

Definitions of Risk Factors for Thrombotic Events (Aim 2)

Category	Risk Factor		Definition
Stasis of Circulation	Alcohol abuse COPD Obesity Thrombophilia	Atrial Fibrillation Heart failure Rheumatologic Disease Neurological disease	ICD-10-CM diagnosis codes
	Older age	Sex	At time of COVID-19 or flu diagnosis
	Thrombocytosis		ICD-10-CM or platelets* >450,000/µL
	Polycythemia		ICD-10-CM or hemoglobin* >16 gm/dL
Endothelial Injury	Diabetes Hypertension Prior CVD	Hyperlipidemia Chronic kidney disease Current tobacco use	ICD-10-CM diagnosis codes
	Antiplatelet drug use		Outpt fill -90 to -3 d prior to index date
Hypercoagulability	Cancer Prior VTE	Pregnancy Antiphospholipid Ab	ICD-10-CM diagnosis codes
	Anticoagulant drug use		Outpt fill -90 to -3 d prior to index date

Diagnoses and labs assessed days (-365, 0); *If multiple lab results available, collected closest to index date

Primary Analysis Design Diagram



COVID-19 identified April 1 – Oct. 31, 2020
Influenza identified Oct 1, 2018 – April 30, 2019

*Exclusion criteria
Other respiratory viruses (diagnosis code) or influenza for COVID cohort (diagnosis code or positive NAAT)

**Covariates:

- Window I: Age, race, sex, ethnicity, geographic location, care setting at diagnosis
- Window II: Medications – including anticoagulants, antiplatelets, ACE inhibitors, ARBs, statins, NSAIDs, anti-cancer therapies, oral contraceptives
- Window III: Recorded history of CVD, venous thromboembolism
- Window IV: Various underlying conditions including asthma, diabetes, COPD, polycythemia, thrombocytosis (diagnosis code or applicable elevated lab test)

Data Analysis

Aim	Statistical Analyses
Aim 1	Characteristics of COVID-19 cohort Calculate **absolute risk** and **incidence rates** (events/1000 persons-years) of outcomes: • By arterial and venous events • Stratify by age, sex, race, setting of diagnosis (ambulatory, hospital, nursing home) • Stratify by disease severity at diagnosis, prior CVD history, prior VTE history • Stratify by baseline anticoagulant use, antiplatelet use Calculate absolute risk and incidence rate of death within 30 days of a primary outcome
Aim 2	**Multivariable Cox regression**: adjusted HRs (95% CIs) of events assoc. with risk factors
Aim 3	Compare characteristics between COVID-19 and influenza cohorts **Weighted Cox regression**, accounting for propensity score: adjusted HRs (95% CIs) of outcomes in persons with COVID-19 vs. influenza • Stratify by setting of diagnosis, prior thromboembolism history

Results:
Baseline Characteristics of COVID-19 Cohort

Primary COVID-19 Cohort

Characteristic	
Patients (N)	240,826
Demographics	
Mean age (SD)	56.8 (17.8)
Male sex	108,689 (45.1%)
Female sex	132,137 (54.9%)
Health Service Utilization Intensity	
Mean number of ambulatory encounters (SD)	16.4 (20.2)
Mean number of inpatient hospital encounters SD)	0.2 (0.7)
Care Setting at Index	
Hospital inpatient	30,136 (12.5%)

COVID-19 and influenza defined by a positive NAAT or diagnosis code in all care settings.
Adjustment performed using propensity score stratum weighting to estimate an ATE after trimming non-overlap.

Primary COVID-19 Cohort

Characteristic	N	%
Patients (N)	240,826	100%
Recorded History (days -365, 0)		
Charlson/Elixhauser comorbidity score, Mean (SD)	1.8 (2.9)	-
Alcohol dependence/abuse	5,848	2.4%
Antiphospholipid antibody syndrome	337	0.1%
Asthma	22,650	9.4%
Atrial fibrillation/flutter	23,684	9.8%
Cancer (excluding NMSC)	32,329	13.4%
Chronic kidney disease	45,753	19.0%
Chronic liver disease	16,972	7.0%
COPD	34,336	14.3%
Diabetes mellitus (any)	63,430	26.3%
Diabetes unspecified	5,108	2.1%
Heart failure	27,834	11.6%
HIV	1,151	0.5%
Hypertension	122,529	50.9%

COVID-19 and influenza defined by a positive NAAT or diagnosis code in all care settings.
Adjustment performed using propensity score stratum weighting to estimate an ATE after trimming non-overlap.

Primary COVID-19 Cohort

Characteristic	N	%
Patients (N)	240,826	100%
Recorded History (days -365, 0)		
Hyperlipidemia	114,558	47.6%
Inherited (primary) thrombophilia	2,495	1.0%
Neurological disease	21,682	9.0%
Obesity	64,318	26.7%
Pregnancy (-90, 0)	5,166	2.1%
Rheumatologic disease	11,042	4.6%
Tobacco use	45,171	18.8%
Prior cardiovascular disease (-365,-1)	64,907	27.0%
Prior VTE (-365,-1)	7,210	3.0%
Polycythemia (dx code or hemoglobin >16 g/dL)	6,036	2.5%
Thrombocytosis (dx code or platelets >450K/uL)	21,072	8.7%

COVID-19 and influenza defined by a positive NAAT or diagnosis code in all care settings.
Adjustment performed using propensity score stratum weighting to estimate an ATE after trimming non-overlap.

Primary COVID-19 Cohort

Characteristic	N	%
Patients (N)	240,826	100%
Recorded History of Use (days -183, -3)		
NSAIDs	34,633	14.4%
Statins	75,415	31.3%
Corticosteroids history	54,276	22.5%
ACE inhibitor	38,562	16.0%
ARBs	33,591	13.9%
Anticoagulant history	20,593	8.6%
Antiplatelet history	13,276	5.5%
Thrombolytic history	300	0.1%
Blood transfusion	949	0.4%
Estrogen replacement therapy	15,762	6.5%
Anti-cancer therapy	3,898	1.6%
Oral contraceptives	11,131	4.6%
Testosterone replacement	2,162	0.9%

COVID-19 and influenza defined by a positive NAAT or diagnosis code in all care settings.
Adjustment performed using propensity score stratum weighting to estimate an ATE after trimming non-overlap.

90-Day Cumulative Incidence and Unadjusted Rates of Primary Arterial and Venous Thrombotic Events Among Patients Diagnosed with COVID-19

Rates of Primary Arterial Thrombotic Events in COVID-19

Characteristic	No. of Patients	No. of Events	Absolute Risk (%)	Incidence Rate per 1,000 person-years (95% CI)
Overall	240,826	6,703	2.8	121.1 (118.2-124.0)
Age				
18-44 years	73,136	82	0.1	4.7 (3.8-5.8)
45-54 years	31,704	230	0.7	30.2 (26.6-34.4)
55-64 years	36,048	713	2.0	84.0 (78.1-90.4)
65-74 years	51,050	2,245	4.4	193.2 (185.3-201.3)
75-84 years	33,248	2,259	6.8	319.8 (306.9-333.3)
≥85 years	15,640	1,174	7.5	389.3 (367.6-412.2)
Sex				
Male	108,689	3,647	3.4	147.8 (143.1-152.7)
Female	132,137	3,056	2.3	99.6 (96.1-103.2)

COVID-19 defined by a positive NAAT or diagnosis code in all care settings.

Rates of Primary Arterial Thrombotic Events in COVID-19

Characteristic	No. of Patients	No. of Events	Absolute Risk (%)	Incidence Rate per 1,000 person-years (95% CI)
Severity of infection at diagnosis				
Mild	184,869	2,005	1.1	45.6 (43.7-47.7)
Hospitalized (not admitted to ICU or mechanically ventilated)	13,278	1,482	11.2	554.1 (526.6-583.1)
Hospitalized (admitted to ICU or mechanically ventilated)	16,858	3,148	18.7	1,219.3 (1,177.5-1,262.7)
Unknown	25,821	68	0.3	11.0 (8.7-14.0)
Prior cardiovascular disease (-365, -1)	64,907	4,997	7.7	366.1 (356.1-376.4)
Prior anticoagulant therapy (-183, -3)	15,206	1,601	10.5	529.0 (503.7-555.6)
No prior anticoagulant therapy (-183, -3)	49,701	3,396	6.8	319.7 (309.2-330.7)

COVID-19 defined by a positive NAAT or diagnosis code in all care settings.

Rates of Primary Venous Thromboembolism Events in COVID-19

Characteristic	No. of Patients	No. of Events	Absolute Risk (%)	Incidence Rate per 1,000 person-years (95% CI)
Overall	240,826	4,232	1.8	76.0 (73.8-78.3)
Age				
18-44 years	73,136	161	0.2	9.2 (7.9-10.7)
45-54 years	31,704	241	0.8	31.7 (28.0-36.0)
55-64 years	36,048	595	1.7	70.0 (64.6-75.8)
65-74 years	51,050	1,437	2.8	122.5 (116.3-129.0)
75-84 years	33,248	1,250	3.8	173.7 (164.3-183.6)
≥85 years	15,640	548	3.5	177.3 (163.1-192.8)
Sex				
Male	108,689	2,231	2.1	89.8 (86.1-93.6)
Female	132,137	2,001	1.5	64.9 (62.1-67.8)

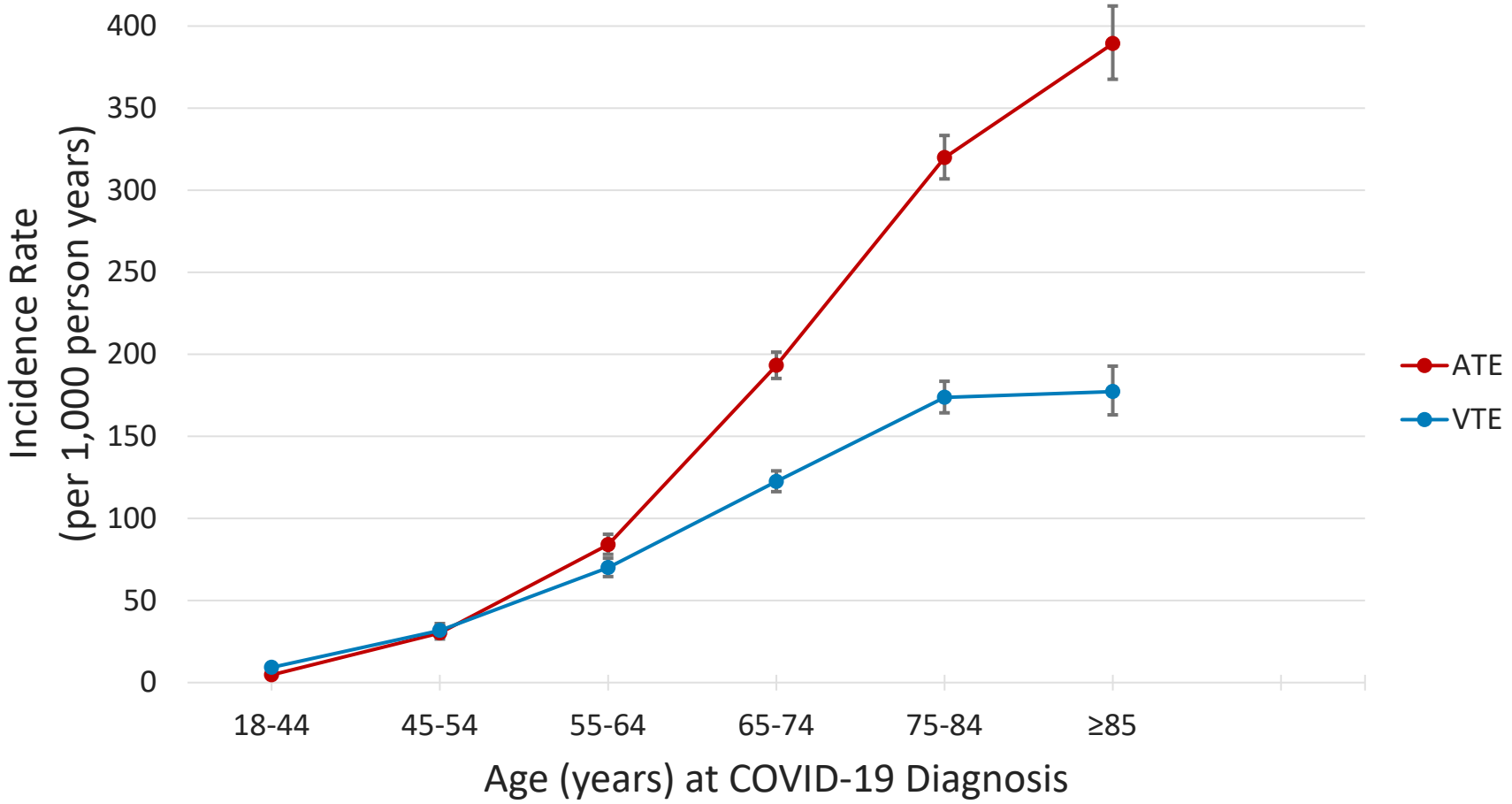
COVID-19 defined by a positive NAAT or diagnosis code in all care settings.

Rates of Primary Venous Thromboembolism Events in COVID-19

Characteristic	No. of Patients	No. of Events	Absolute Risk (%)	Incidence Rate per 1,000 person-years (95% CI)
Severity of infection at diagnosis				
Mild	184,869	1,396	0.8	31.7 (30.1-33.5)
Hospitalized (not admitted to ICU or mechanically ventilated)	13,278	923	7.0	332.7 (311.9-354.9)
Hospitalized (admitted to ICU or mechanically ventilated)	16,858	1,815	10.8	658.2 (628.6-689.2)
Unknown	25,821	98	0.4	15.9 (13.0-19.4)
Prior VTE (-365, -1)	7,210	1,008	14.0	731.3 (687.5-777.9)
Prior anticoagulant therapy (-183, -3)	4,414	621	14.1	733.9 (678.4-794.0)
No prior anticoagulant therapy (-183, -3)	2,796	387	13.8	727.2 (658.2-803.4)

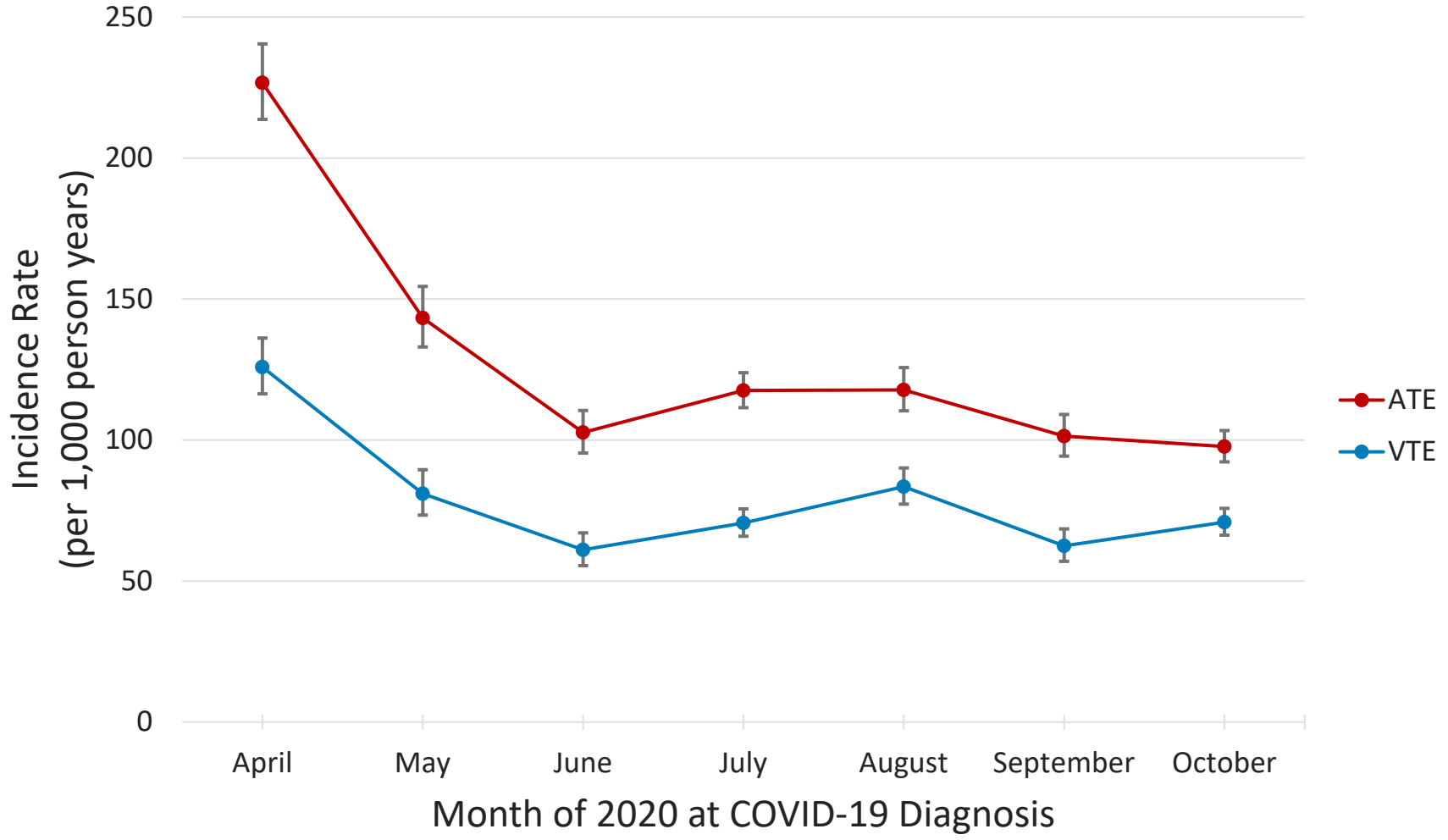
COVID-19 defined by a positive NAAT or diagnosis code in all care settings.

Rates of Primary Arterial and Venous Thrombotic Events, by Age at COVID-19 Diagnosis



COVID-19 defined by a positive NAAT or diagnosis code in all care settings.

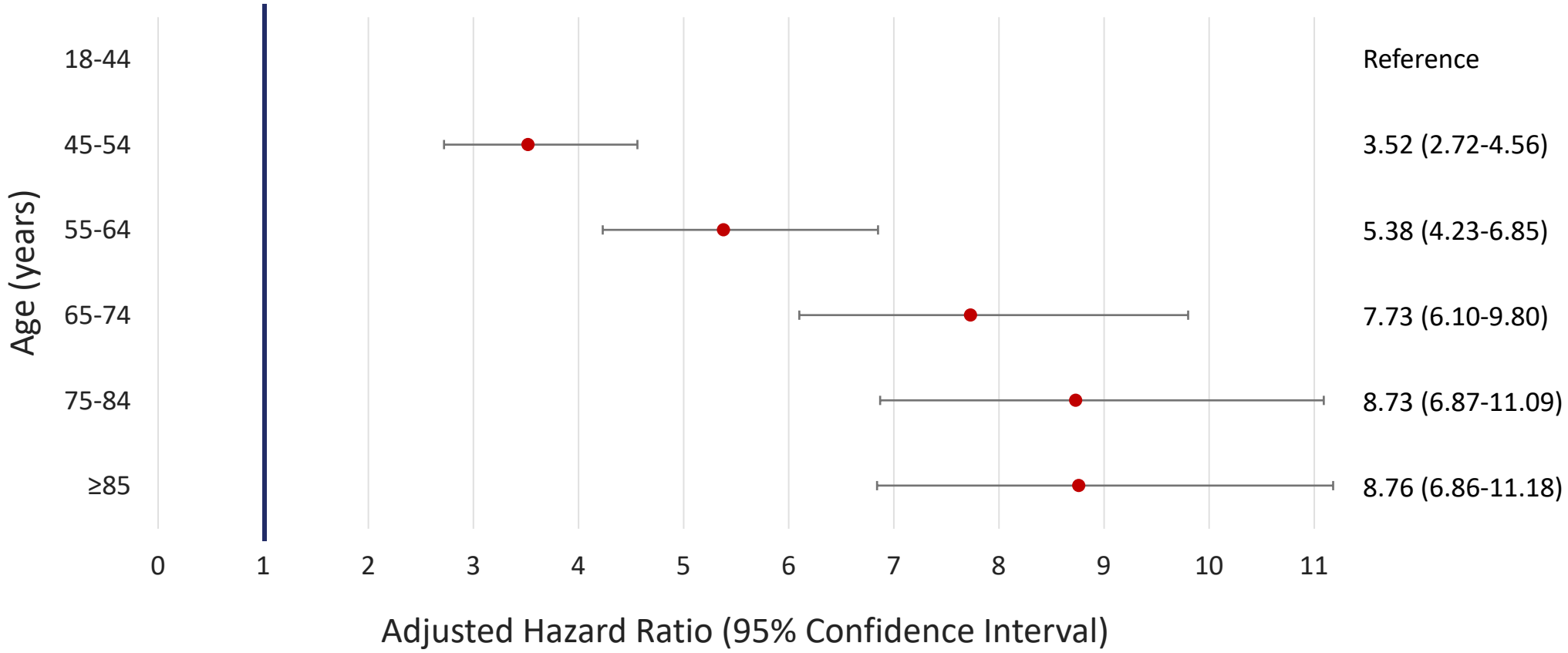
Rates of Primary Arterial and Venous Thrombotic Events, by Month of COVID-19 Diagnosis



COVID-19 defined by a positive NAAT or diagnosis code in all care settings.

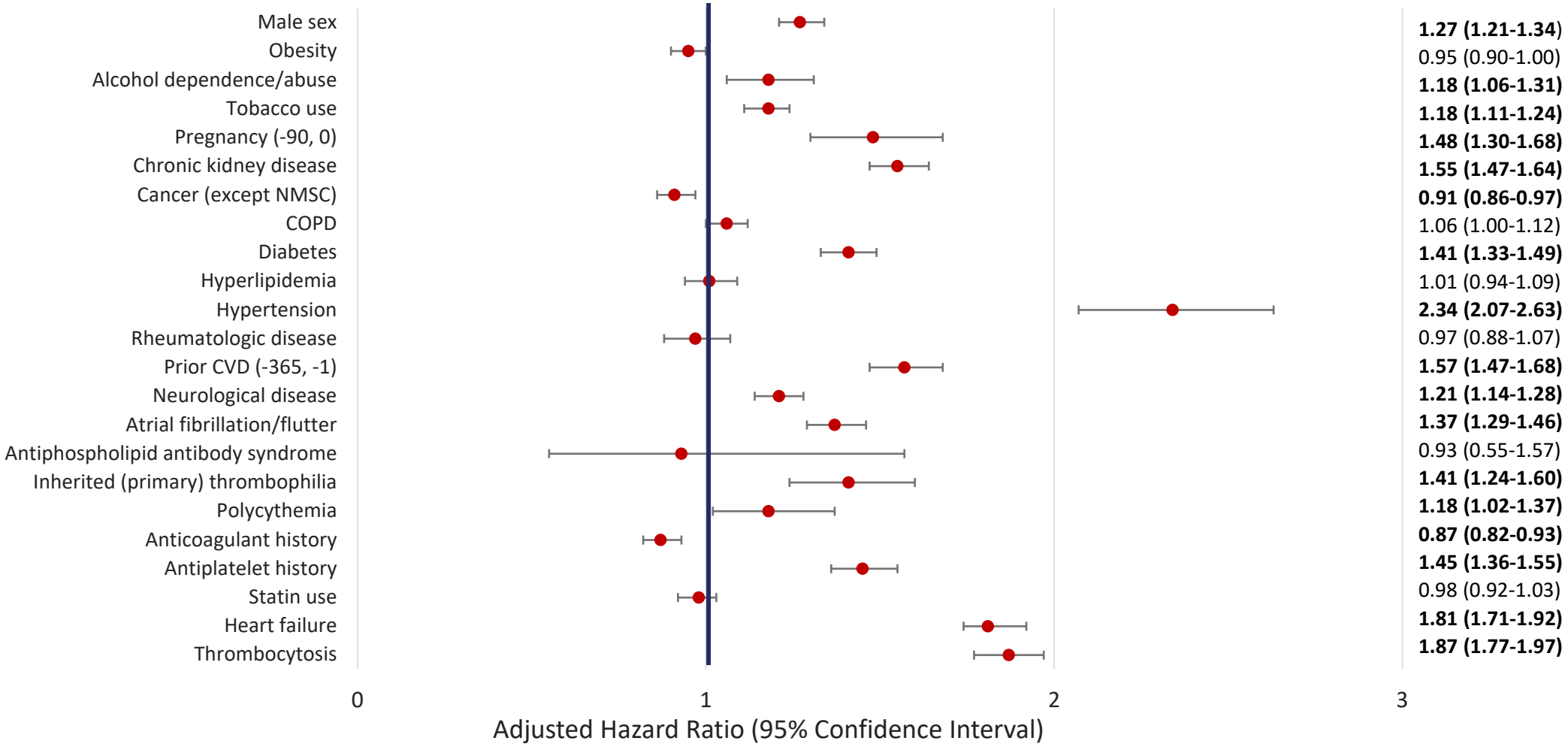
Risk Factors for Primary Arterial and Venous Thrombotic Events Among Patients Diagnosed with COVID-19

Risk Factors for Primary Arterial Thrombotic Events in COVID-19



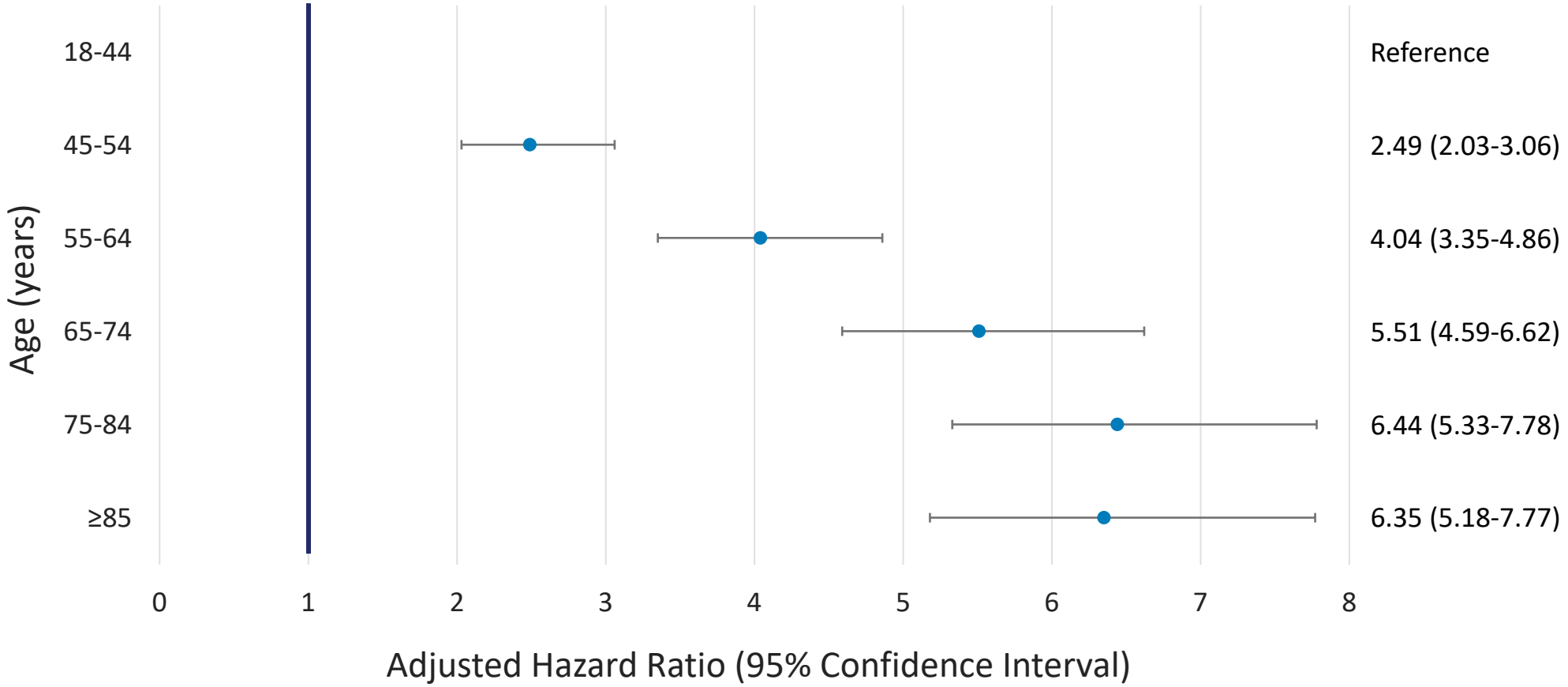
COVID-19 defined by a positive NAAT or diagnosis code in all care settings.

Risk Factors for Primary Arterial Thrombotic Events in COVID-19



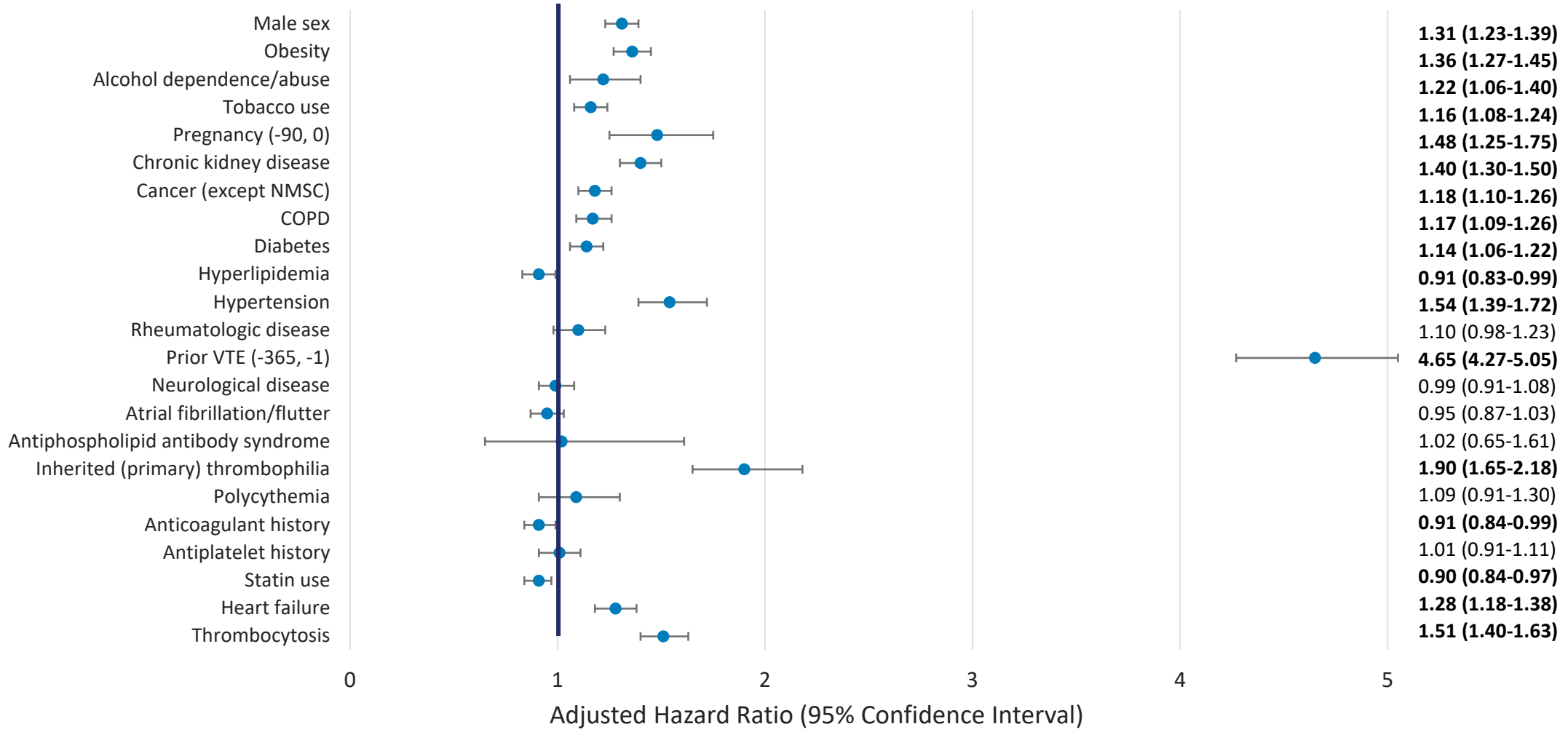
COVID-19 defined by a positive NAAT or diagnosis code in all care settings.

Risk Factors for Primary Venous Thrombotic Events in COVID-19



COVID-19 defined by a positive NAAT or diagnosis code in all care settings.

Risk Factors for Primary Venous Thrombotic Events in COVID-19



COVID-19 defined by a positive NAAT or diagnosis code in all care settings.

Risk of Primary Arterial and Venous Thrombotic Events in Persons Diagnosed With COVID-19 vs. Influenza

COVID-19 and Influenza Cohorts Before and After Propensity Score Adjustment

Characteristic	COVID-19	Influenza	*Before Adjustment*	*After Adjustment*
	Before Adjustment			
	N/Mean	N/Mean	Standardized Difference	Standardized Difference
Patients (N)	240,826	127,117	-	-
Demographics				
Mean age (SD)	56.8 (17.8)	52.3 (16.8)	0.256	0.065
Male sex	108,689 (45.1%)	51,549 (40.6%)	0.093	-0.000
Female sex	132,137 (54.9%)	75,568 (59.4%)	-0.093	0.000
Health Service Utilization Intensity				
Mean number of ambulatory encounters (SD)	16.4 (20.2)	14.4 (16.5)	0.108	0.027
Mean number of inpatient hospital encounters SD)	0.2 (0.7)	0.1 (0.6)	0.108	0.016
Care Setting at Index				
Hospital inpatient	30,136 (12.5%)	8,216 (6.5%)	0.208	0.013

COVID-19 and influenza defined by a positive NAAT or diagnosis code in all care settings.
Adjustment performed using propensity score stratum weighting to estimate an average treatment effect after trimming non-overlap.

COVID-19 and Influenza Cohorts Before and After Propensity Score Adjustment

Characteristic	COVID-19		Influenza		*Before Adjustment*	*After Adjustment*
	Before Adjustment					
	N	%	N	%	Standardized Difference	Standardized Difference
Patients (N)	240,826	100%	127,117	100%	-	-
Recorded History (days -365, 0)						
Charlson/Elixhauser comorbidity score, Mean (SD)	1.8 (2.9)	-	1.2 (2.2)	-	0.236	0.031
Alcohol dependence/abuse	5,848	2.4%	2,149	1.7%	0.052	0.005
Antiphospholipid antibody syndrome	337	0.1%	174	0.1%	0.001	-0.001
Asthma	22,650	9.4%	15,126	11.9%	-0.081	-0.011
Atrial fibrillation/flutter	23,684	9.8%	8,535	6.7%	0.113	0.014
Cancer (excluding NMSC)	32,329	13.4%	14,535	11.4%	0.060	0.013
Chronic kidney disease	45,753	19.0%	15,914	12.5%	0.179	0.026
Chronic liver disease	16,972	7.0%	7,057	5.6%	0.062	0.009
COPD	34,336	14.3%	19,383	15.2%	-0.028	0.017
Diabetes mellitus (any)	63,430	26.3%	24,172	19.0%	0.176	0.027
Diabetes unspecified	5,108	2.1%	1,765	1.4%	0.056	-0.001
Heart failure	27,834	11.6%	9,376	7.4%	0.143	0.020

COVID-19 and influenza defined by a positive NAAT or diagnosis code in all care settings.
Adjustment performed using propensity score stratum weighting to estimate an average treatment effect after trimming non-overlap.

COVID-19 and Influenza Cohorts Before and After Propensity Score Adjustment

Characteristic	COVID-19		Influenza		*Before Adjustment*	*After Adjustment*
	Before Adjustment					
	N	%	N	%	Standardized Difference	Standardized Difference
Patients (N)	240,826	100%	127,117	100%	-	-
Recorded History (days -365, 0)						
HIV	1,151	0.5%	442	0.3%	0.020	-0.001
Hypertension	122,529	50.9%	52,928	41.6%	0.186	0.056
Hyperlipidemia	114,558	47.6%	50,197	39.5%	0.164	0.048
Inherited (primary) thrombophilia	2,495	1.0%	710	0.6%	0.054	0.012
Neurological disease	21,682	9.0%	4,456	3.5%	0.229	0.021
Obesity	64,318	26.7%	30,340	23.9%	0.065	0.023
Pregnancy (-90, 0)	5,166	2.1%	3,208	2.5%	-0.025	-0.004
Rheumatologic disease	11,042	4.6%	5,959	4.7%	-0.005	0.007
Tobacco use	45,171	18.8%	23,053	18.1%	0.016	0.024
Prior cardiovascular disease (-365,-1)	64,907	27.0%	24,185	19.0%	0.189	0.040
Prior VTE (-365,-1)	7,210	3.0%	2,492	2.0%	0.067	0.014
Polycythemia (dx code or hemoglobin >16 g/dL)	6,036	2.5%	3,474	2.7%	-0.014	-0.007
Thrombocytosis (dx code or platelets >450K/uL)	21,072	8.7%	6,813	5.4%	0.133	0.018

COVID-19 and influenza defined by a positive NAAT or diagnosis code in all care settings.
Adjustment performed using propensity score stratum weighting to estimate an average treatment effect after trimming non-overlap.

COVID-19 and Influenza Cohorts Before and After Propensity Score Adjustment

Characteristic	COVID-19		Influenza		*Before Adjustment*	*After Adjustment*
	Before Adjustment					
	N	%	N	%	Standardized Difference	Standardized Difference
Patients (N)	240,826	100%	127,117	100%	-	-
Recorded History of Use (days -183, -3)						
NSAIDs	34,633	14.4%	18,705	14.7%	-0.009	0.012
Statins	75,415	31.3%	31,632	24.9%	0.143	0.031
Corticosteroids history	54,276	22.5%	34,587	27.2%	-0.108	0.011
ACE inhibitor	38,562	16.0%	17,806	14.0%	0.056	0.021
ARBs	33,591	13.9%	14,252	11.2%	0.083	0.017
Anticoagulant history	20,593	8.6%	8,009	6.3%	0.086	0.012
Antiplatelet history	13,276	5.5%	5,365	4.2%	0.060	0.014
Thrombolytic history	300	0.1%	110	0.1%	0.012	0.001
Blood transfusion	949	0.4%	349	0.3%	0.021	-0.000
Estrogen replacement therapy	15,762	6.5%	10,864	8.5%	-0.076	-0.012
Anti-cancer therapy	3,898	1.6%	1,671	1.3%	0.025	0.002
Oral contraceptives	11,131	4.6%	7,674	6.0%	-0.063	-0.012
Testosterone replacement	2,162	0.9%	1,322	1.0%	-0.015	-0.000

COVID-19 and influenza defined by a positive NAAT or diagnosis code in all care settings.
Adjustment performed using propensity score stratum weighting to estimate an average treatment effect after trimming non-overlap.

Risk of Arterial Thrombotic Events in COVID-19 vs. 2018-19 Influenza, by Index Care Setting

Cohort	No. of patients	No. of patients after trimming	No. of events	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
All care settings (primary cohorts)					
COVID-19	240,826	240,811	6,703	1.98 (1.88-2.09)	**1.09 (1.03-1.16)**
Influenza	127,117	127,115	1,674		
Ambulatory					
COVID-19	184,869	184,825	2,005	2.16 (1.96-2.37)	**1.60 (1.44-1.78)**
Influenza	118,620	118,615	535		
Inpatient					
COVID-19	30,136	30,116	4,630	1.11 (1.04-1.18)	0.99 (0.93-1.06)
Influenza	8,216	8,165	1,138		

COVID-19 and influenza defined by a positive NAAT or diagnosis code.
Adjustment performed using propensity score stratum weighting to estimate an average treatment effect after trimming non-overlap.

Risk of Secondary Arterial Thrombotic Events and Death in COVID-19 vs. 2018-19 Influenza

Cohort	No. of patients	No. of patients after trimming	No. of events	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Secondary arterial thrombotic outcome definition					
COVID-19	240,826	240,811	19,430	1.80 (1.74-1.85)	**1.08 (1.05-1.12)**
Influenza	127,117	127,115	5,408		
Mortality among those with an arterial thrombotic event					
COVID-19	6,703	6,666	1,417	3.43 (2.83-4.15)	**3.42 (2.72-4.32)**
Influenza	1,674	1,612	114		

COVID-19 and influenza defined by a positive NAAT or diagnosis code in all care settings.
Adjustment performed using propensity score stratum weighting to estimate an average treatment effect after trimming non-overlap.

Risk of Arterial Thrombotic Events in COVID-19 vs. 2018-19 Influenza, by CVD History

Cohort	No. of patients	No. of patients after trimming	No. of events	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Among those with CVD history					
COVID-19	64,907	64,892	4,997	1.63 (1.52-1.73)	**1.09 (1.02-1.17)**
Influenza	24,185	24,172	1,182		
Among those without CVD history					
COVID-19	175,919	175,894	1,706	1.95 (1.76-2.16)	**1.15 (1.03-1.28)**
Influenza	102,932	102,931	492		

COVID-19 and influenza defined by a positive NAAT or diagnosis code in all care settings.
Adjustment performed using propensity score stratum weighting to estimate an average treatment effect after trimming non-overlap.

Risk of Venous Thromboembolism Events in COVID-19 vs. 2018-19 Influenza, by Index Care Setting

Cohort	No. of patients	No. of patients after trimming	No. of events	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
All care settings (primary cohorts)					
COVID-19	240,826	240,811	4,232	3.27 (3.01-3.55)	**1.89 (1.73-2.07)**
Influenza	127,117	127,115	648		
Ambulatory					
COVID-19	184,869	184,825	1,396	3.75 (3.25-4.33)	**2.92 (2.50-3.41)**
Influenza	118,620	118,615	220		
Inpatient					
COVID-19	30,136	30,116	2,738	1.73 (1.56-1.91)	**1.62 (1.45-1.80)**
Influenza	8,216	8,198	427		

COVID-19 and influenza defined by a positive NAAT or diagnosis code.
Adjustment performed using propensity score stratum weighting to estimate an average treatment effect after trimming non-overlap.

Risk of Secondary Venous Thromboembolism Events and Death in COVID-19 vs. 2018-19 Influenza

Cohort	No. of patients	No. of patients after trimming	No. of events	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Secondary venous thromboembolism outcome definition					
COVID-19	240,826	240,811	4,643	3.14 (2.91-3.40)	**1.88 (1.72-2.04)**
Influenza	127,117	127,115	745		
Mortality among those with a venous thromboembolism event					
COVID-19	4,232	4,167	709	3.09 (2.22-4.30)	**3.18 (2.15-4.71)**
Influenza	648	610	37		

COVID-19 and influenza defined by a positive NAAT or diagnosis code in all care settings.
Adjustment performed using propensity score stratum weighting to estimate an average treatment effect after trimming non-overlap.

Risk of Venous Thromboembolism Events in COVID-19 vs. 2018-19 Influenza, by History of Venous Thromboembolism

Cohort	No. of patients	No. of patients after trimming	No. of events	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Among those with venous thromboembolism history					
COVID-19	7,210	7,131	1,008	1.84 (1.58-2.15)	**1.34 (1.13-1.59)**
Influenza	2,492	2,430	198		
Among those without venous thromboembolism history					
COVID-19	233,616	233,605	3,224	3.64 (3.30-4.02)	**2.18 (1.96-2.43)**
Influenza	124,625	124,624	450		

COVID-19 and influenza defined by a positive NAAT or diagnosis code in all care settings.
Adjustment performed using propensity score stratum weighting to estimate an average treatment effect after trimming non-overlap.

Potential Study Limitations

Limitation	Reasons Limitation May Occur
Selection Bias	Variations in COVID-19 testing by: • Geography • Calendar time • Disease severity
Misclassification	Lack of validation of ICD-10 diagnoses for thromboembolic events
Uncontrolled Confounding	Incomplete data on race Calculated propensity scores in primary cohorts only
Generalizability	Assessed COVID-19 April – October 2020

Conclusions and Potential Implications

Conclusions: Aim 1

- **Among COVID-19 patients, unadjusted rates of arterial and venous thrombotic events were high in:**
  - Older age groups
  - Male sex
  - Greater severity of disease at COVID-19 diagnosis
  - Hospitalized persons
  - Prior CVD, VTE
- **Unadjusted rates of arterial, venous thrombotic events decreased over time**

Conclusions: Aim 2

- **Factors associated with arterial thrombotic events included:**
  - Older age
  - Male sex
  - Alcohol abuse
  - Tobacco use
  - Pregnancy
  - Kidney disease
  - Diabetes
  - Prior CVD
  - Neurologic disease
  - Atrial fibrillation
  - Inherited thrombophilia
  - Polycythemia
  - Thrombocytosis
  - Heart failure
  - Antiplatelet use
  - Anticoagulant use (↓ risk)
  - Cancer (↓ risk)

Conclusions: Aim 2

- **Factors associated with venous thromboembolic events included:**
  - Older age
  - Male sex
  - Alcohol abuse
  - Tobacco use
  - Pregnancy
  - Kidney disease
  - Diabetes
  - Cancer
  - Obesity
  - Hypertension
  - Prior VTE
  - COPD
  - Atrial fibrillation
  - Inherited thrombophilia
  - Polycythemia
  - Thrombocytosis
  - Heart failure
  - Antiplatelet use
  - Hyperlipidemia (↓ risk)
  - Anticoagulant use (↓ risk)
  - Statin use (↓ risk)

Conclusions: Aim 3

- **Risk of primary and secondary arterial thrombotic events higher in COVID-19 than influenza patients in all care settings**
  - No difference when results were stratified by history of CVD
- **Risk of primary and secondary venous thrombotic events higher in COVID-19 than influenza patients in all care settings**
  - Association between COVID-19 and venous thromboembolic events stronger in persons without history of VTE
- **30-day mortality >3x higher for COVID-19 vs influenza patients after arterial or venous thrombotic events**

Acknowledgements: Sentinel COVID-19 Coagulopathy Working Group

- **University of Pennsylvania**:
  - Dena M. Carbonari, MS
  - Sean Hennessy, PharmD, PhD
  - Rebecca Hubbard, PhD
  - Allyson M. Pishko, MD, MSCE
- **Sentinel Operations Center**:
  - Meighan Rogers Driscoll, MPH
  - John Connolly, ScM, ScD
  - Laura Hou, MS, MPH
  - Maria E. Kempner, BA
  - Jenice Ko, BS
  - Jolene Mosley
  - Andrew Petrone, MPH
- **Data Partners**:
  - Aetna; Cheryl Walraven, Audrey Djibo Carla Brannan
  - HealthPartners; Pamela Pawloski, Terese Defor
  - Humana; Thomas Harkins, Yunping Zhou, Vinit Nair
  - Kaiser Permanente Colorado; Claudia Steiner, Karen Glenn, Mahesh Maiyani
  - Kaiser Permanente Northwest; Jennifer Kuntz, Catherine Cleveland
  - Kaiser Permanente Washington; Laura Harrington, Monica Fuji
- **US Food & Drug Administration**:
  - Sarah K. Dutcher, PhD, MS
  - Silvia Perez-Vilar, PharmD, PhD
  - Brian Kit, MD, MPH

Funding: US FDA Contract 75F40119D10037

Sentinel

Extra Slides

Risk Factors for Primary ATE Events in COVID-19

Characteristic	Adjusted Hazard Ratio (95% CI)
Age	
18-44 years	Reference
45-54 years	**3.52 (2.72-4.56)**
55-64 years	**5.38 (4.23-6.85)**
65-74 years	**7.73 (6.10-9.80)**
75-84 years	**8.73 (6.87-11.09)**
≥85 years	**8.76 (6.86-11.18)**
Male sex	**1.27 (1.21-1.34)**
Obesity	0.95 (0.90-1.00)
Alcohol abuse	**1.18 (1.06-1.31)**
Tobacco use	**1.18 (1.11-1.24)**

Characteristic	Adjusted Hazard Ratio (95% CI)
Pregnancy (-90, 0)	**1.48 (1.30-1.68)**
Chronic kidney dz	**1.55 (1.47-1.64)**
Cancer (not NMSC)	**0.91 (0.86-0.97)**
COPD	1.06 (1.00-1.12)
Diabetes	**1.41 (1.33-1.49)**
Hyperlipidemia	1.01 (0.94-1.09)
Hypertension	**2.34 (2.07-2.63)**
Rheumatologic dz	0.97 (0.88-1.07)
Prior CVD (-365, -1)	**1.57 (1.47-1.68)**
Neurological dz	**1.21 (1.14-1.28)**
Atrial fibrillation	**1.37 (1.29-1.46)**

COVID-19 defined by a positive NAAT or diagnosis code in all care settings.

Risk Factors for Primary ATE Events in COVID-19

Characteristic	Adjusted Hazard Ratio (95% CI)
Antiphospholipid antibody syndrome	0.93 (0.55-1.57)
Inherited (primary) thrombophilia	**1.41 (1.24-1.60)**
Polycythemia*	**1.18 (1.02-1.37)**
Anticoagulant history	**0.87 (0.82-0.93)**
Antiplatelet history	**1.45 (1.36-1.55)**
Statin use	0.98 (0.92-1.03)
Heart failure	**1.81 (1.71-1.92)**
Thrombocytosis†	**1.87 (1.77-1.97)**

* Diagnosis code or hemoglobin >16 g/dL

† Diagnosis code or platelet count >450K/uL

COVID-19 defined by a positive NAAT or diagnosis code in all care settings.

Risk Factors for Primary VTE Events in COVID-19

Characteristic	Adjusted Hazard Ratio (95% CI)
Age	
18-44 years	Reference
45-54 years	**2.49 (2.03-3.06)**
55-64 years	**4.04 (3.35-4.86)**
65-74 years	**5.51 (4.59-6.62)**
75-84 years	**6.44 (5.33-7.78)**
≥85 years	**6.35 (5.18-7.77)**
Male sex	**1.31 (1.23-1.39)**
Obesity	**1.36 (1.27-1.45)**
Alcohol abuse	**1.22 (1.06-1.40)**
Tobacco use	**1.16 (1.08-1.24)**

Characteristic	Adjusted Hazard Ratio (95% CI)
Pregnancy (-90, 0)	**1.48 (1.25-1.75)**
Chronic kidney dz	**1.40 (1.30-1.50)**
Cancer (not NMSC)	**1.18 (1.10-1.26)**
COPD	**1.17 (1.09-1.26)**
Diabetes	**1.14 (1.06-1.22)**
Hyperlipidemia	**0.91 (0.83-0.99)**
Hypertension	**1.54 (1.39-1.72)**
Rheumatologic dz	1.10 (0.98-1.23)
Prior VTE (-365, -1)	**4.65 (4.27-5.05)**
Neurological dz	0.99 (0.91-1.08)
Atrial fibrillation	0.95 (0.87-1.03)

COVID-19 defined by a positive NAAT or diagnosis code in all care settings.

Risk Factors for Primary VTE Events in COVID-19

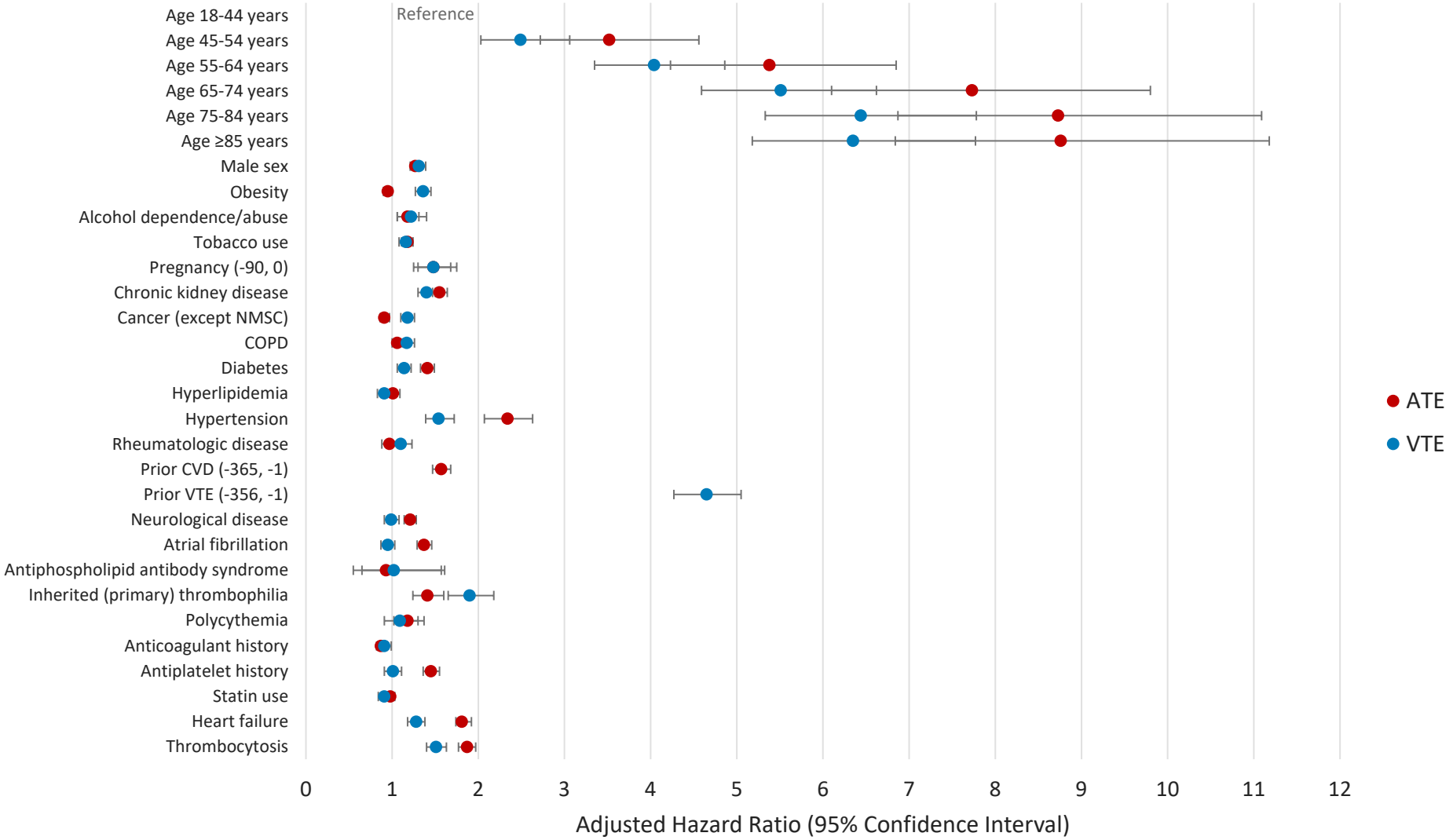
Characteristic	Adjusted Hazard Ratio (95% CI)
Antiphospholipid antibody syndrome	1.02 (0.65-1.61)
Inherited (primary) thrombophilia	**1.90 (1.65-2.18)**
Polycythemia*	1.09 (0.91-1.30)
Anticoagulant history	**0.91 (0.84-0.99)**
Antiplatelet history	1.01 (0.91-1.11)
Statin use	**0.90 (0.84-0.97)**
Heart failure	**1.28 (1.18-1.38)**
Thrombocytosis†	**1.51 (1.40-1.63)**

* Diagnosis code or hemoglobin >16 g/dL

† Diagnosis code or platelet count >450,000/µL

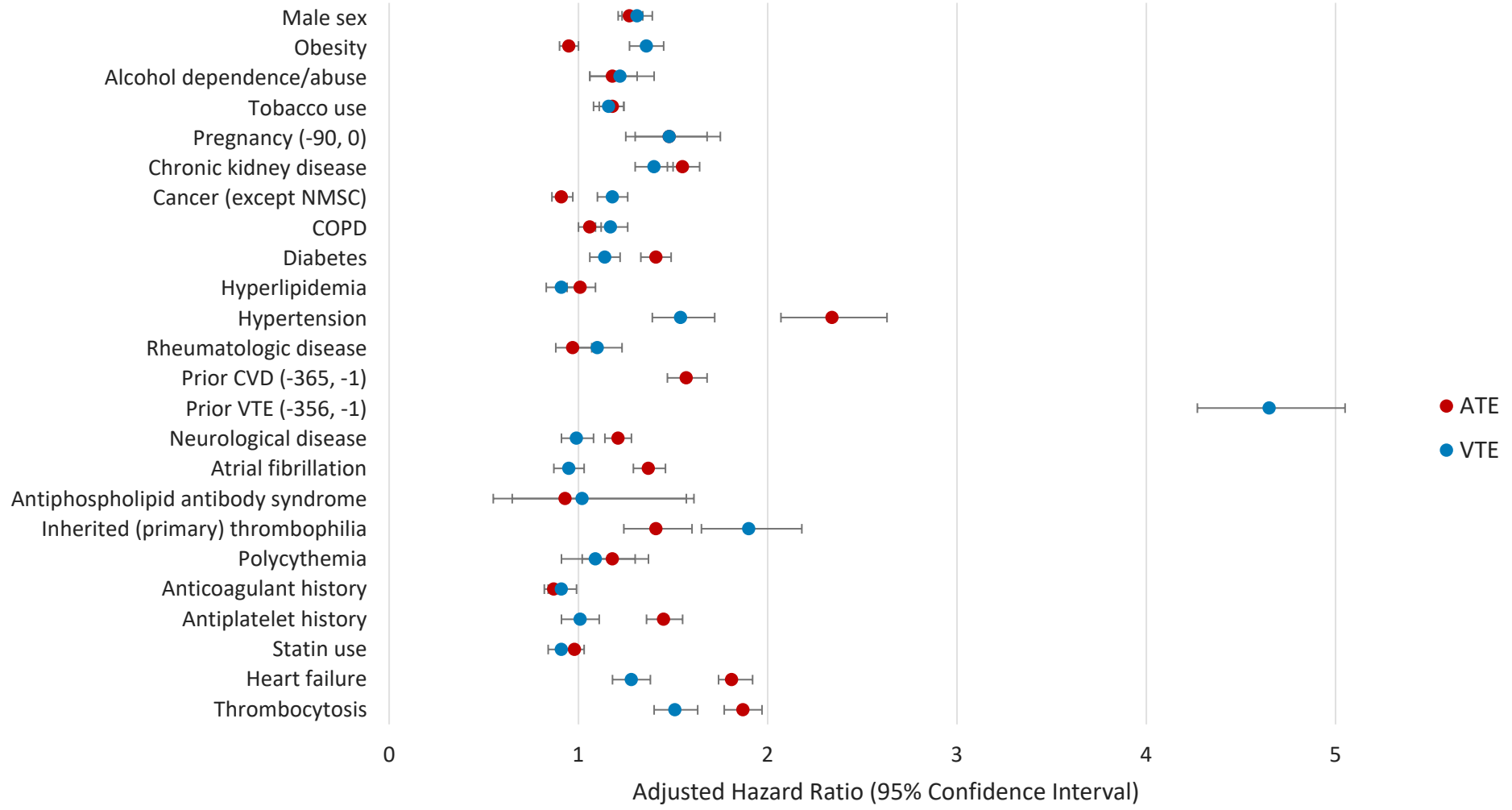
COVID-19 defined by a positive NAAT or diagnosis code in all care settings.

Risk Factors for Primary ATE and VTE Events in COVID-19



COVID-19 defined by a positive NAAT or diagnosis code in all care settings.

Risk Factors for Primary ATE and VTE Events in COVID-19



COVID-19 defined by a positive NAAT or diagnosis code in all care settings.

Published Estimates on 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.