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Thromboembolism risk of COVID-19: a focus on the ethnicity

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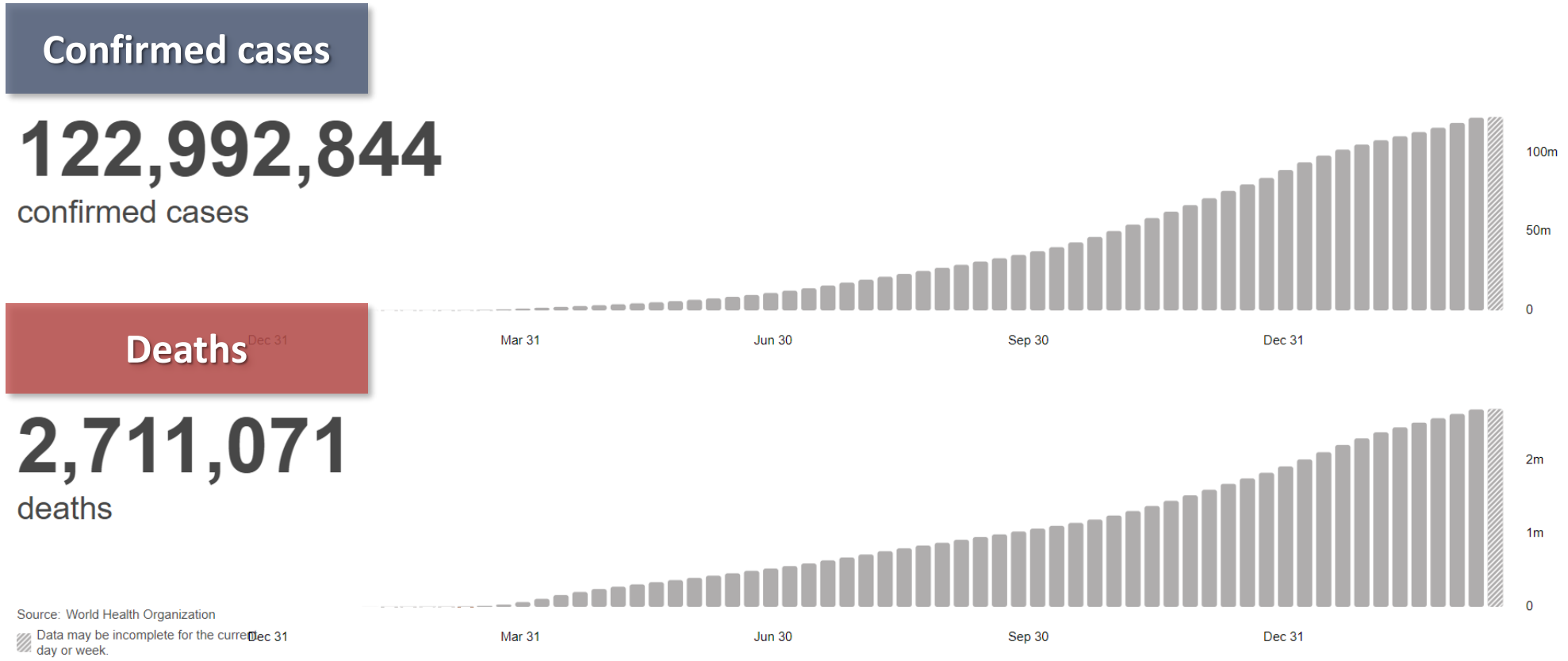
2021.04.10.

Conflict of Interest

- I have nothing to declare regarding this presentation.

Introduction

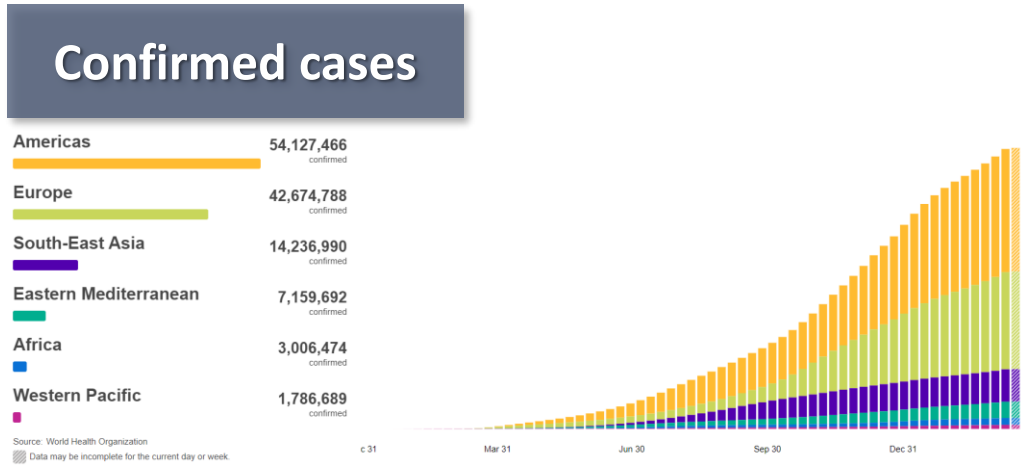
- **Epidemiology of COVID-19**

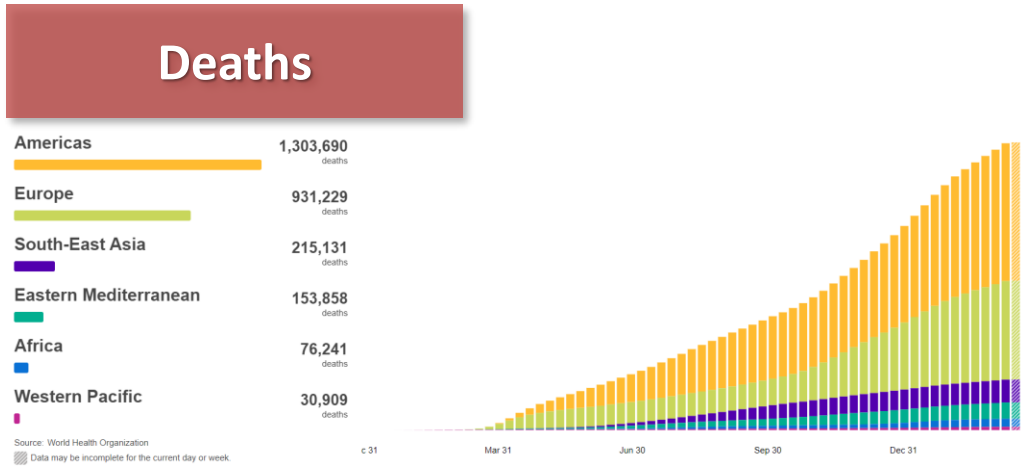


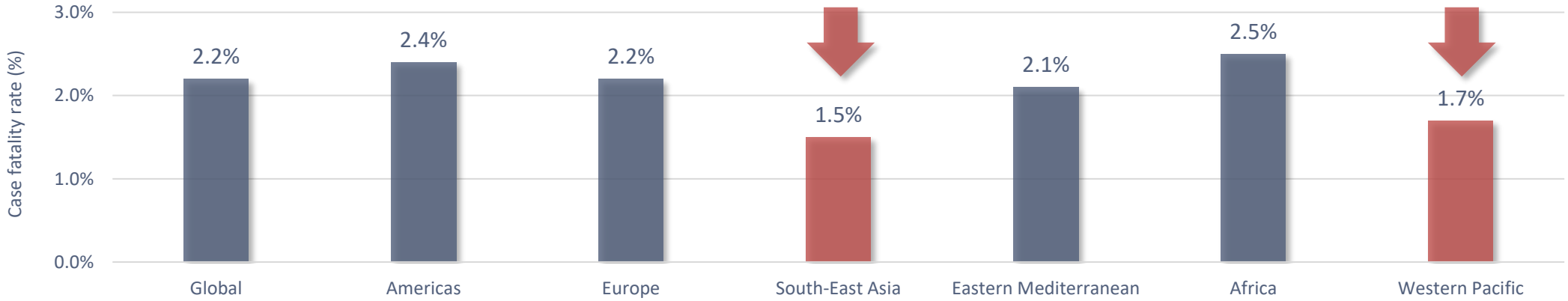
https://covid19.who.int, accessed 22 Mar 2021.

Introduction

- **Regional differences in fatality of COVID-19**







https://covid19.who.int, accessed 22 Mar 2021.

Introduction

Risk of COVID-19-related fatality by ethnicity

- **White = Asian < Black = Hispanic**

REVIEW

Annals of Internal Medicine

Racial and Ethnic Disparities in COVID-19–Related Infections, Hospitalizations, and Deaths

A Systematic Review

Katherine Mackey, MD, MPP; Chelsea K. Ayers, MPH; Karli K. Kondo, PhD; Somnath Saha, MD, MPH; Shailesh M. Advani, MD, MPH; Sarah Young, MPH; Hunter Spencer, DO; Max Rusek, MD; Johanna Anderson, MPH; Stephanie Veazie, MPH; Mia Smith, MPH; and Devan Kansagara, MD, MCR

Background: Data suggest that the effects of coronavirus disease 2019 (COVID-19) differ among U.S. racial/ethnic groups.

Purpose: To evaluate racial/ethnic disparities in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection rates and COVID-19 outcomes, factors contributing to disparities, and interventions to reduce them.

Data Sources: English-language articles in MEDLINE, PsycINFO, CINAHL, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus, searched from inception through 31 August 2020. Gray literature sources were searched through 2 November 2020.

Study Selection: Observational studies examining SARS-CoV-2 infections, hospitalizations, or deaths by race/ethnicity in U.S. settings.

Data Extraction: Single-reviewer abstraction confirmed by a second reviewer; independent dual-reviewer assessment of quality and strength of evidence.

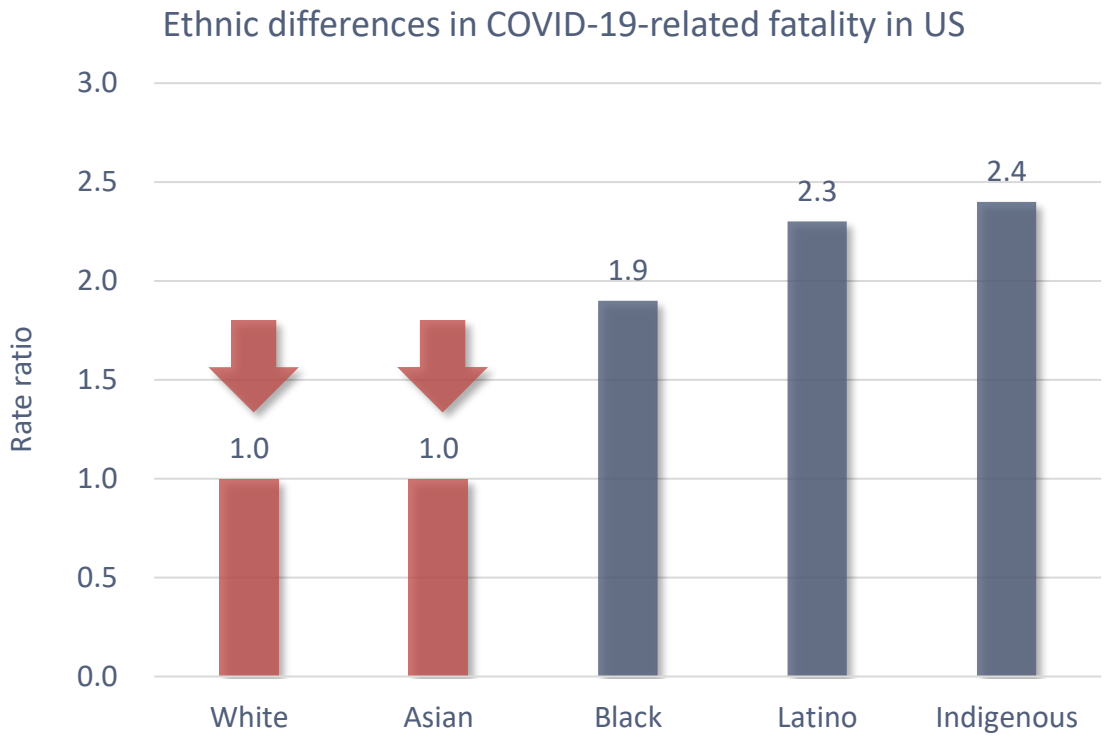
Data Synthesis: 37 mostly fair-quality cohort and cross-sectional studies, 15 mostly good-quality ecological studies, and data from the Centers for Disease Control and Prevention and APM Research Lab were included. African American/Black and Hispanic populations experience disproportionately higher rates of SARS-CoV-2 infection, hospitalization, and COVID-19–related mortality compared with non-Hispanic White populations, but not higher case-fatality rates (mostly reported as in-hospital mortality) (moderate- to high-strength evidence). Asian populations experience similar outcomes to non-Hispanic White populations (low-strength evidence). Outcomes for other racial/ethnic groups have been insufficiently studied. Health care access and exposure factors may underlie the observed disparities more than susceptibility due to comorbid conditions (low-strength evidence).

Limitations: Selection bias, missing race/ethnicity data, and incomplete outcome assessments in cohort and cross-sectional studies must be considered. In addition, adjustment for key demographic covariates was lacking in ecological studies.

Conclusion: African American/Black and Hispanic populations experience disproportionately higher rates of SARS-CoV-2 infection and COVID-19–related mortality but similar rates of case fatality. Differences in health care access and exposure risk may be driving higher infection and mortality rates.

Primary Funding Source: Department of Veterans Affairs, Veterans Health Administration, Health Services Research & Development. (PROSPERO: CRD42020187078)

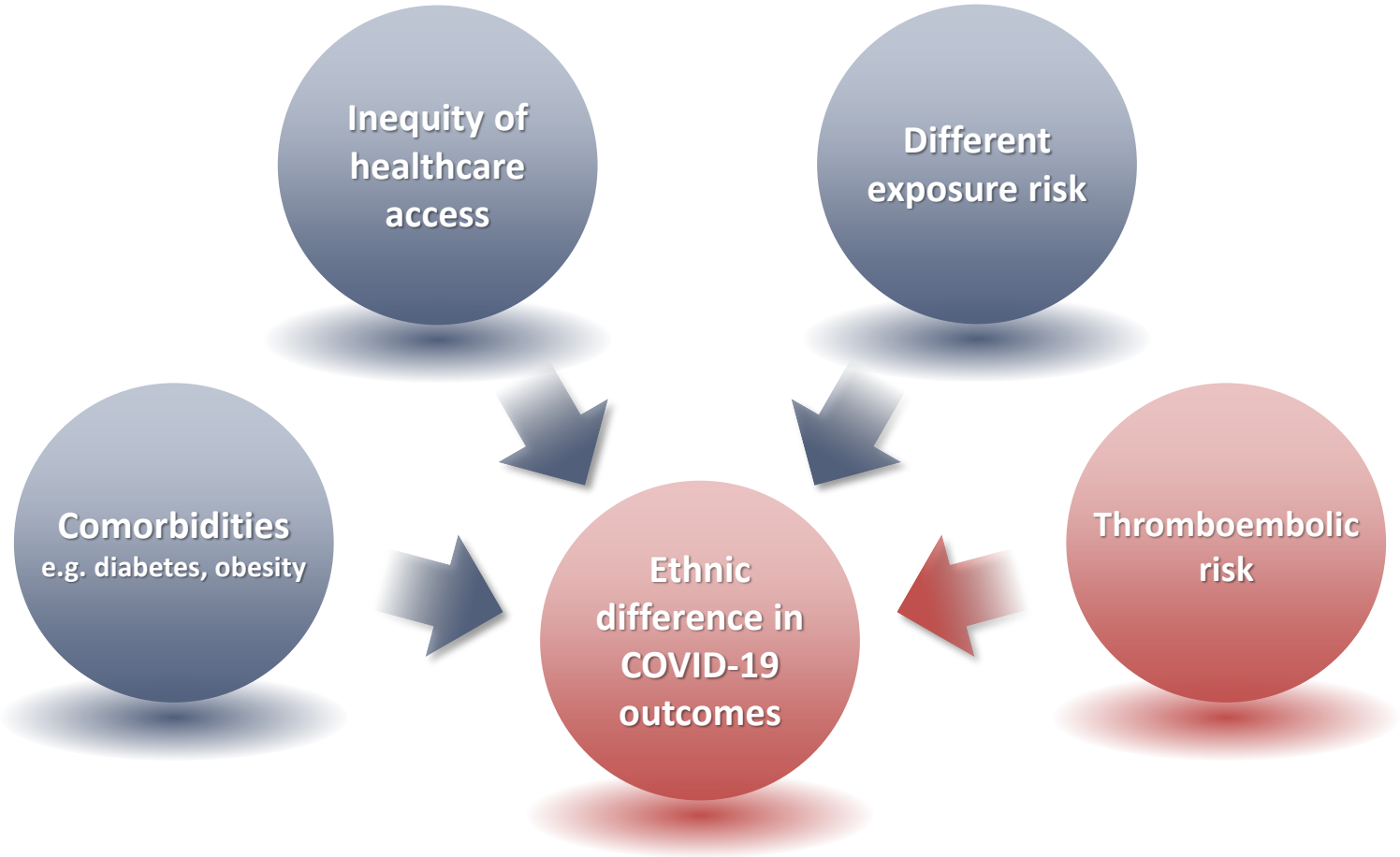
Ann Intern Med. 2021;174:362-373. doi:10.7326/M20-6306 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 1 December 2020.



Mackey, Ann Intern Med. 2021. and https://www.cdc.gov, accessed 22 Mar 2021.

Introduction

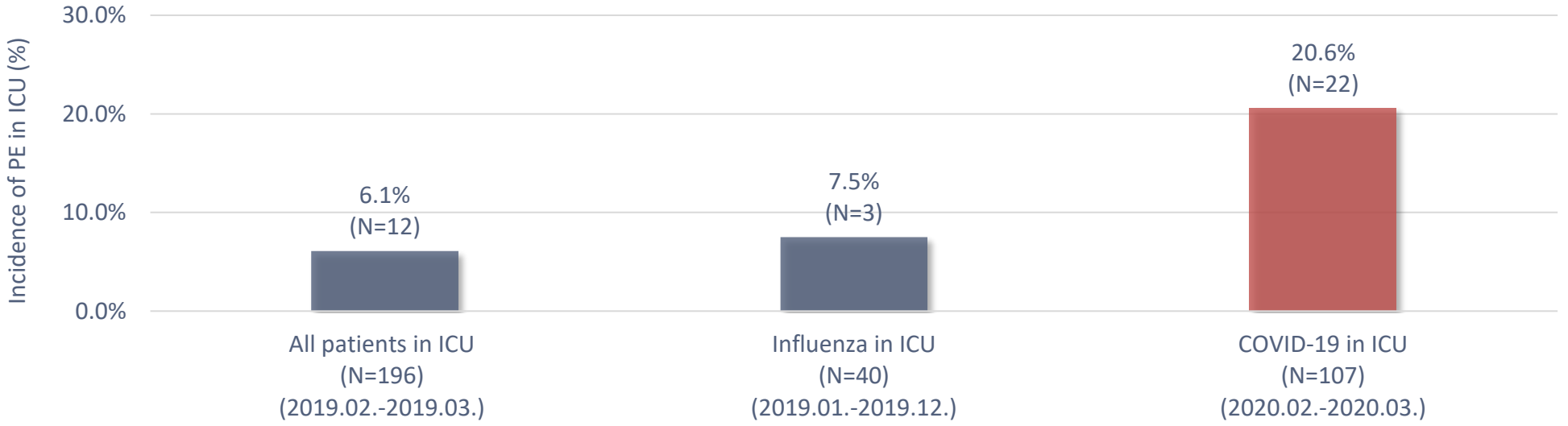
- **Factors that may affect ethnic difference in COVID-19 outcomes**



Evans, N Engl J Med. 2020. and Iba, Int J Hematol. 2021.

Epidemiology of VTE in COVID-19

- **Pulmonary embolism events in ICU: COVID-19 vs. others**
  - **All patients in ICU (N=196) (2019.02.-2019.03.): 6.1% (N=12)**
  - **Influenza in ICU (N=40) (2019.01.-2019.12.): 7.5% (N=3)**
  - **COVID-19 in ICU (N=107) (2020.02.-2020.03.): 20.6% (N=22)**



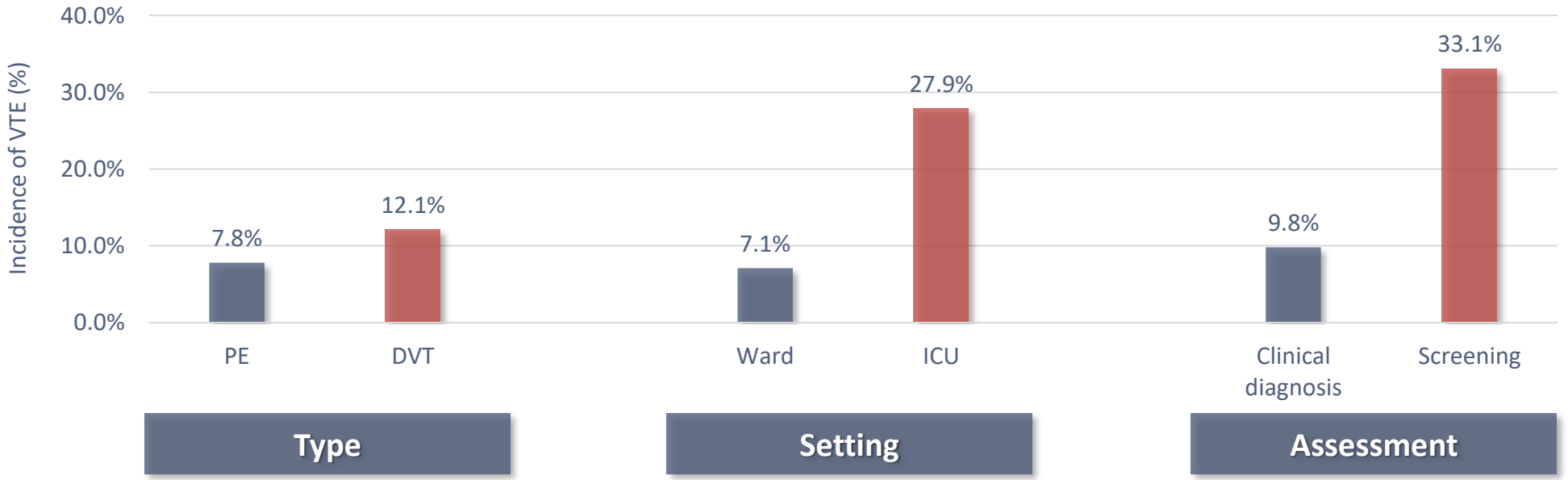
Abbreviations: ICU, intensive care unit; PE, pulmonary embolism.

Poissy, Circulation. 2020.

Epidemiology of VTE in COVID-19

Incidence of VTE in COVID-19

- **Pooled analysis of 18,093 patients from 48 studies**
- **Incidence of VTE in COVID-19: 17.0% (95% CI, 13.4-20.9)**



Abbreviations: DVT, deep vein thrombosis; ICU, intensive care unit; PE, pulmonary embolism; VTE, venous thromboembolism.

Jimenez, Chest. 2021.

Risk factors for VTE in COVID-19

Risk factors for thromboembolic events in COVID-19

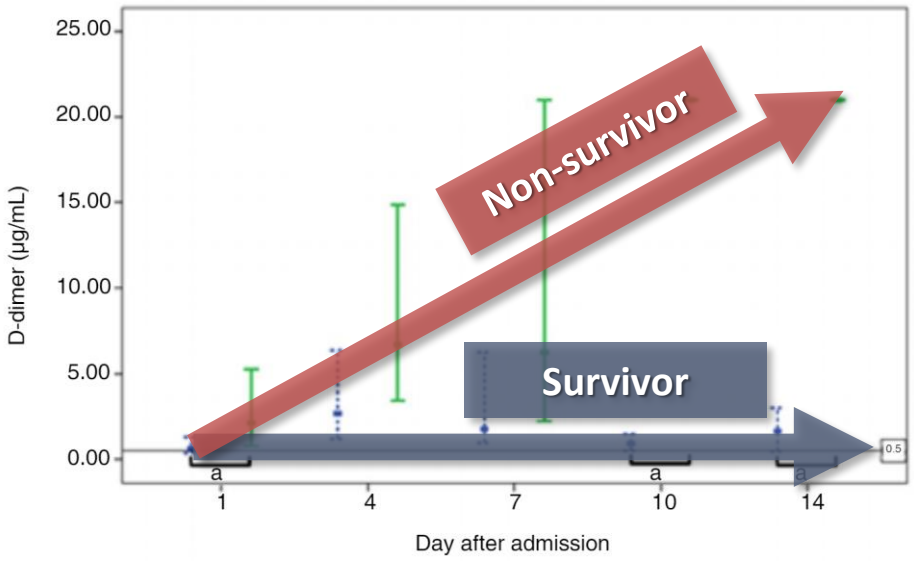
Study	Prevalence of thromboembolic event, N (%)	Risk factors
Demelo-Rodriguez (N=156)	23 (14.7)	Elevated D-dimer
Zhang (N=143)	66 (46.1)	Higher Padua prediction score, CURB-65 score, elevated D-dimer
Artifoni (N=71)	23 (32.5)	Elevated D-dimer
Xu (N=138)	4 (2.9)	ICU hospitalization
Middeldorp (N=198)	33 (17)	Elevated D-dimer
Chen (N=88)	40 (46)	Elevated D-dimer, hypoalbuminemia, higher SOFA score, inpatient status
Cui (N=81)	20 (25)	Elevated D-dimer, older age, lower lymphocyte counts, longer aPTT
Klok (N=184)	31 (16.8)	Older age
Whyte (N=214)	80 (37)	Elevated D-dimer
Grillet (N=100)	23 (23)	Invasive mechanical ventilation, ICU hospitalization, delay from onset of symptoms to CT scan
Leonard-Lorant (N=106)	32 (30)	Elevated D-dimer, ICU hospitalization, delay from onset of symptoms to CT scan
Fraisse (N=92)	37 (40)	Chronic renal failure, invasive mechanical ventilation, elevated D-dimer
Bompard (N=135)	32 (23.7)	More frequently hospitalized in ICU, under mechanical ventilation, longer median hospitalization duration, elevated D-dimer

Abbreviations: aPTT, activated partial thromboplastin time; CT, computed tomography; ICU, intensive care unit; SOFA, sequential organ failure assessment.

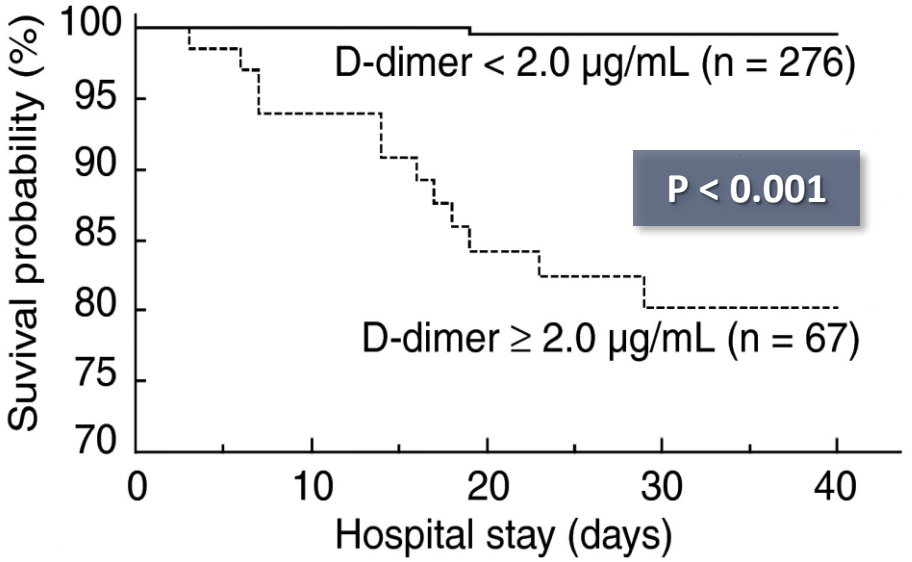
Kafale, Clin Appl Thromb Hemost. 2020.

Risk factors for VTE in COVID-19

- **D-dimer as a prognostic factor in COVID-19**
  - **183 patients with COVID-19 from China**



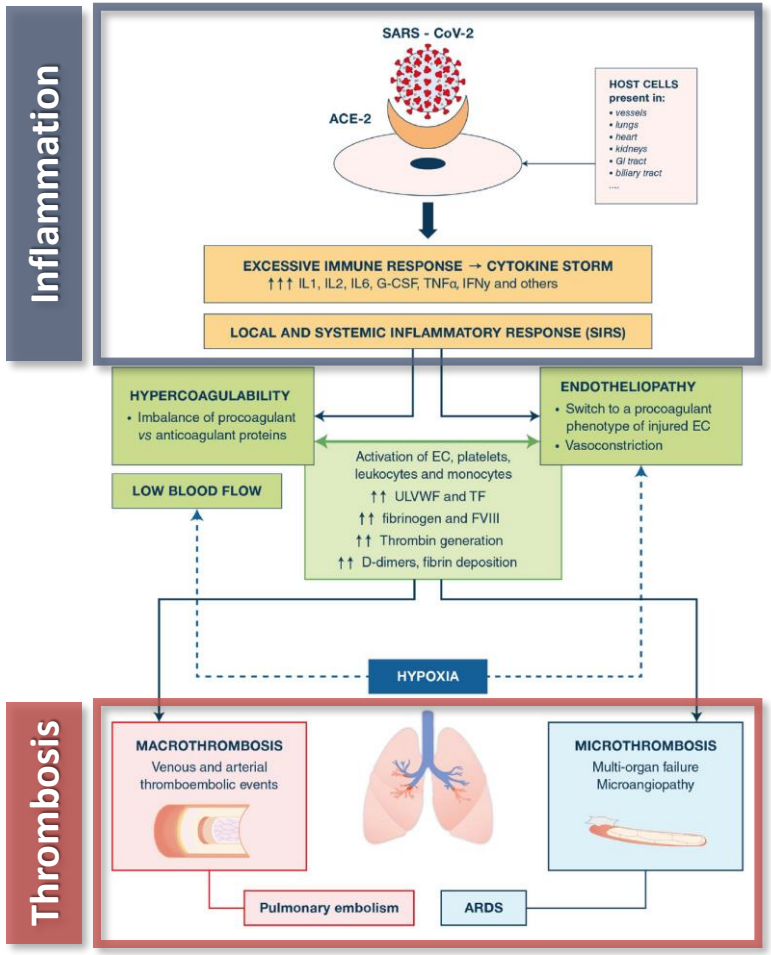
  - **343 patients with COVID-19 from China**

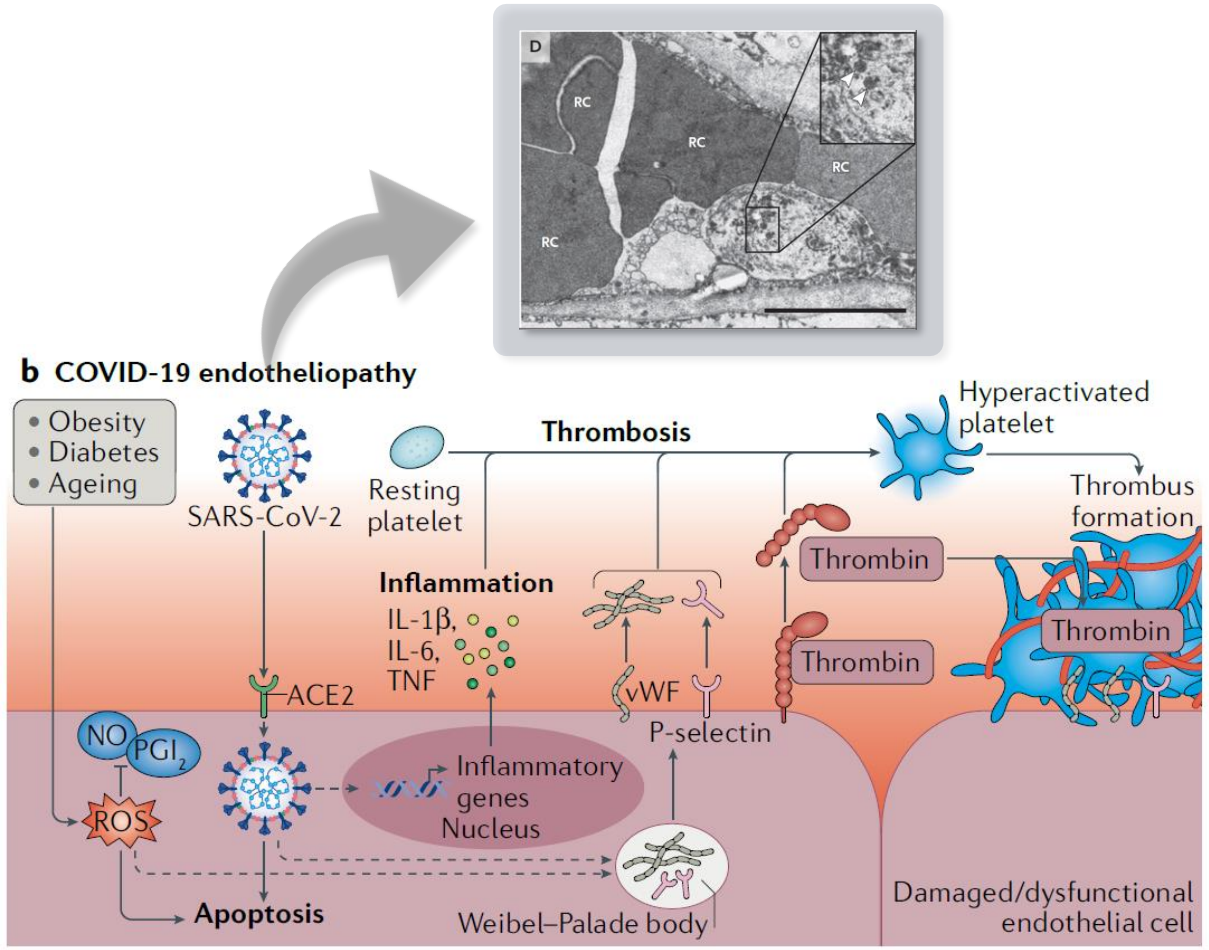


Tang, J Thromb Haemost. 2020. and Zhang, J Thromb Haemost. 2020.

COVID-19-associated Coagulopathy

- **Thromboinflammation in COVID-19**

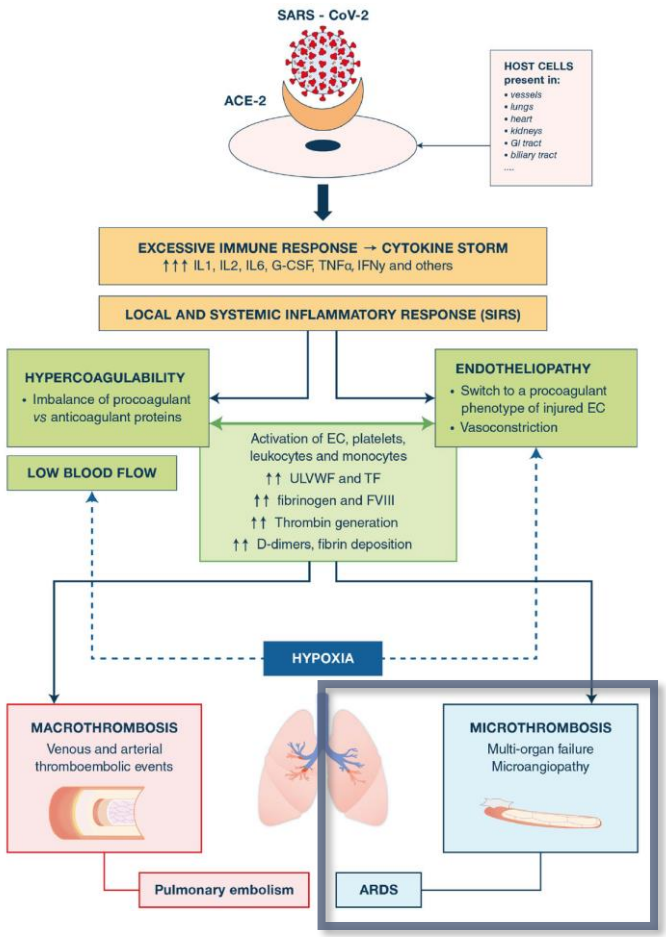


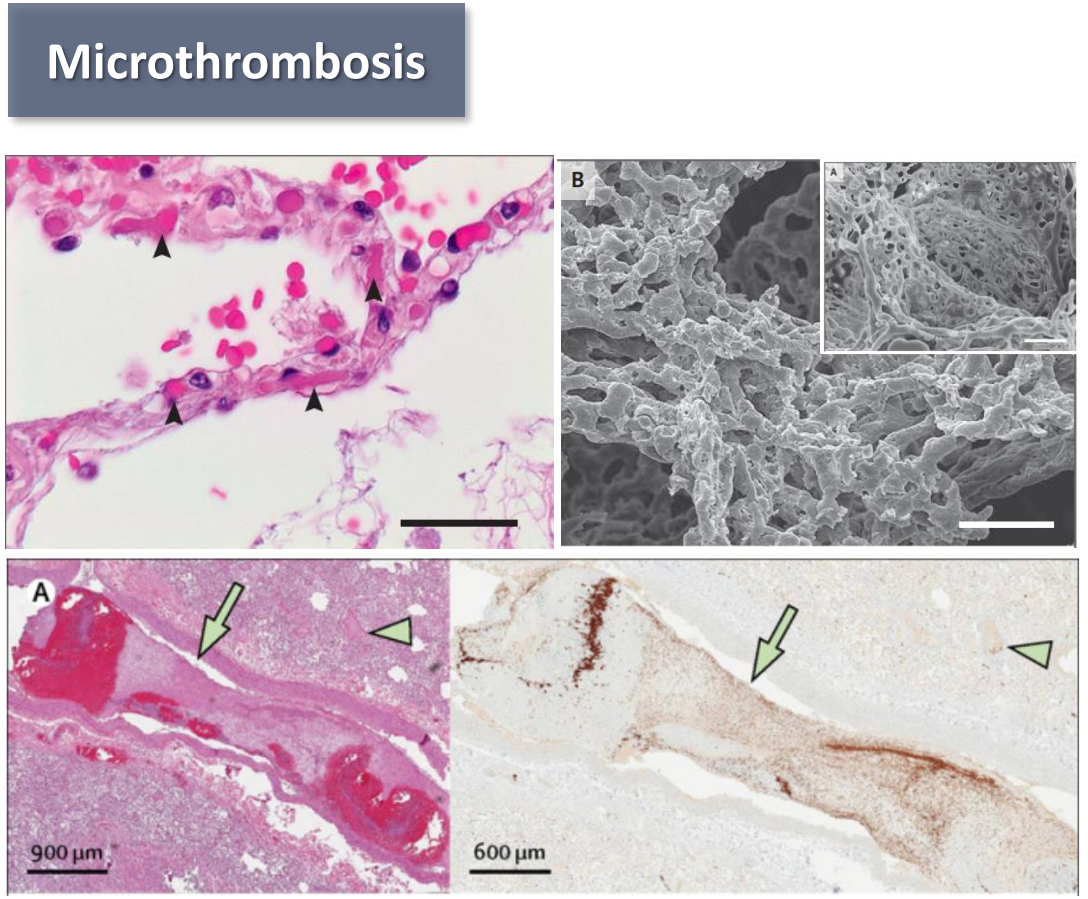


Joly, Intensive Care Med. 2020., Gu, Nat Rev Cardiol. 2021., and Ackermann, N Engl J Med. 2020.

COVID-19-associated Coagulopathy

- **Thromboinflammation in COVID-19**

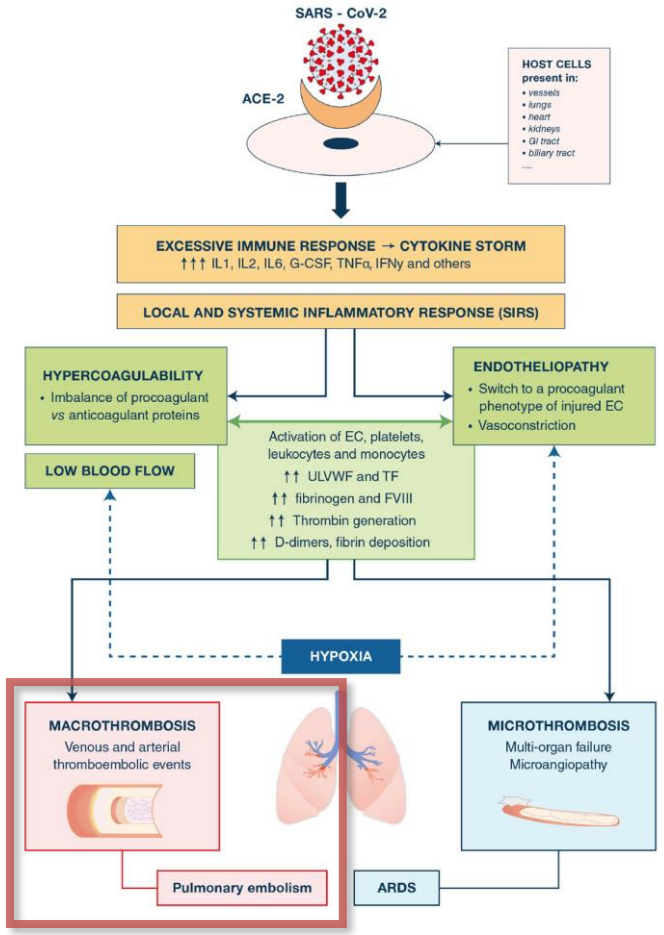




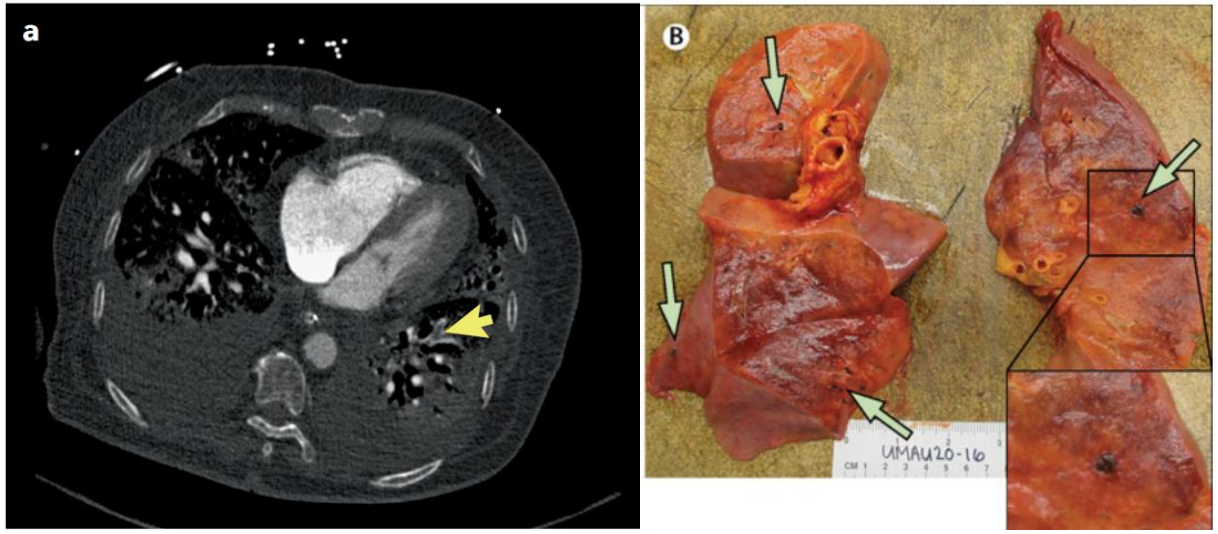
Joly, Intensive Care Med. 2020., Gu, Nat Rev Cardiol. 2021. and Fox, Lancet Respir Med. 2020.

COVID-19-associated Coagulopathy

- **Thromboinflammation in COVID-19**



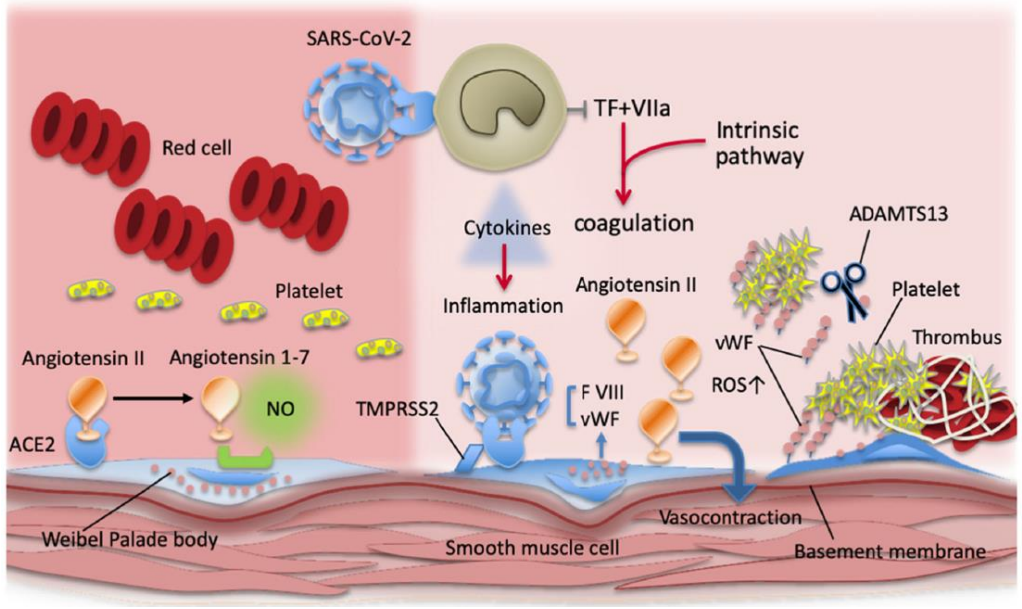
Macrothrombosis



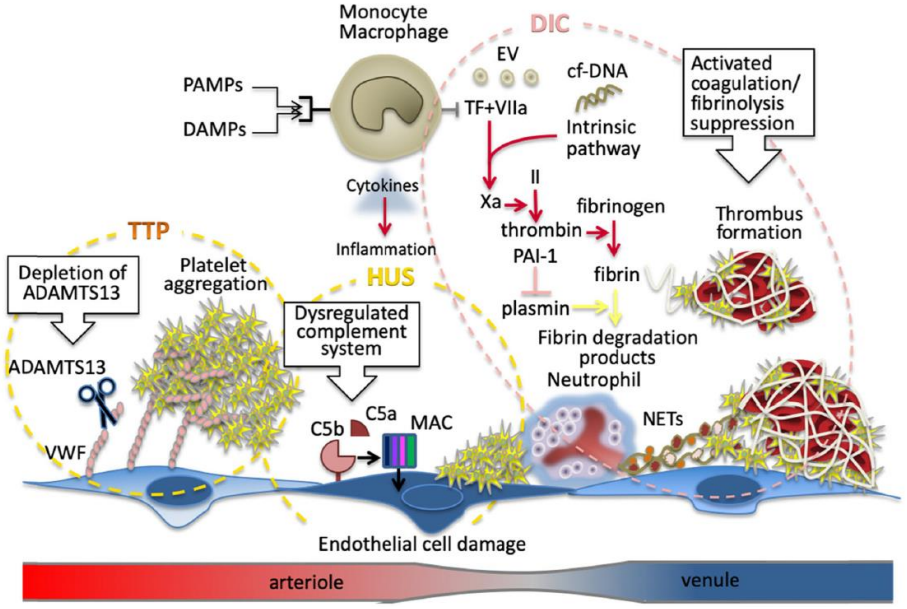
Joly, Intensive Care Med. 2020., Gu, Nat Rev Cardiol. 2021. and Fox, Lancet Respir Med. 2020.

COVID-19-associated Coagulopathy

- **Similarities and differences in thrombosis: COVID-19 vs. others**



COVID-19



DIC / TTP / HUS

Abbreviations: DIC, disseminated intravascular coagulation; HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura.

Toshiaki Iba, et al. Crit Care. 2020.

COVID-19-associated Coagulopathy

Similarities and differences in thrombosis: COVID-19 vs. others

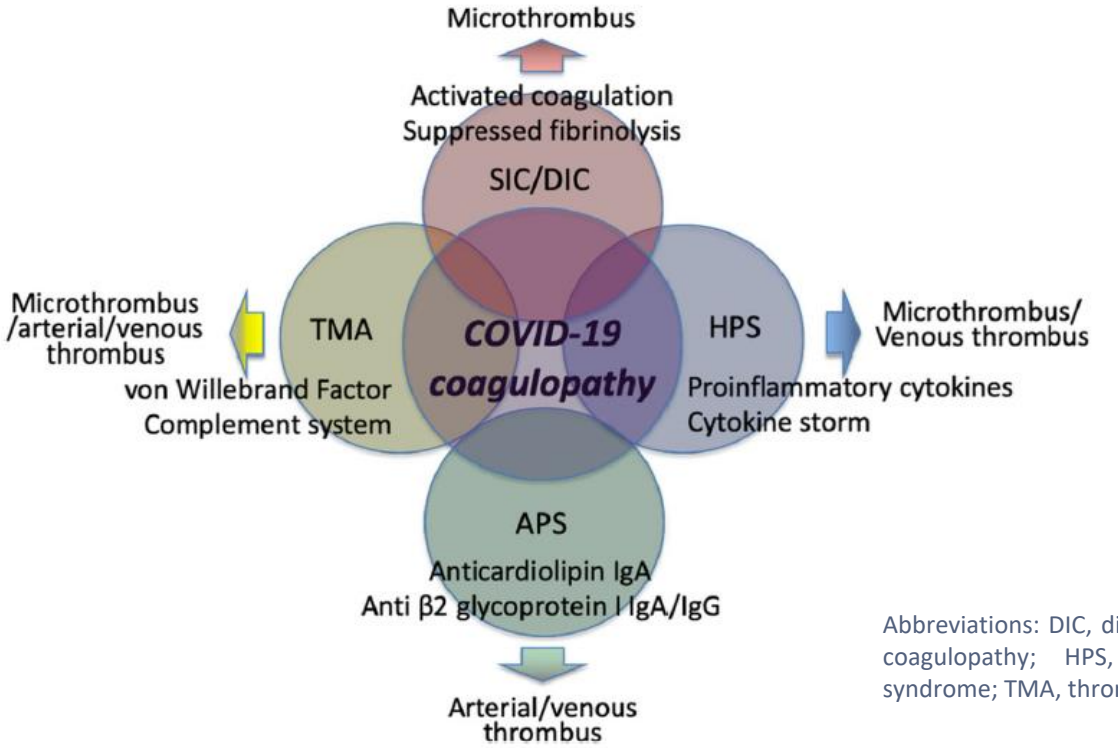
	Primary cause and target of coagulopathy	Thrombo-embolism	Platelet count	D-dimer	PT/aPTT	Fibrinogen	Anti-thrombin	Activated complement system/vWF	Anti-phospholipid antibody	Inflammatory cytokines (IL-1β, IL-6)
COVID-19	Macrophage Endothelial cell	Micro Venous	↑↓	↑	→↑	↑	→	+	+	↑
DIC/SIC	Macrophage Endothelial cell	Micro	↓	↑	↑	→↓	↓	-	-	↑
HPS	Inflammatory cytokines	Micro Venous	↓	→	→	→	→	-	-	↑
APS	Antiphospholipid antibody	Arterial Venous	↓	→	PT → aPTT ↑	→	→	-	+	-
TMA (aHUS/TTP)	Complement system ADAMTS13	Micro Arterial Venous	↓	→↑	→	→	→	aHUS +/- TTP -/+	-	-

Abbreviations: DIC, disseminated intravascular coagulation; SIC, sepsis-induced coagulopathy; HPS, hemophagocytic syndrome; APS, antiphospholipid syndrome; TMA, thrombotic microangiopathy; aHUS, atypical hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura; PT, prothrombin time; aPTT, activated partial thromboplastin time; vWF, von Willebrand factor; IL, interleukin.

Toshiaki Iba, et al. Crit Care. 2020.

COVID-19-associated Coagulopathy

- **Characteristic features of COVID-19-associated coagulopathy**



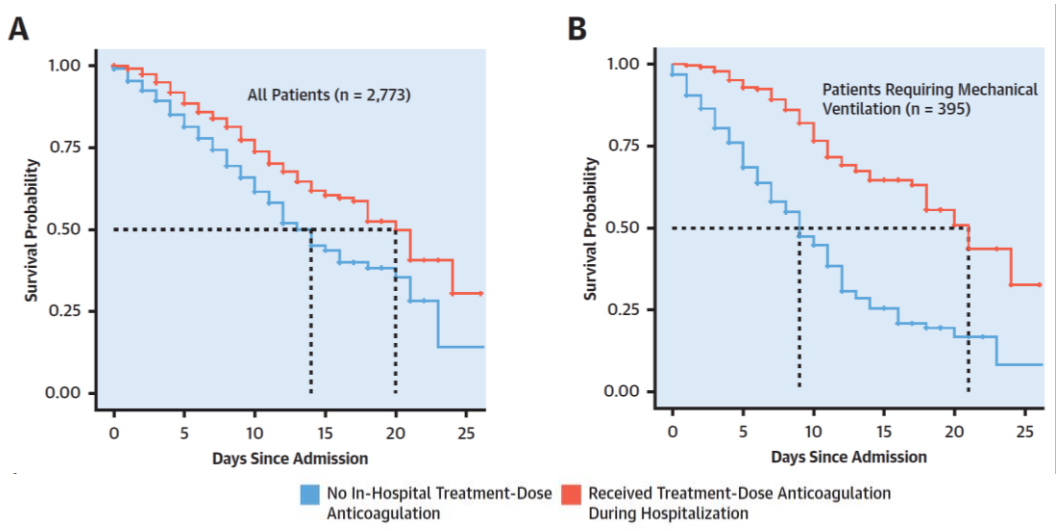
Abbreviations: DIC, disseminated intravascular coagulation; SIC, sepsis-induced coagulopathy; HPS, hemophagocytic syndrome; APS, antiphospholipid syndrome; TMA, thrombotic microangiopathy.

CAC partially overlaps with SIC/DIC, HPS, APS, and TMA.
However, it does not perfectly match with any of these coagulopathies.

Toshiaki Iba, et al. Crit Care. 2020.

Thromboprophylaxis Strategies in COVID-19

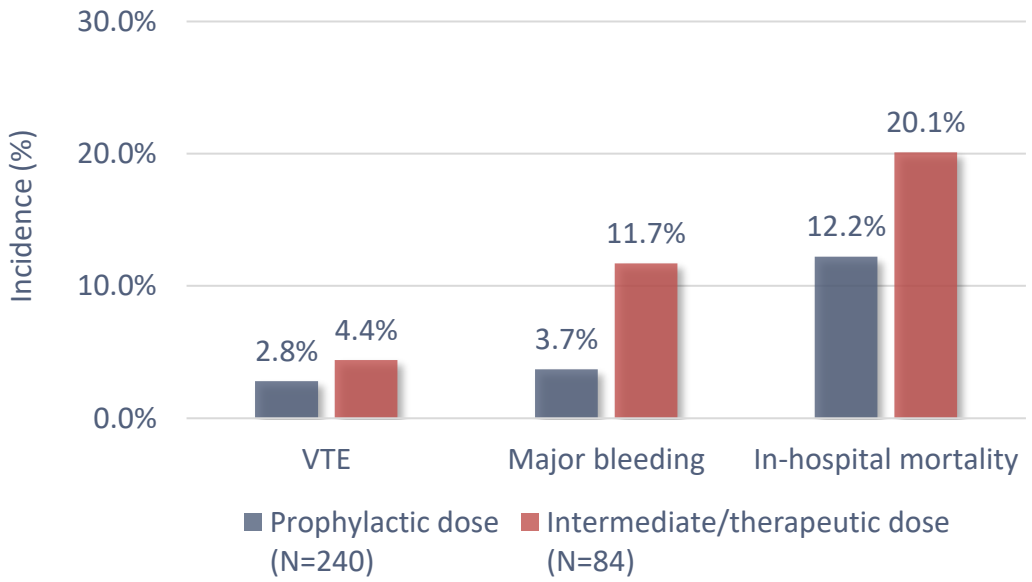
- **Early experience of New York City**
  - **Therapeutic (N=786) vs. Non-therapeutic [prophylactic + no anticoagulation] (N=1,987)**
    - ✓ **In-hospital mortality: 22.5% vs. 22.8%**
    - ✓ **Median survival: 21 days vs. 14 days**
  - **Patients with mechanical ventilation: Therapeutic (N=234) vs. Non-therapeutic (N=161)**
    - ✓ **In-hospital mortality: 29.1% vs. 62.7%**
    - ✓ **Median survival: 21 days vs. 9 days**



Paranjpe, J Am Coll Cardio. 2020.

Thromboprophylaxis Strategies in COVID-19

- **Observational study from Italy**
  - **324 patients with COVID-19 in medical ward**
  - **Prophylactic dose (N=240) vs. Intermediate/therapeutic dose (N=84)**



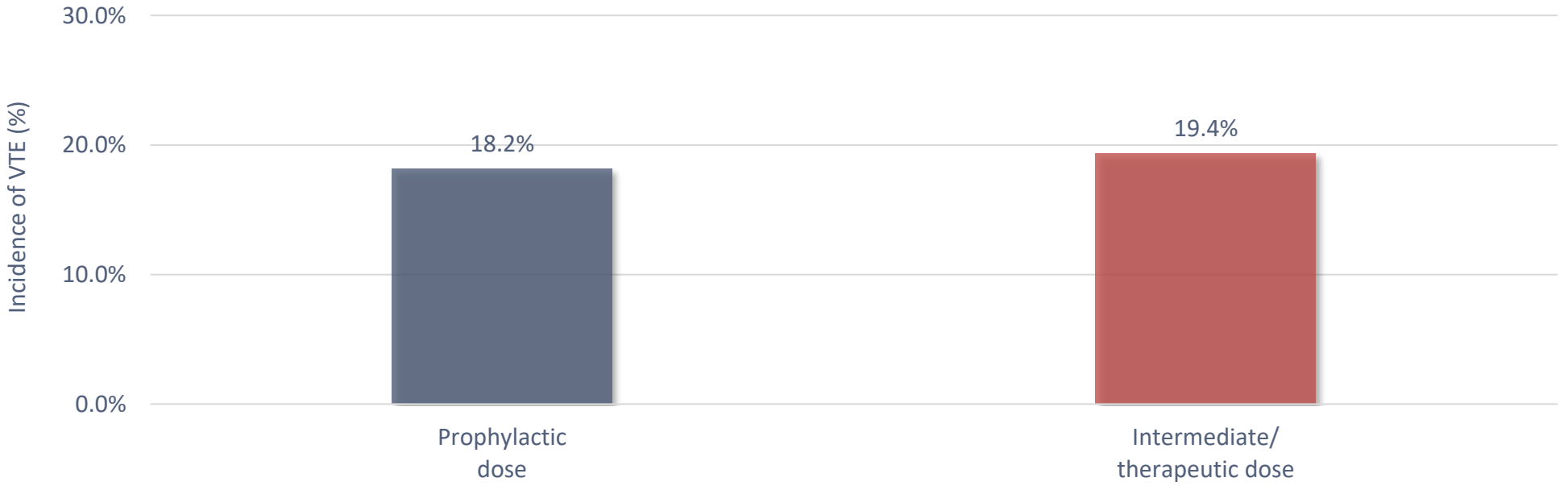
Variables	Major bleeding and clinically relevant non-major bleeding		
	Adjusted HR*	95% CI	P-value
Anticoagulation with intermediate or therapeutic doses	3.89	1.90-7.97	<0.001
Age >80 years	3.40	1.51-7.65	0.003
Dual antiplatelet agents	9.40	2.60-33.70	<0.001

*Adjusted for GFR, D-dimer, history of VTE, concomitant antiplatelet therapy.
Abbreviations: CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism.

Pesavento, J Thromb Haemost. 2020.

Thromboprophylaxis Strategies in COVID-19

- **Meta-analysis: incidence of VTE by intensity of thromboprophylaxis**
  - **Prophylactic dose (N=7,008): 18.2% (12.6%-24.5%)**
  - **Intermediate or therapeutic dose (N=1,549): 19.4% (10.5%-30.2%)**



Abbreviations: VTE, venous thromboembolism.

Jimenez, Chest. 2021.

Thromboprophylaxis Strategies in COVID-19

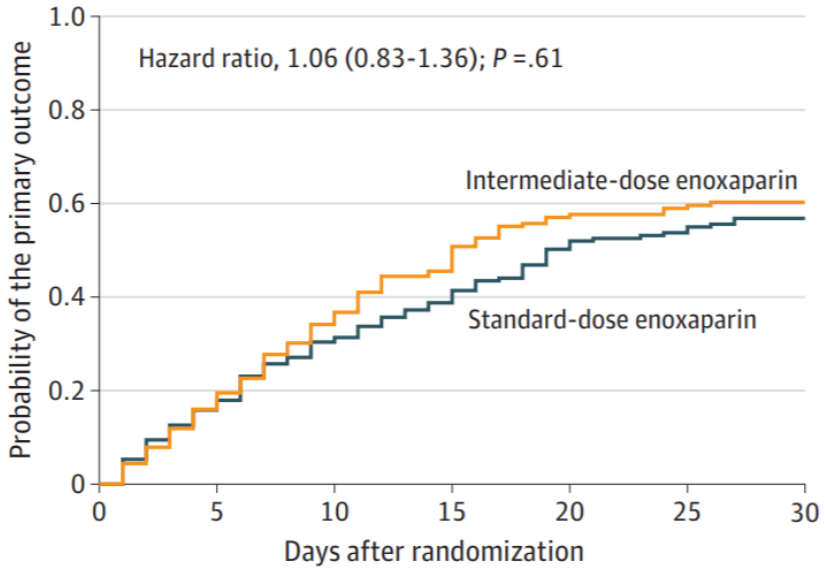
- **Meta-analysis: intermediate vs. prophylactic doses in critically-ill COVID-19**
  - **Mortality (N=141): OR 0.73 (0.33-1.76)**
  - **Pulmonary embolism (N=82): OR 0.09 (0.02-0.57)**
  - **Deep vein thrombosis (N=41): OR 0.35 (0.06-2.02)**
  - **Venous thromboembolism (N=118): OR 0.87 (0.45-1.67)**
  - **Major bleeding (N=141): OR 3.84 (1.44-10.21)**

Abbreviations: OR, odds ratio.

https://guidelines.ash.gradepro.org/profile/3CQ7J0SWt58, accessed 22 Mar 2021.

Thromboprophylaxis Strategies in COVID-19

- **INSPIRATION trial: intermediate vs. prophylactic doses in critically-ill COVID-19**
  - **Primary outcome: composite of venous or arterial thrombosis, ECMO, mortality within 30 days**



	Intermediate dose (N=276)	Prophylactic dose (N=286)	Absolute difference % (95% CI)	Odds ratio (95% CI)	P-value
Primary outcome, N (%)	126 (45.7)	126 (44.1)	1.5 (-6.6-9.8)	1.06 (0.76-1.48)	0.70
All-cause mortality, N (%)	119 (43.1)	117 (40.9)	2.2 (-5.9-10.3)	1.09 (0.78-1.53)	0.50
VTE, N (%)	9 (3.3)	10 (3.5)	-0.2 (-3.2-2.7)	0.93 (0.37-2.32)	0.87
Ventilator-free days, median (IQR)	30 (3-30)	30 (1-30)	0 (0-0)	NA	0.50
Major bleeding, N (%)	7 (2.5)	4 (1.4)	1.1 (-1.1-3.4)	1.83 (0.53-5.93)	0.33
Non-major bleeding, N (%)	12 (4.3)	5 (1.7)	2.5 (-0.2-5.4)	2.55 (0.92-7.04)	0.07
Composite of major and non-major bleeding, N (%)	17 (6.2)	9 (3.1)	3.0 (-0.4-6.4)	2.02 (0.89-4.61)	0.08

Abbreviations: VTE, venous thromboembolism.

INSPIRATION Investigators, JAMA. 2021.

Thromboprophylaxis Strategies in COVID-19

Current recommendations for thromboprophylaxis in COVID-19

Society	Release date	Indication	Intensity
Anticoagulation forum	2020.05.	Acute illness (ward) Critical illness (ICU)	Prophylactic Intermediate
International Society on Thrombosis and Haemostasis (ISTH)	2020.05.	Acute illness (GW) Critical illness (ICU)	Prophylactic Intermediate for high risk
American College of Cardiology (ACC)	2020.06.	Hospitalized	Prophylactic
CHEST	2020.09.	Acute illness (ward) Critical illness (ICU)	Prophylactic
National Institute of Health (NIH)	2021.02.	Hospitalized	Prophylactic
American Society of Hematology (ASH)	2021.02.	Acute illness (ward) Critical illness (ICU)	Prophylactic
British Thoracic Society (BTS)	2021.02.	Acute illness (ward) Critical illness (ICU)	Prophylactic Intermediate
Surviving sepsis campaign guidelines (SSC)	2021.03.	Acute illness (ward) Critical illness (ICU)	Prophylactic

Abbreviations: ICU, intensive care unit.

Barnes, J Thromb Thromboilysis. 2020., Spyropoulos, J Thromb Haemost. 2020, Bikdeli, J Am Coll Cardiol. 2020., Moores, Chest. 2020., Cuker, Blood Adv. 2021. and Alhazzani, Crit Care Med. 2021. https://www.covid19treatmentguidelines.nih.gov/antithrombotic-therapy and https://www.evidence.nhs.uk, assessed 22 Mar 2021.

Thromboprophylaxis Strategies in COVID-19

- **Multiplatform RCTs**
  - **ATTACC: antithrombotic therapy to ameliorate complications of COVID-19**
    - ✓ **58 sites in Canada, US, Brazil, and Mexico**
  - **REMAP-CAP: randomized embedded multifactorial adaptive platform trial**
    - ✓ **290 sites in Canada, US, UK, Ireland, EU, Saudi Arabia, Australia, New Zealand, Nepal, India, Pakistan**
  - **ACTIV-4a: accelerating COVID-19 therapeutic interventions and vaccines**
    - ✓ **60 sites in US and Spain**

East Asian population is not included.

ATTACC

REMAP-CAP

ACTIV-4
Acute Inpatient Anti-Thrombotic Study
Master Platform for ATTACC, REMAP & PROTECT

Abbreviations: RCT, randomized controlled trial.

https://nhlbi-connects.org, accessed 22 Mar 2021.

Thromboprophylaxis Strategies in COVID-19

- **Multiplatform RCTs**
  - **Population**
    - ✓ **Adult patients hospitalized for COVID-19**
  - **Study design**
    - ✓ **Randomized, open-label, adaptive Bayesian trial**
    - ✓ **Intervention: therapeutic dose of anticoagulation**
    - ✓ **Control: prophylactic dose of anticoagulation**
    - ✓ **Duration of therapy: 14 days or hospital discharge**

      (or liberation form oxygen supplement in ATTACC)

Abbreviations: RCT, randomized controlled trial.

https://nhlbi-connects.org, accessed 22 Mar 2021.

Thromboprophylaxis Strategies in COVID-19

- **Multiplatform RCTs**
  - **Primary outcome**
    - ✓ **Organ support-free days to day 21**
  - **Secondary outcomes**
    - ✓ **Efficacy: mortality, intubation, major thrombosis, pulmonary embolism, venous thromboembolism, stroke, MI, length of stays in ICU and hospital**
    - ✓ **Safety: major bleeding and HIT**

Abbreviations: HIT, heparin induced thrombocytopenia; ICU, intensive care unit; RCT, randomized controlled trial.

https://nhlbi-connects.org, accessed 22 Mar 2021.

Thromboprophylaxis Strategies in COVID-19

- **Multiplatform RCTs**
  - **Stratification in main analysis**
    - ✓ **Moderate state (non-ICU) patients**
      - ✓ **High D-dimer (≥ 2X ULN)**
      - ✓ **Low D-dimer (< 2X ULN)**
      - ✓ **Unknown**
    - ✓ **Severe state (ICU) patients**

Abbreviations: ICU, intensive care unit; RCT, randomized controlled trial; ULN, upper limit of normal.

https://nhlbi-connects.org, accessed 22 Mar 2021.

Thromboprophylaxis Strategies in COVID-19

- **Multiplatform RCTs**
  - **Decision rules**
    - ✓ **Declare superiority**

      >99% posterior probability of superiority on primary outcome

      (proportional odds ratio >1)
    - ✓ **Declare futility**

      <5% posterior probability of at least a 20% improvement for primary outcome

      (proportional odds ratio >1.2)
    - ✓ **Decisions are evaluated separately for each stratum of D-dimer**

Abbreviations: RCT, randomized controlled trial.

https://nhlbi-connects.org, accessed 22 Mar 2021.

Thromboprophylaxis Strategies in COVID-19

Multiplatform RCTs

Enrollment at interim analysis (21 Jan 2021)

	Randomized (N)			Known OSFD (N)		
	Moderate	Severe	Total	Moderate	Severe	Total
ATTACC	1,036	35	1,071	906	35	941
ACTIV-4a	468	110	578	278	91	369
PROTECT*	52	19	71	52	19	71
REMAP-CAP	216	959	1,175	162	750	912
Total	1,772	1,123	2,895	1,398	895	2,293

*PROTECT is a pilot phase of ACTIV-4a.
Abbreviations: OSFD, organ support-free days.

https://nhlbi-connects.org, accessed 22 Mar 2021.

Thromboprophylaxis Strategies in COVID-19

Multiplatform RCTs

Interim analysis (28 Jan 2021)

	Proportional odds ratio median (95% CrI)	Trial statistical conclusion
Moderate state		
Low D-dimer	1.57 (1.14-2.19)	Superiority (probability of OR >1 = 0.997)
High D-dimer	1.53 (1.09-2.17)	Superiority (probability of OR >1 = 0.991)
Unknown	1.51 (1.06-2.15)	Not evaluated for stopping at interim analysis
Severe state	0.76 (0.60-0.97)	Futility* (probability of OR >1.2 <0.001)

*Posterior probability of inferiority: probability of OR<1 = 0.985.
Abbreviations: CrI, credible interval; OR, odds ratio.

Discontinuation due to superiority

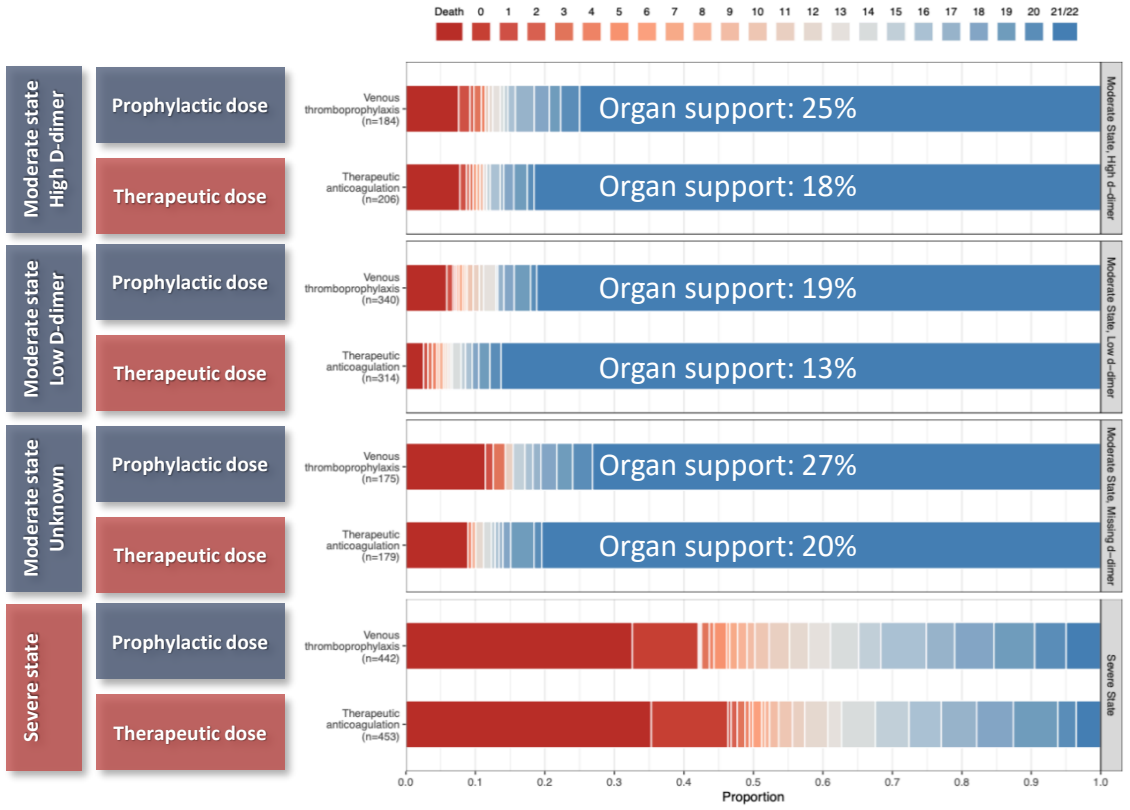
Discontinuation due to futility

https://nhlbi-connects.org, accessed 22 Mar 2021.

Thromboprophylaxis Strategies in COVID-19

Multiplatform RCTs

Interim analysis (28 Jan 2021)



	Moderate state		Severe state	
	Prophylactic (N=699)	Therapeutic (N=699)	Prophylactic (N=442)	Therapeutic (N=453)
Mortality	54 (7.7%)	40 (5.7%)	144 (32.6%)	160 (35.3%)

	Moderate state		Severe state	
	Prophylactic (N=742)	Therapeutic (N=853)	Prophylactic (N=448)	Therapeutic (N=460)
Major bleeding	7 (0.9%)	14 (1.6%)	8 (1.8%)	17 (3.7%)

	Moderate state		Severe state	
	Prophylactic (N=742)	Therapeutic (N=853)	Prophylactic (N=448)	Therapeutic (N=460)
Thrombotic events*	24 (3.2%)	16 (1.9%)	53 (11.8%)	31 (6.7%)

*Defined as deep vein thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, and other thrombotic events.

https://nhlbi-connects.org, accessed 22 Mar 2021.

Thromboprophylaxis Strategies in COVID-19

- **Multiplatform RCTs: interim conclusion**
  - **Moderate state: hospitalized, but not in ICU at baseline**
    - ✓ **Therapeutic dose superior to prophylactic dose**
    - ✓ **Major bleeding rate <2% with therapeutic dose anticoagulation**
  - **Severe state: requiring organ support in ICU at baseline**
    - ✓ **Therapeutic dose anticoagulation dose not improve organ support-free days to day 21.**
    - ✓ **Probability that therapeutic dose is inferior compared to prophylactic dose is 98.5%.**
    - ✓ **Numeric increase in major bleeding events and mortality**

https://nhlbi-connects.org, accessed 22 Mar 2021.

Thromboprophylaxis Strategies in COVID-19

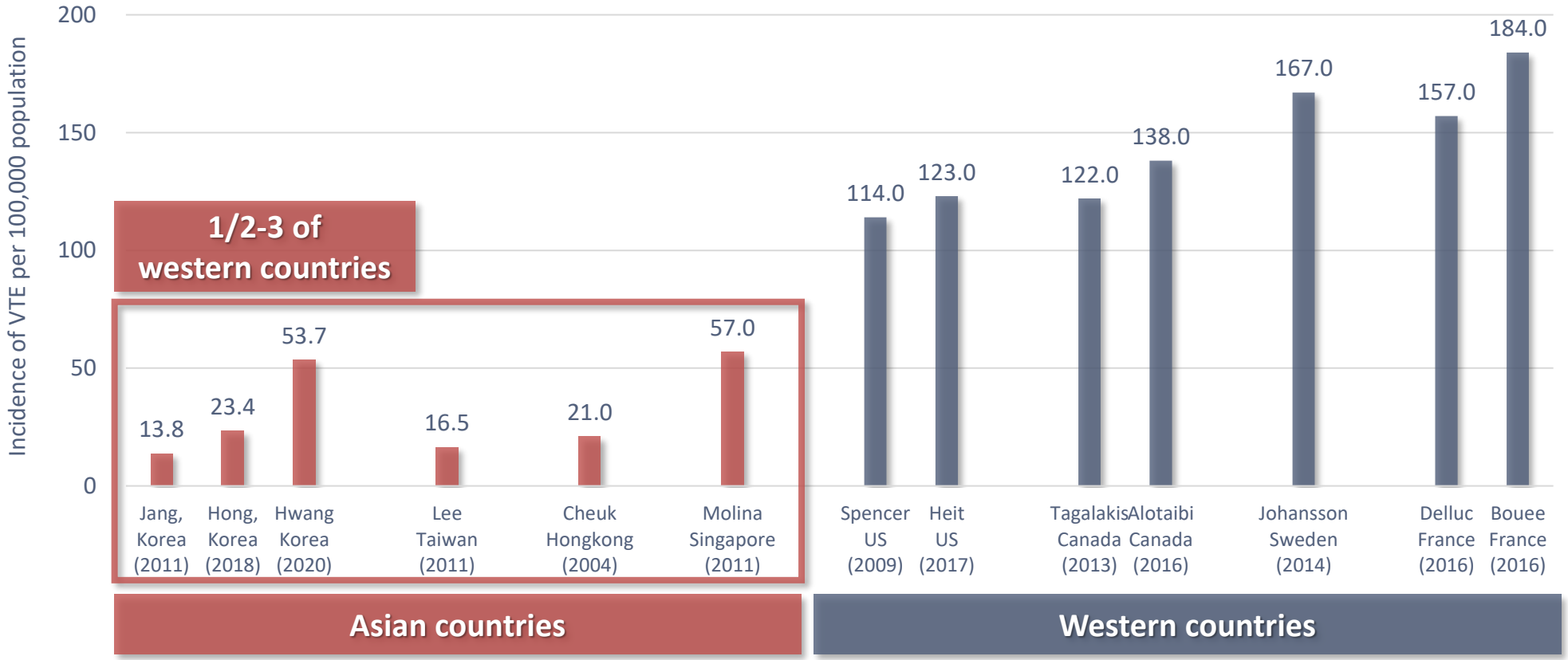
- **Multiplatform RCTs: interim conclusion**
  - **Moderate state → Severe state: transition from ward to ICU**
    - ✓ **The trial protocol specified therapeutic dose anticoagulation to continue when patients became critically ill.**

      → The protocol arm was overall superior to prophylactic dose anticoagulation.
    - ✓ **It is unknown whether therapeutic dose anticoagulation would have had greater overall benefit in moderate state if it had been discontinued in patients who became critically ill.**

https://nhlbi-connects.org, accessed 22 Mar 2021.

Ethnic Differences in Thrombogenicity

- **Incidence of VTE: Asian vs. Western countries (non-COVID-19)**

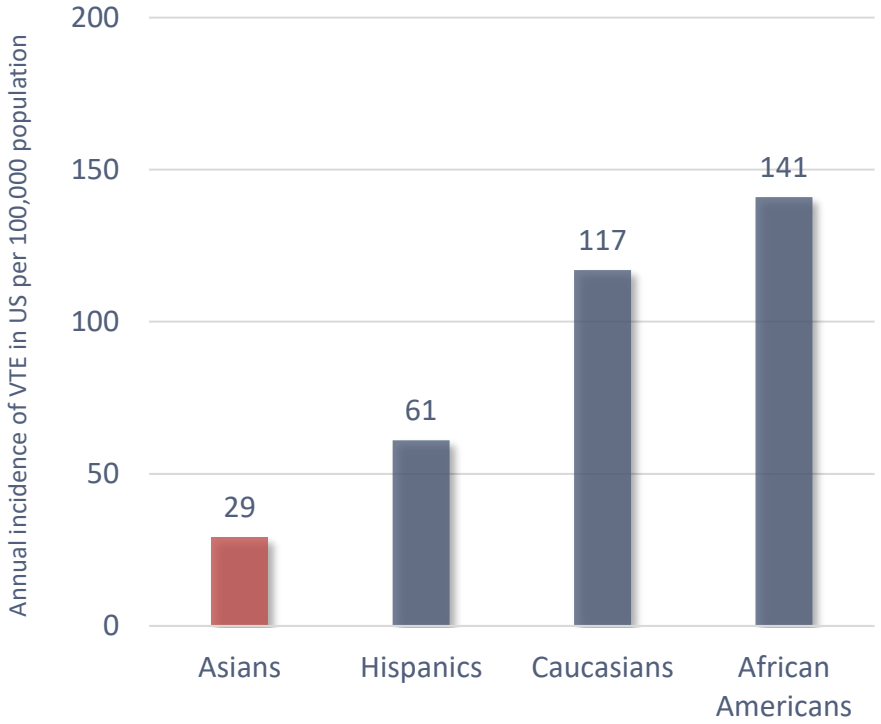


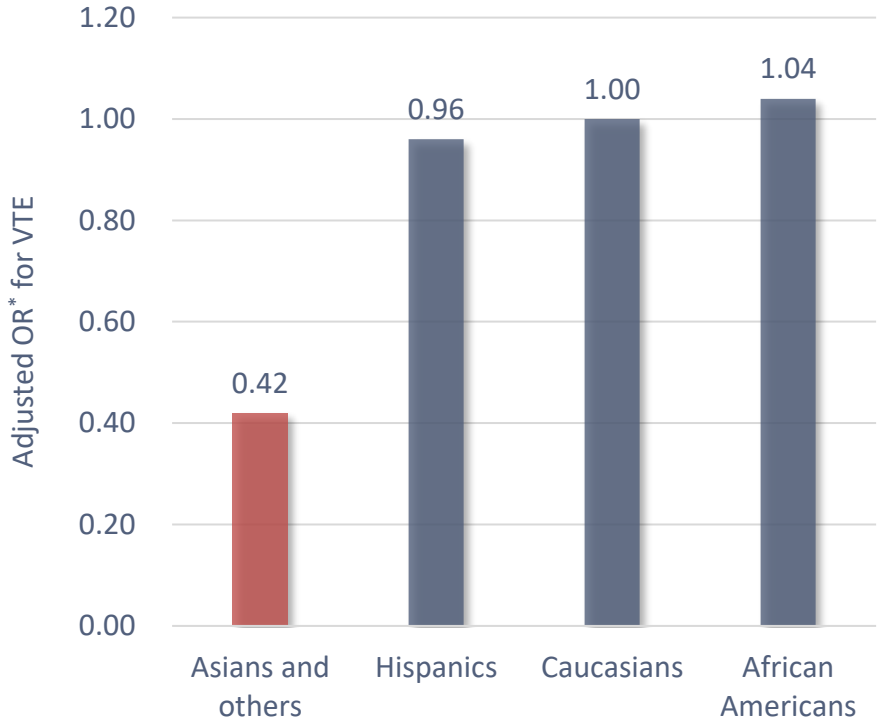
Abbreviations: VTE, venous thromboembolism.

Hong, PLoS One. 2018.

Ethnic Differences in Thrombogenicity

- **Incidence and risk of VTE in US by ethnicity (non-COVID-19)**





*Adjusted for comorbidities.

Abbreviations: OR, odds ratio; VTE, venous thromboembolism.

Beckman, Am J Prev Med. 2010. and Deitelzweig, J Thromb Thrombolysis. 2011.

Ethnic Differences in Thrombogenicity

- **Ethnic differences in thrombogenic profiles (non-COVID-19)**

Factors	Ethnic differences	Component
Platelet		
Platelet count	African Americans > Hispanics > Caucasians	Hemostasis
Regulation of Gq pathway after PAR-4 stimulation	African Americans > Caucasians	Platelet activation
Coagulation		
Factor V leiden mutation	Caucasians > African Americans > Hispanics = Asians	Coagulant activity
Prothrombin G20210A mutation	Caucasians > African Americans = Hispanics = Asians	Coagulant activity
vWF level	African Americans > Caucasians = Hispanics ≥ East Asians	Endothelial adhesion factor
Fibrinogen, factor VII and VIII, and thrombin levels	African Americans ≥ Caucasians = Hispanics ≥ East Asians	Coagulant activity
D-dimer level	African Americans > Caucasians = Hispanics > East Asians	Prothrombotic and hypofibrinolytic state
Anticlotting activity		
Effect of activated protein C	Asians = Hispanics ≥ African Americans > Caucasians	Anti-coagulant activity
PAI-1 level	Caucasians > Hispanics > East Asians ≥ African Americans	Anti-fibrinolytic activity

Abbreviations: PAI-1, plasminogen activator inhibitor-1; PAR, proteinase-activated receptor; vWF, von Willebrand factor.

Chaudhary, EClinicalMedicine. 2020. and Kim, Thromb Haemost. 2021.

Ethnic Differences in Thrombogenicity

- **Ethnic differences in thrombogenic profiles (non-COVID-19)**

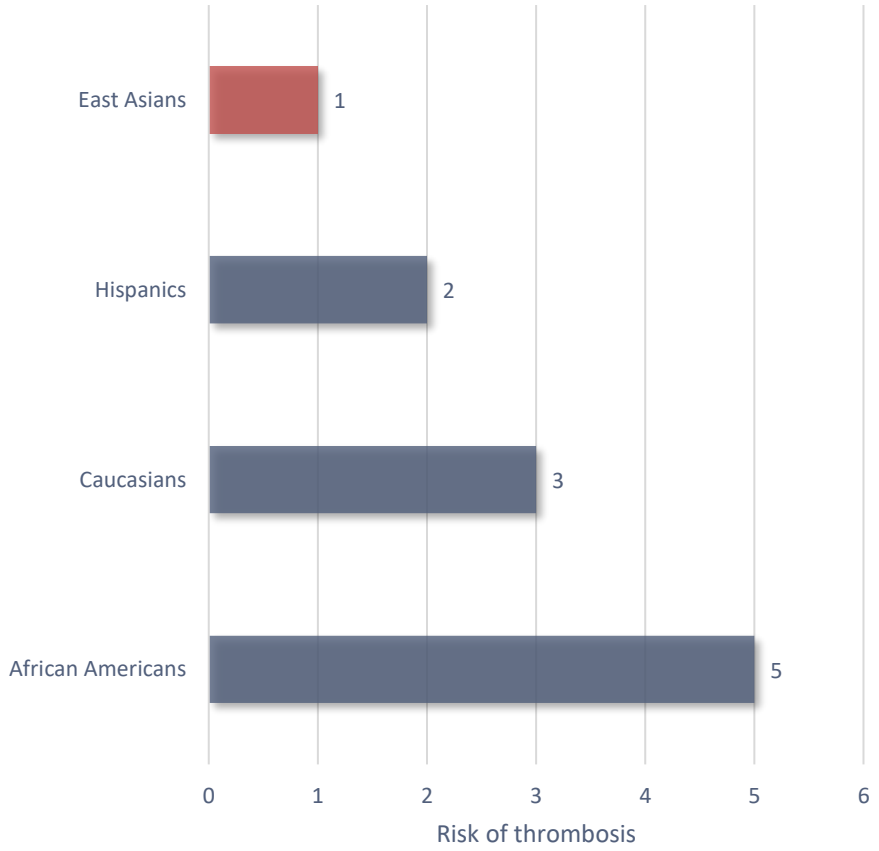
Factors	Ethnic differences	Component
Inflammation		
CRP level	African Americans > Hispanics > Caucasians > East Asians	Inflammation
Endothelial marker		
ICAM-1	Caucasians = Hispanics > African Americans > East Asians	Endothelial activity
E-selectin	African Americans = Hispanics > Caucasians = East Asians	Endothelial activity
Obesity		
Prevalence of obesity	African Americans ≥ Hispanics > Caucasians >> East Asians	Prothrombotic state
Thromboelastography		
R time	East Asians > Caucasians	Coagulant parameter (inverse)
Maximal amplitude	African Americans > Caucasians > East Asians	Platelet-fibrin clot strength

Abbreviations: CRP, C-reactive protein; ICAM-1, intercellular adhesion molecule-1.

Chaudhary, EClinicalMedicine. 2020. and Kim, Thromb Haemost. 2021.

Ethnic Differences in Thrombogenicity

- **Overall risk of thrombosis by ethnicity (non-COVID-19)**



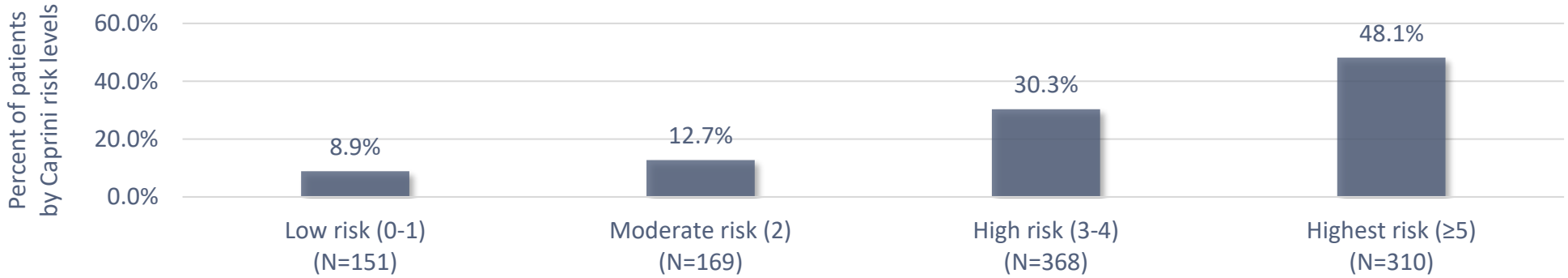
	Increased risk of thrombosis	Decreased risk of thrombosis
East Asians	↓ Thromboprophylaxis	↓ Obesity
		↓ Thrombogenic profiles
		↓ Genetic predisposition
Hispanics	↑ Obesity	↓ Genetic predisposition
	↑ Inflammation	
Caucasians	↑ Obesity	↑ Thromboprophylaxis
	↑ Inflammation	
	↑ Genetic predisposition	
African Americans	↑↑ Obesity	↓ Genetic predisposition
	↑ HIV	
	↑↑ Thrombogenic profiles	
	↑ Sickle cell trait	

Abbreviations: HIV, human immunodeficiency virus.

Kim, Thromb Haemost. 2021.

Ethnic Differences in Thrombogenicity

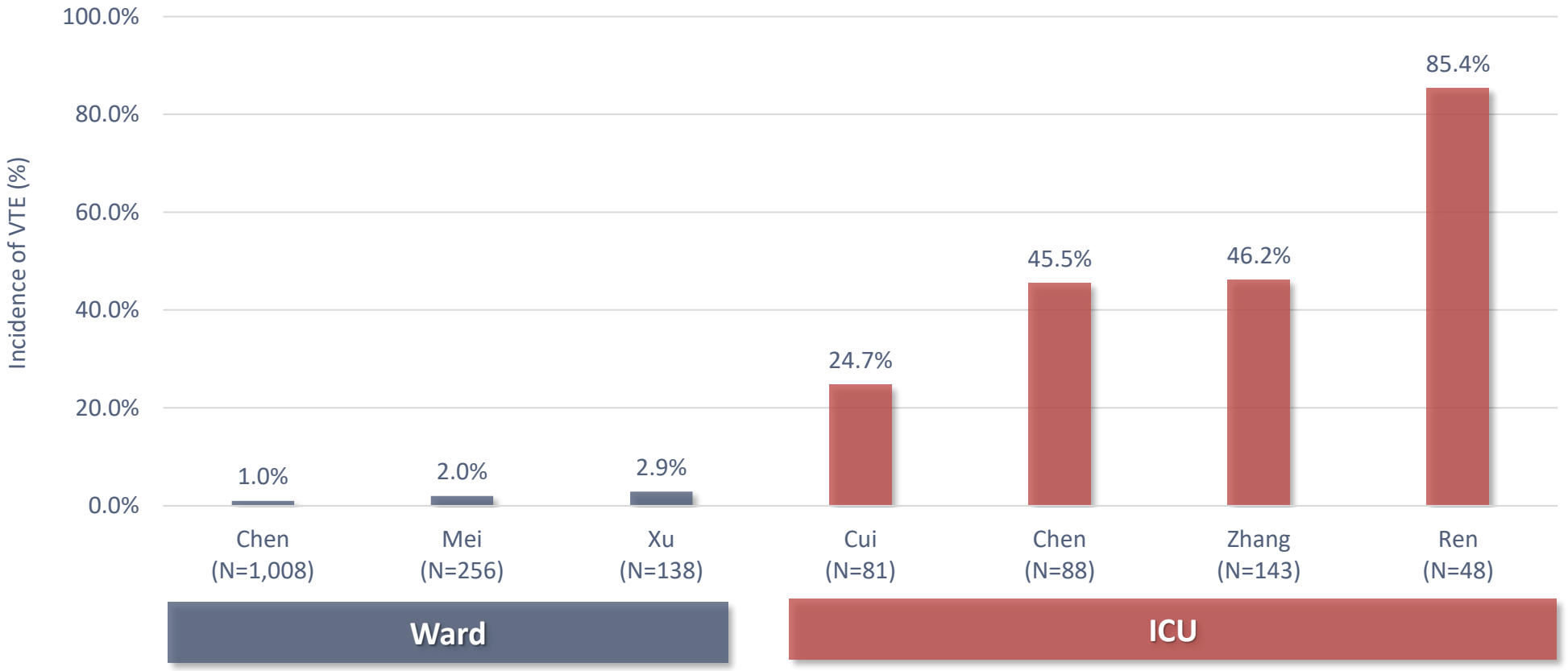
- **Asian VTE guidelines: updated in 2017**
  - **Assessment of risk factors for VTE**
    - ✓ **Advanced age, obesity, pregnancy, malignancy, major abdominal surgery, critical illness, prolonged immobility, stroke, and trauma**
  - **Risk assessment tool**
    - ✓ **Caprini risk assessment model, Rogers score, and Padua prediction score**



Liew, Int Angiol. 2017. and Zhou, J Atheroscler Thromb. 2014.

Risk for COVID-19-related Thrombosis in Asians

- **Early experience of China: incidence of VTE**

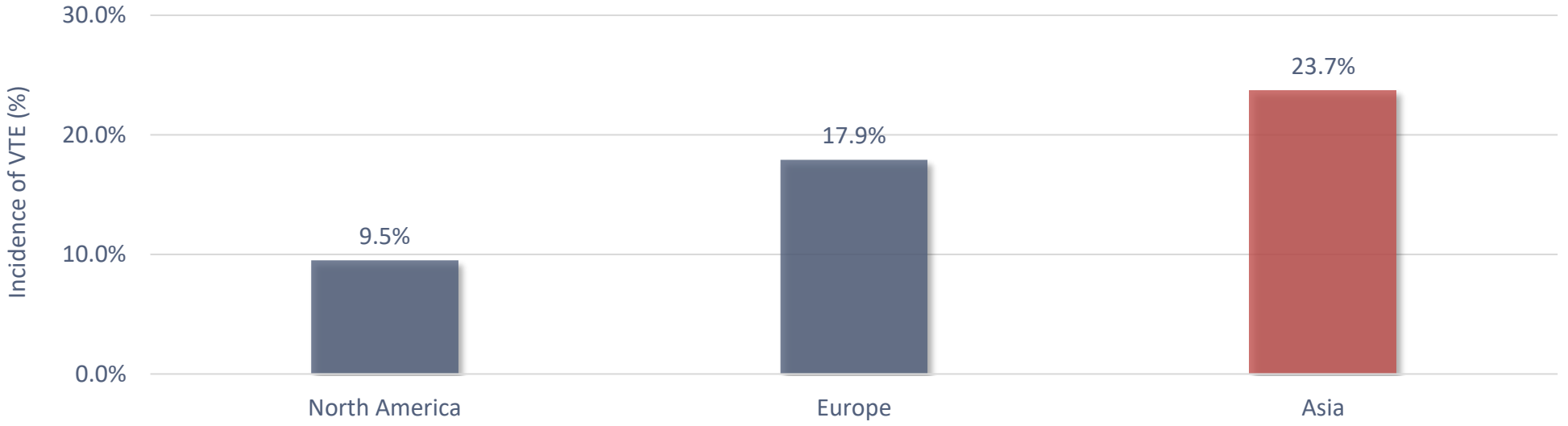


Abbreviations: ICU, intensive care unit; VTE, venous thromboembolism.

Cui, J Thromb Haemost. 2020.

Risk for COVID-19-related Thrombosis in Asians

- **Meta-analysis: incidence of VTE by geographical area**
  - **North America (N=7,991): 9.5% (4.4%-16.2%)**
  - **Europe (N=8,340): 17.9% (13.6%-22.7%)**
  - **Asia (N=1,762): 23.7% (6.2%-47.9%)**

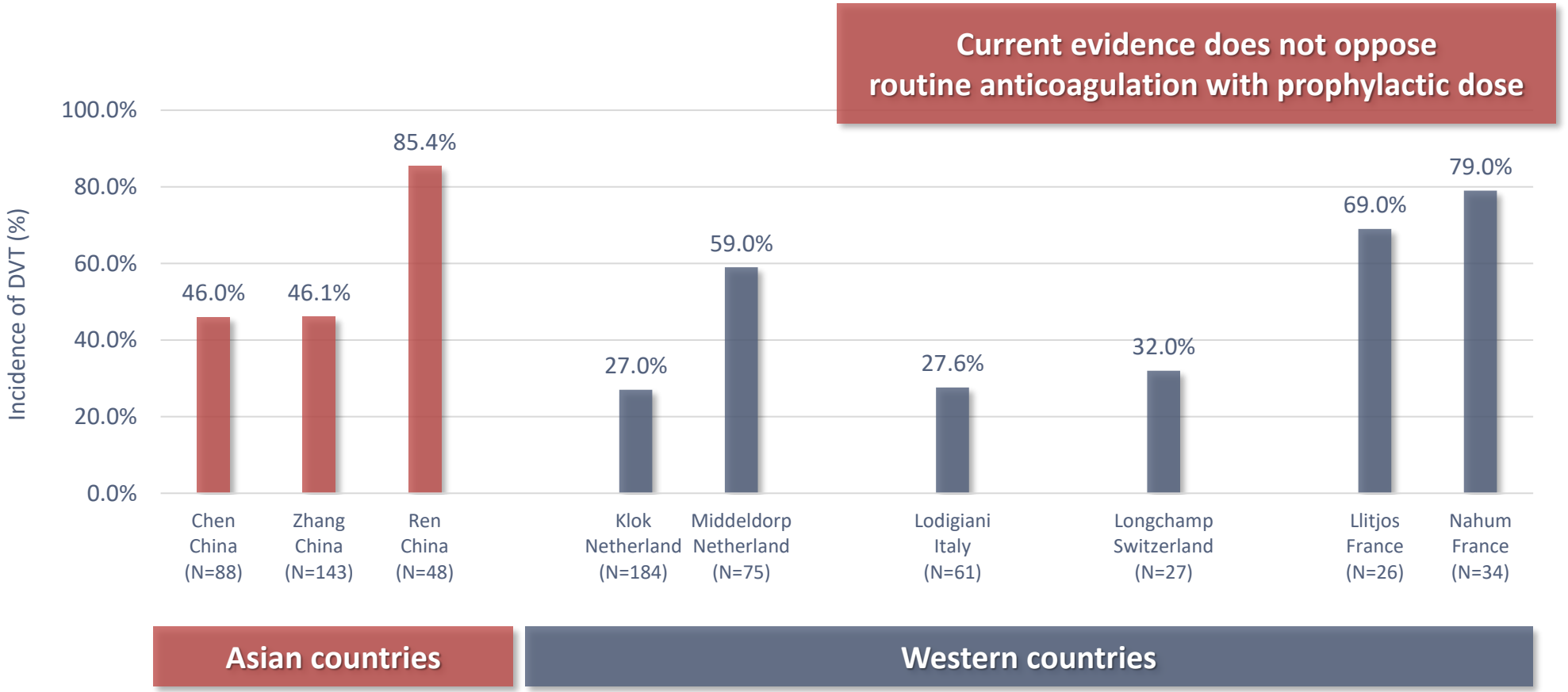


Abbreviations: VTE, venous thromboembolism.

Jimenez, Chest. 2021.

Risk for COVID-19-related Thrombosis in Asians

- **Meta-analysis: incidence of DVT in ICU on thromboprophylaxis**

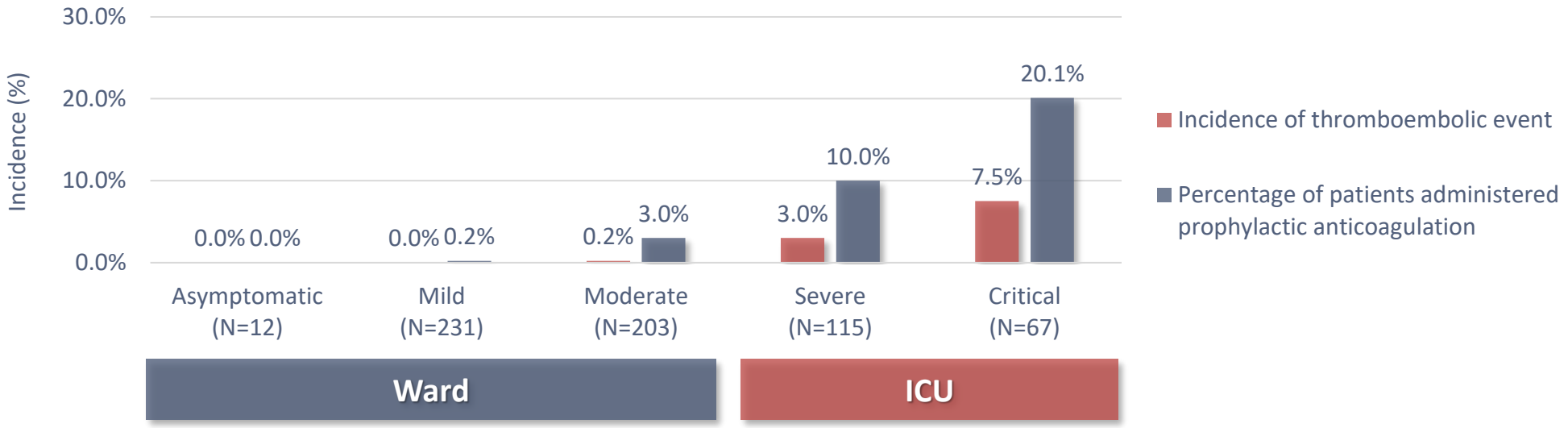


Abbreviations: VTE, venous thromboembolism.

Iba, Int J Hematol. 2021.

Risk for COVID-19-related Thrombosis in Asians

- **Recently published observational studies from Asian countries (Japan)**
  - **628 patients from 2 hospitals (2020.02.-2020.08.)**
  - **Prophylactic anticoagulation: 10% (N=63)**
  - **Overall incidence of VTE: 2.9% (N=18)**

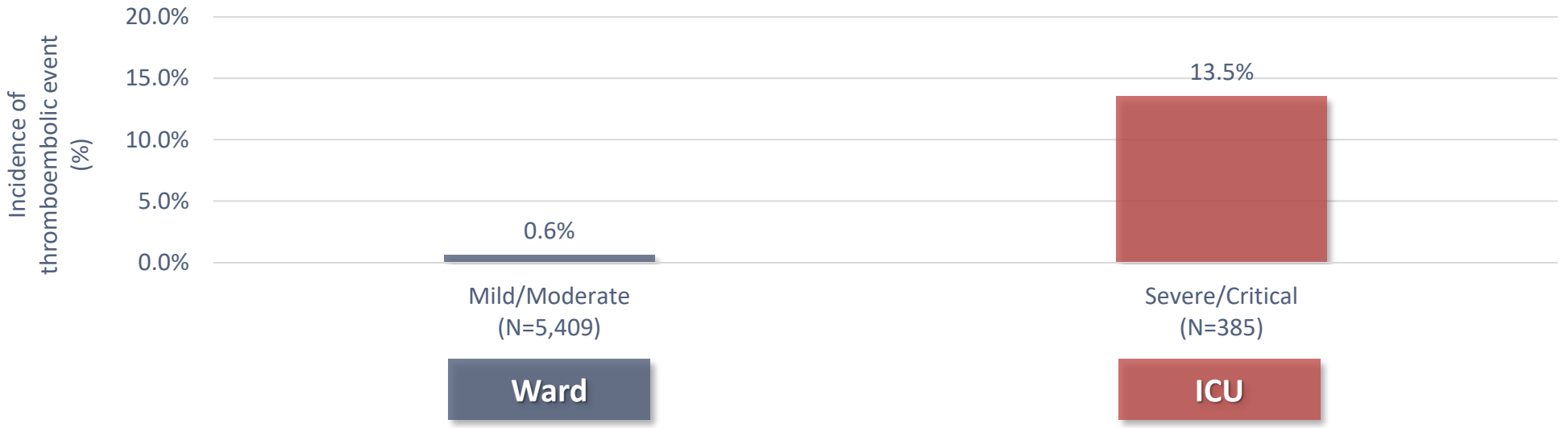


Abbreviations: ICU, intensive care unit; VTE, venous thromboembolism.

Fujiwara, J Infect Chemother. 2021.

Risk for COVID-19-related Thrombosis in Asians

- **Recently published observational studies from Asian countries (Japan)**
  - **6,202 patients from 388 hospitals (2020.01.-2020.08.)**
  - **Prophylactic anticoagulation: 14.6% (N=893/6,119)**
  - **Incidence of thromboembolic event: 1.9% (N=108/5,807)**

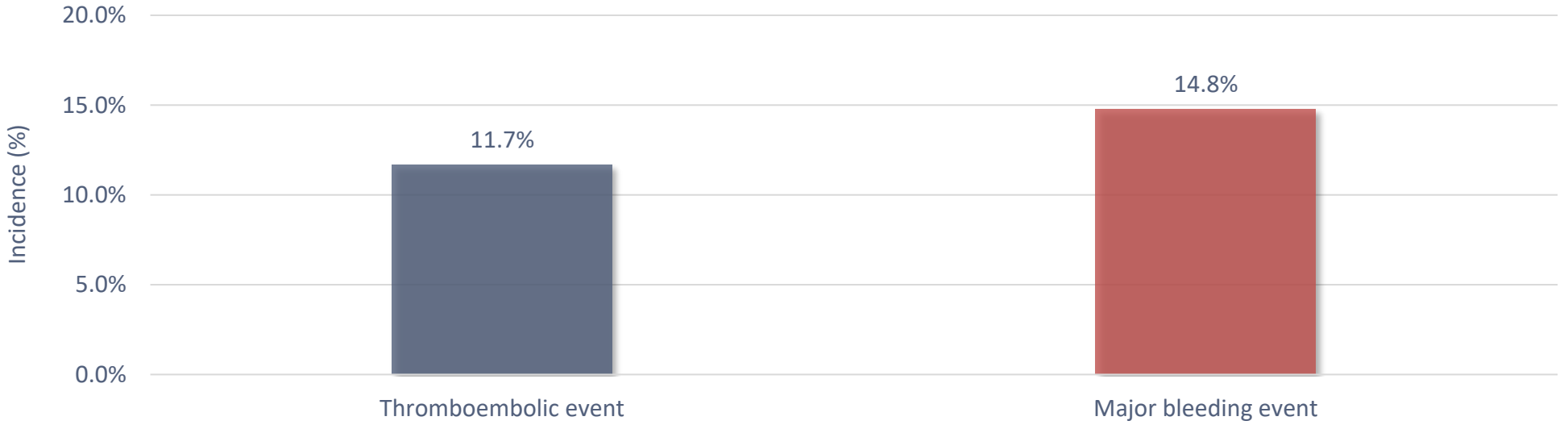


Abbreviations: ICU, intensive care unit.

Horiuchi, J Atheroscler Thromb. 2021.

Risk for COVID-19-related Thrombosis in Asians

- **Recently published observational studies from Asian countries (Singapore)**
  - **108 patients from 8 ICUs (2020.01.-2020.04.)**
  - **Prophylactic anticoagulation: 63.9% (N=69)**
  - **Incidence of thromboembolic event: 11.7% (N=13)**



Abbreviations: ICU, intensive care unit.

Tan, Thromb J. 2021.

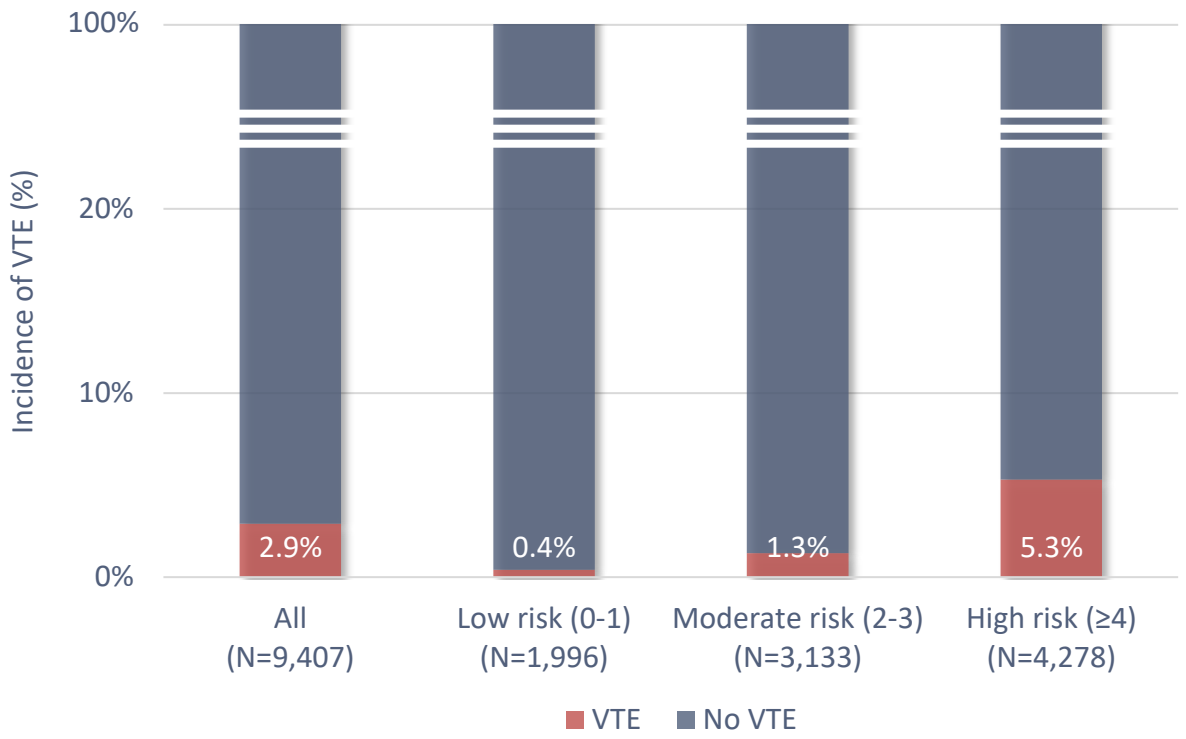
Future Direction of Thromboprophylaxis in COVID-19

Individualized risk assessment and thromboprophylaxis in COVID-19

IMPROVE-DD risk assessment model

Variables	Score
Prior episode of VTE	3
Thrombophilia	2
Paralysis of lower extremity during hospitalization	2
Cancer	2
Max D-dimer >2X ULN	2
Immobilization for at least 7 days	1
ICU stay	1
Age >60 years	1

Abbreviations: ICU, intensive care unit; ULN, upper limit of normal; VTE, venous thromboembolism.



Spyropoulos, Res Pract Thromb Haemost. 2021.

Take Home Messages

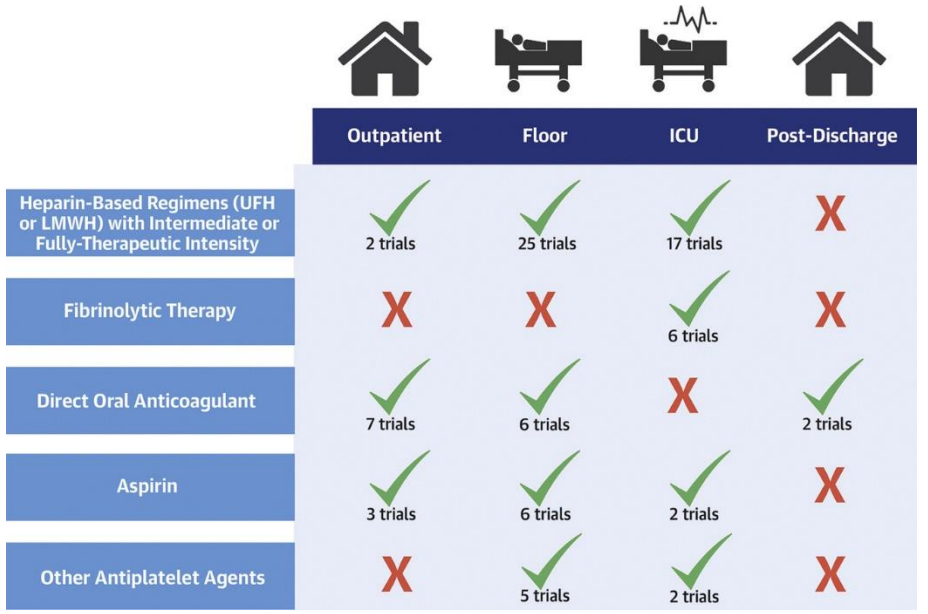
- **Thromboembolic risk and prophylaxis in COVID-19**
  - **COVID-19 increase thromboembolic risk in hospitalized patients.**
    - ✓ **VTE: 7.1% in ward vs. 27.9% in ICU**
  - **Current guidelines on thromboprophylaxis**
    - ✓ **Prophylactic dose of anticoagulation in all hospitalized patients**
    - ✓ **Increase intensity of anticoagulation is generally not recommended.**
  - **Interim analysis of multiplatform RCTs**
    - ✓ **Moderate state: therapeutic dose of anticoagulation**
    - ✓ **Severe state: prophylactic dose of anticoagulation**

Take Home Messages

- **Thromboembolic risk and prophylaxis in COVID-19**
  - **Special consideration is needed for the characteristics of Asian ethnicity.**
    - ✓ **Thrombogenicity ↓ and bleeding tendency ↑**
  - **More studies on COVID-19-related thromboembolic events are required from Asian society.**
    - ✓ **No available domestic report**
  - **Individualized risk assessment and thromboprophylaxis**
    - ✓ **IMPROVE-DD risk assessment model**
    - ✓ **Validation of the risk assessment model in Asian society**

Conclusions

- COVID-19 increases thromboembolic risk in hospitalized patients.
- However, optimal thromboprophylaxis in COVID-19 is yet to be determined.
- Results of ongoing RCTs and prospective meta-analyses will help clarify the optimal strategies.



	Outpatient	Floor	ICU	Post-Discharge
Heparin-Based Regimens (UFH or LMWH) with Intermediate or Fully-Therapeutic Intensity	✓ 2 trials	✓ 25 trials	✓ 17 trials	X
Fibrinolytic Therapy	X	X	✓ 6 trials	X
Direct Oral Anticoagulant	✓ 7 trials	✓ 6 trials	X	✓ 2 trials
Aspirin	✓ 3 trials	✓ 6 trials	✓ 2 trials	X
Other Antiplatelet Agents	X	✓ 5 trials	✓ 2 trials	X

Halasaz, J Am Coll Cardiol. 2021.

Q & A