Welcome! We will get started momentarily

Using “Chat,” please enter your name and organization

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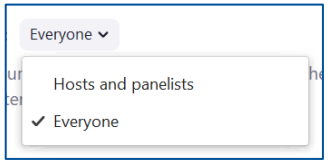
1. Click on the “Chat” icon
2. Select who you want to send your message to (individual or everyone)
3. Type and send your message



Please use “Chat” to submit questions for our speakers

Thromboprophylaxis in Hospitalized COVID-19 Patients

Telligen, IPRO, Alliant and Compass Joint HQIC Learning Event

February 24, 2022

Please note, this event is being recorded

ALLIANT HEALTH SOLUTIONS | COMPASS | IPRO HQIC | Healthcentric Advisors ■ Qlarant ■ Kentucky Hospital Association ■ Q3 Health Innovation Partners ■ Superior Health Quality Alliance | Telligen QI Connect™ | HQIC Hospital Quality Improvement Contractors CENTERS FOR MEDICARE & MEDICAID SERVICES iQUALITY IMPROVEMENT & INNOVATION GROUP

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Today's Agenda

- Welcome & Introductions
- Data Review
- Thromboprophylaxis in Hospitalized COVID-19 Patients
- Key Takeaways
- Q&A

Anticoagulant-Related Adverse Drug Events: Program Data Review

Meg Nugent, MHA, RN, Telligen HQIC

Lynda Martin, MPA, BSN, RN, CPHQ, IPRO HQIC

Karen Holtz, MT (ASCP), MS, CPHQ, Alliant HQIC

Charisse Coulombe, MS, MBA, CPHQ, Compass HQIC

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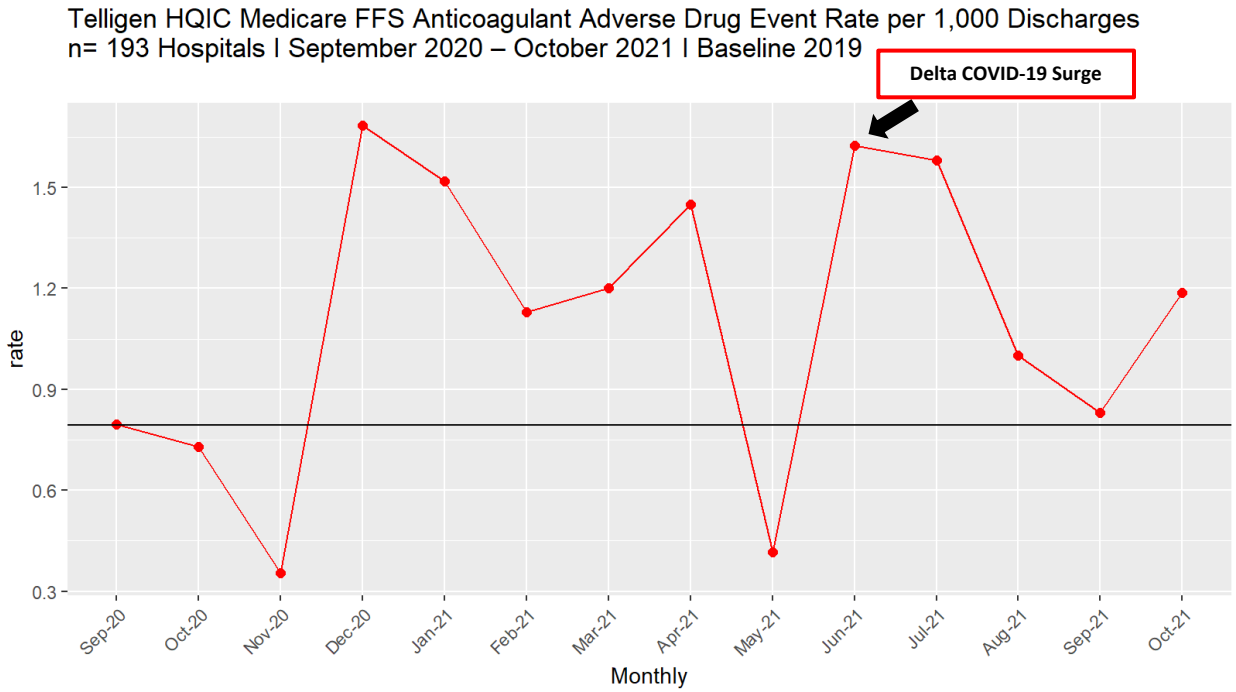
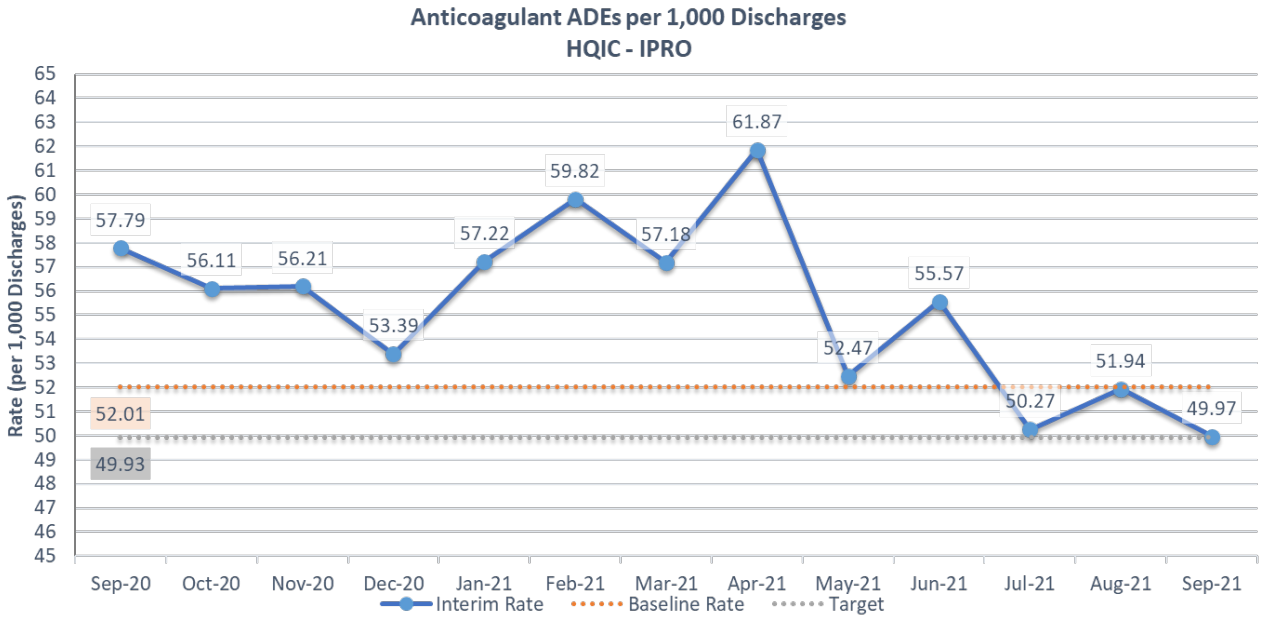
Anticoagulant-Related ADEs – Telligen HQIC All Project Average (n=193 Hospitals)



Question for Reflection:

Consider data trends across HQICs, what could be contributing to ADE rates?

IPRO HQIC – Anticoagulant ADEs per 1000 Discharges



- Rates are trending down

Hospitals Reporting = 271

- Critical Access: 140
- Rural IPPS: 95
- Urban Targeted: 36

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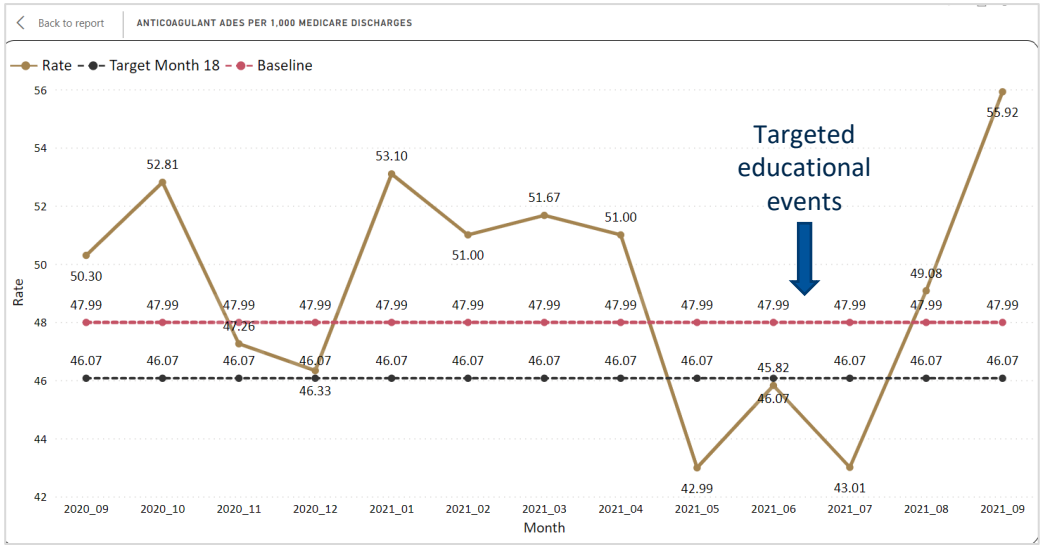
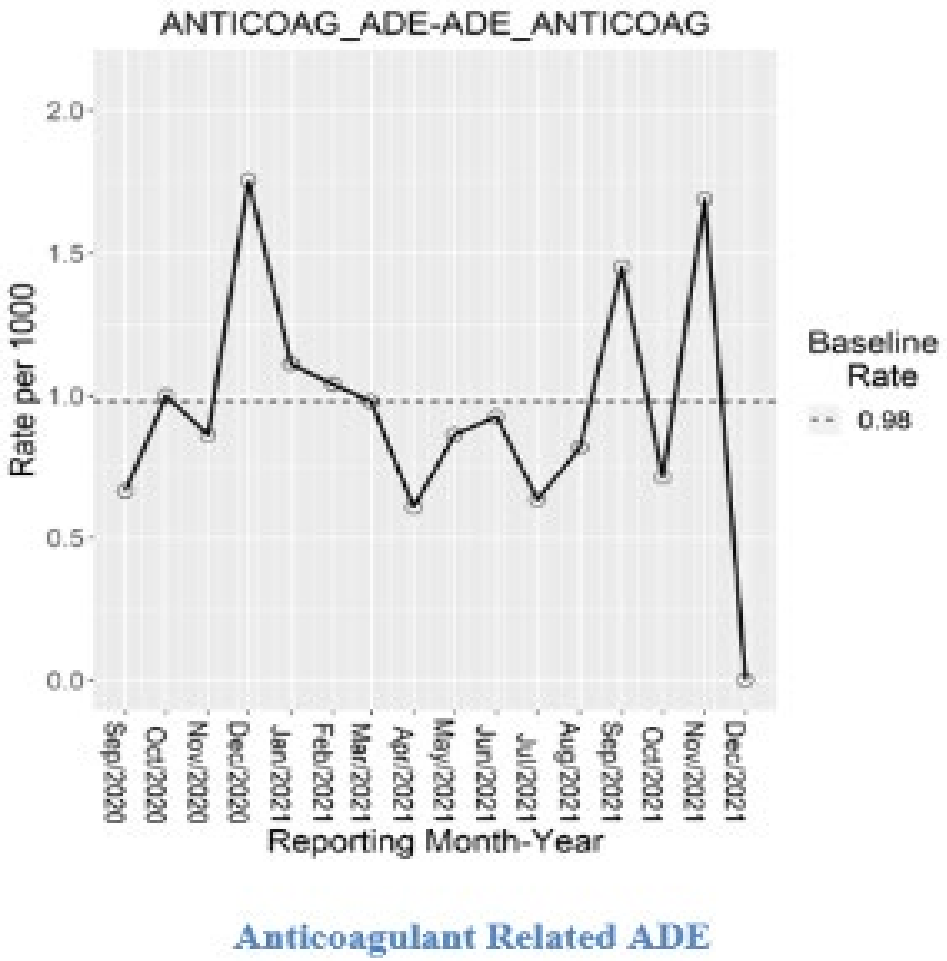
Anticoagulant ADEs per 1,000 Discharges - Alliant HQIC



- Overall downward trend until July 2021
- Increased rates in Aug and Sep 2021
- Most likely attributed to COVID surge of hospital patients

N = 147/150 (98%) hospitals
Source: CMS Claims (Power BI)

Anticoagulant-Related ADEs – IHC/Compass HQIC All Project Average (n= 277 Hospitals)



Data Source: Statewide Database

Thromboprophylaxis in Hospitalized COVID-19 Patients

Alex C Spyropoulos, MD, FACP, FCCP, FRCPC

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Welcome and Introduction of Today's Guest Speaker

Alex C Spyropoulos, MD, FACP, FCCP, FRCPC
Professor of Medicine – The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell
Professor - The Institute for Health Innovations and Outcomes Research - The Feinstein Institutes for Medical Research
System Director – Anticoagulation and Clinical Thrombosis Services
Northwell Health at Lenox Hill Hospital

Today's Objectives

- Understand the thrombotic risk in hospitalized COVID-19 patients
- Review the randomized trial data in this population, both in critical and noncritical care settings
- Formulate an evidence-based algorithm for optimal thromboprophylaxis in high risk hospitalized COVID-19 patients

The Management of Inpatient COVID-19 Associated Coagulopathy

Alex C. Spyropoulos MD, FACP, FCCP, FRCPC
Professor of Medicine
The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell
Professor – The Institute for Health Innovations and Outcomes Research
The Feinstein Institutes for Medical Research
System Director – Anticoagulation and Clinical Thrombosis Service
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New York, NY

DONALD AND BARBARA
ZUCKER SCHOOL *of* MEDICINE
AT HOFSTRA/NORTHWELL

Disclosures for Alex C Spyropoulos, MD

I have the following disclosures to the session audience:

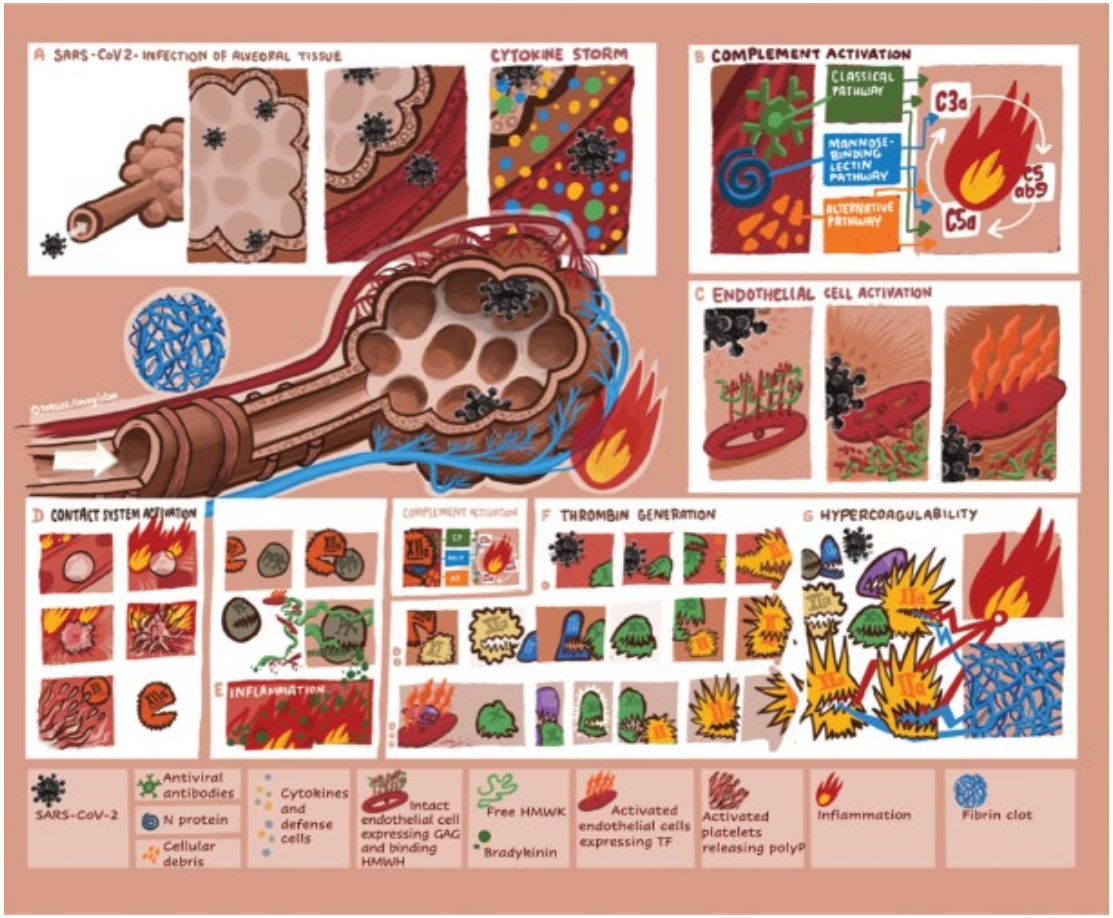
Research Support/P.I.	**Janssen, Boehringer Ingelheim**
Employee	**No relevant conflicts of interest to declare**
Consultant	**Janssen, Bayer, BMS, Boehringer Ingelheim**
Major Stockholder	**No relevant conflicts of interest to declare**
Speakers Bureau	**No relevant conflicts of interest to declare**
Honoraria	**Sanofi**
Scientific Advisory Board	**ATLAS Group**

Introduction

1. Implications of COVID-19 caused by SARS-CoV-2
   - In US over 76 million cases and 903,000 deaths
   - Coagulopathy established in hospitalized patients, esp venous thromboembolism
   - Microvascular thrombosis has been implicated in progression to ARDS
   - Thrombotic complications associated with up to 60% of deaths, esp in patients with CV disease
     - Autopsy series reveal high incidence of unsuspected VTE or pulmonary arterial thrombosis
2. Hospitalized medical patients, including those with pneumonia/sepsis, are at moderate venous thromboembolism (VTE) risk (~1.5%)
   - A subset of these patients (~25%) are at high risk of thrombosis post-discharge
3. Previous experience with viral pneumonias/ARDS (SARS, MERS, H1N1) show a 18-fold increased risk for VTE
   - Early empiric therapeutic anticoagulation (AC) reduces hospital-based complications such as thrombosis and mortality by 71% and 14%, respectively

WHO COVID Dashboard 2022
Spyropoulos AC Thromb Haemost 2017
Obi AT J Vasc Surg 2018
Wichmann D et al Ann Intern Med 2020
Berger J et al Lancet 2021
Paranjpe I et al JACC 2020

Coagulopathy and cytokine storm in SARS-CoV2 pneumonia: Thromboinflammation



Gerotziafas G et al Thromb Haemost 2020

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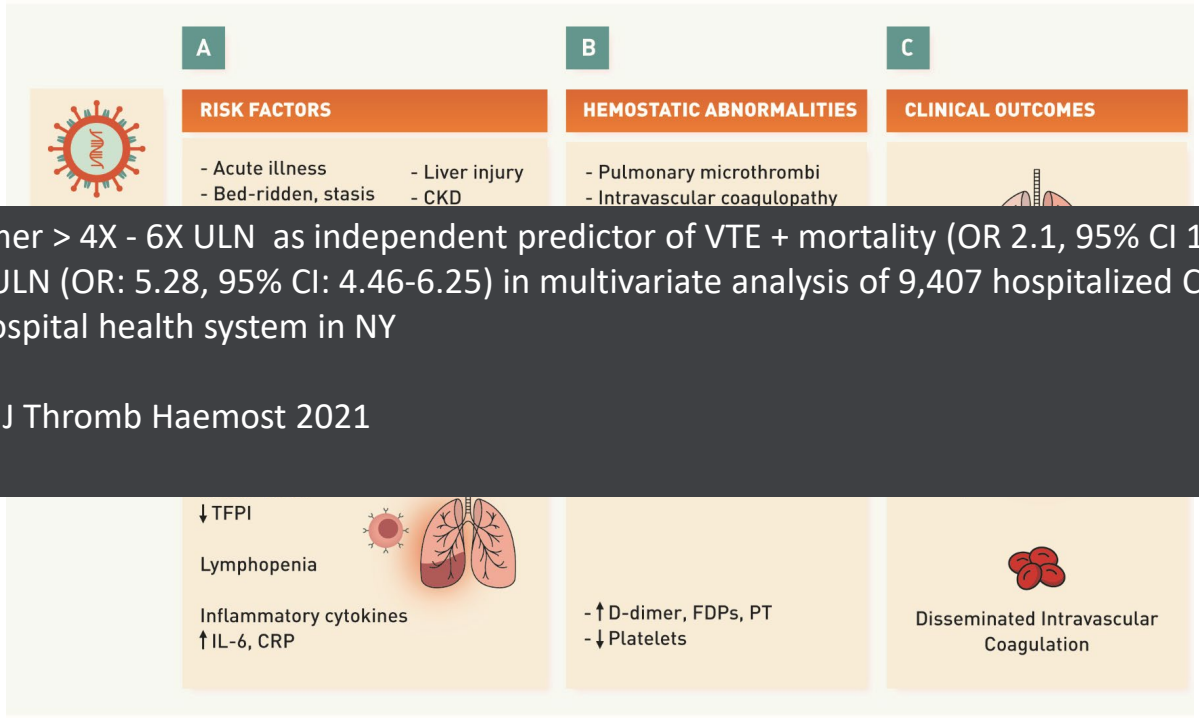
Risk factors for Thrombosis in Sars-CoV-2

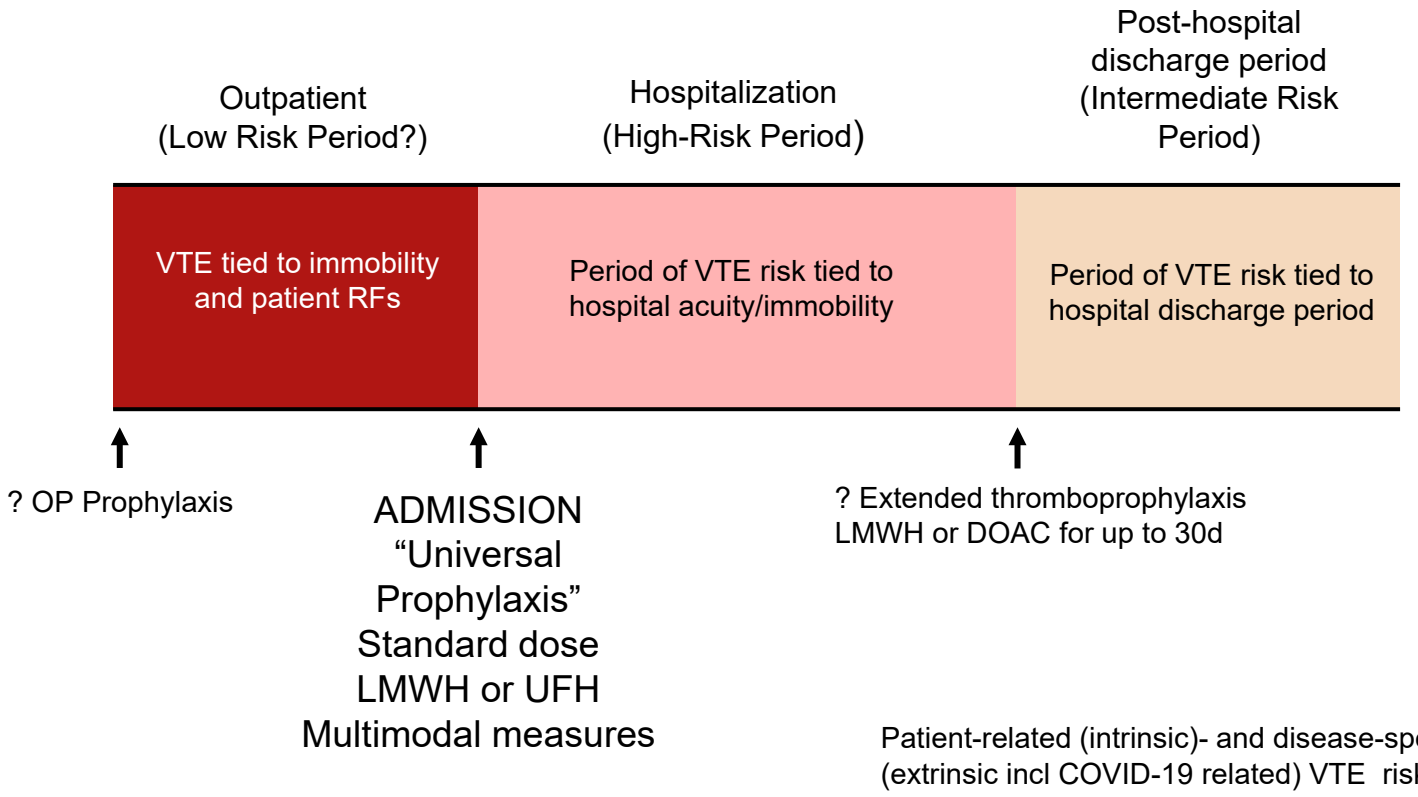


Elevated D-dimer > 4X - 6X ULN as independent predictor of VTE + mortality (OR 2.1, 95% CI 1.61 – 2.74) and D-dimer > 6X ULN (OR: 5.28, 95% CI: 4.46-6.25) in multivariate analysis of 9,407 hospitalized COVID patients from a multihospital health system in NY

Cohen SL et al J Thromb Haemost 2021

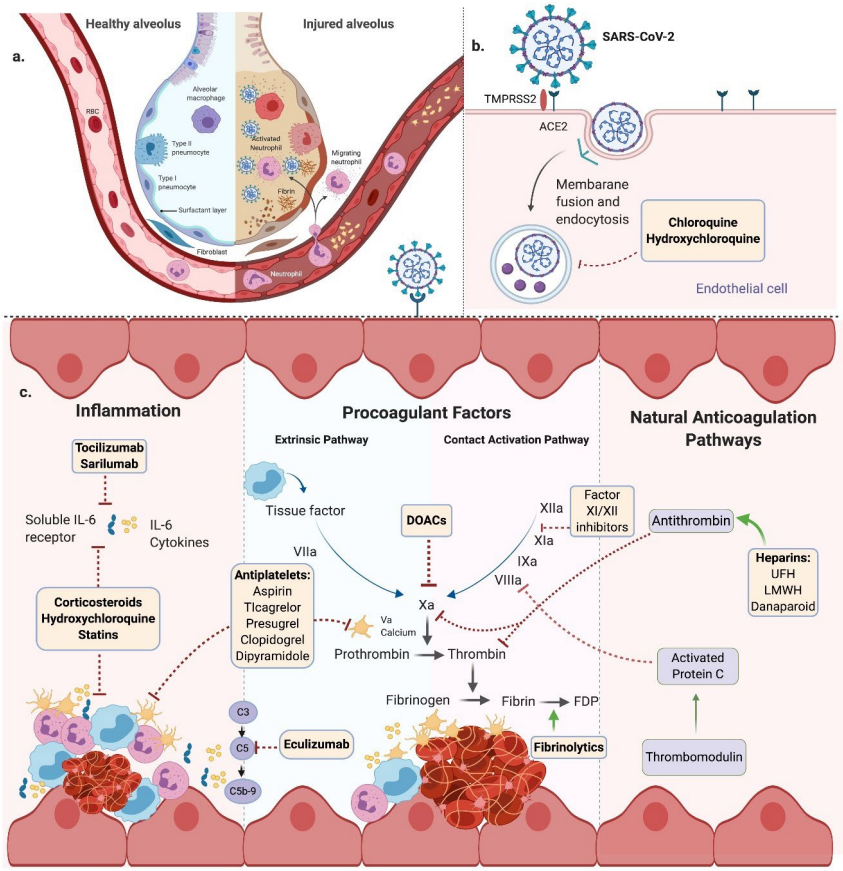
Bikdeli B et al JACC 2020

Periods of Thrombotic Risk for COVID-19 Patients



Patient-related (intrinsic)- and disease-specific (extrinsic incl COVID-19 related) VTE risk factors

Antithrombotic Strategies for COVID-19 Coagulopathy



Bikedeli B et al Thromb Haemost 2020

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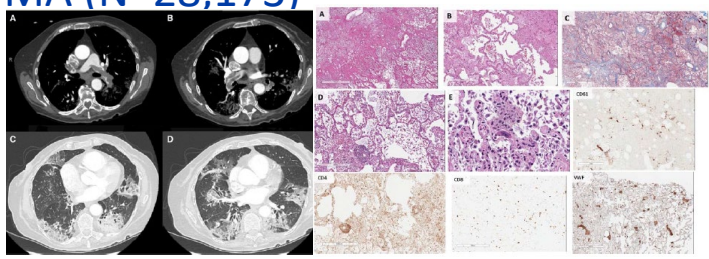
Unusual nature of thrombotic complications in hospitalized and critically ill COVID-19 patients

1. **High prevalence of thrombotic complications in hospitalized and critically ill COVID-19 patients**
   a. VTE – later reports 2.9% to 6.2%: time bias; pooled MA (N=28,173)
   - LE U/S screening: 14.1% (95% CI: 11.6 -16.9)
   - No LE U/S screening: 9.5% (95% CI: 7.5 -11.7)

   b. Pulmonary Embolism (PE): 20% - 42%
   - 3 fold higher risk compared to historical matched controls

   c. Arterial Thromboembolism (ATE) – initial reports 3.7%, later reports lower



2. **Unusual nature of thrombosis in COVID-19 patients**
   a. Thromboinflammation/in situ pulmonary microthrombi/megakaryocytes
3. **"Breakthrough thrombosis" despite standard thromboprophylaxis**

Spyropoulos AC and Weitz J Circulation 2020

Summary of US and International Guidance on Anticoagulant Dosing in Patients Hospitalized With COVID-19

VTE prophylaxis	ACC[1]	ASH[2]	CHEST[3]	ISTH[4]	NIH[5]	WHO[6]
Ward patients	Prophylactic dose	Prophylactic dose	Prophylactic dose	Prophylactic dose	Prophylactic dose	Prophylactic dose
ICU patients	Prophylactic dose	Prophylactic dose	Prophylactic dose	Prophylactic/ intermediate* dose	Prophylactic dose	Prophylactic dose
Post-discharge thromboprophylaxis	Dependent on patient type		Inpatient prophylaxis only	14-30 days	Inpatient prophylaxis only	
VTE treatment						
Confirmed VTE		Therapeutic dose	Therapeutic dose	Therapeutic dose	Therapeutic dose	
Length of therapy			3 months	3 months		

*Intermediate LMWH can be considered in high-risk patients. ACC: American College of Cardiology; ASH: American Society of Hematology; CHEST: American College of Chest Physicians; COVID-19: coronavirus disease 2019; ICU: intensive care unit; ISTH: International Society on Thrombosis and Haemostasis; NIH: National Institutes of Health; VTE: venous thromboembolism; WHO: World Health Organization.

1. American College of Cardiology. Thrombosis and COVID-19: FAQs for current practice. https://www.acc.org/latest-in-cardiology/articles/2020/04/17/14/42/thrombosis-and-coronavirus-disease-2019-covid-19-faqs-for-current-practice. Updated April 22, 2020. Accessed November 10, 2020. **2.** American Society of Hematology. COVID-19 and VTE/anticoagulation: frequently asked questions. https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation. Updated September 18, 2020. Accessed November 10, 2020. **3.** Moores LK, et al. *Chest*. 2020;158:1143-1163. **4.** Spyropoulos A, et al. *J Thromb Haemost*. 2020;18:1859-1865. **5.** National Institutes of Health. Antithrombotic therapy in patients with COVID-19. https://covid19treatmentguidelines.nih.gov/antithrombotic-therapy/. Updated December 17, 2020. Accessed December 18, 2020. **6.** World Health Organization. Clinical management of COVID-19: interim guidance. https://www.who.int/publications/i/item/clinical-management-of-covid-19. Updated May 27, 2020. Accessed November 10, 2020.

Randomized Trials of Escalated/Treatment dose Heparin vs SOC Heparin in Hospitalized COVID 19 patients (N=20)

Study Acronym or PI	Study design	Population[1]	Intervention	Control	Primary outcome (time frame)
COVID-HEP	Randomized, open-label, multicenter,	1) Non-ICU patients with D-dimer >1000 μg/L or 2)	Therapeutic LMWH or UFH	Prophylactic LMWH or UFH (augmented	Composite outcome of arterial or venous thrombosis, DIC and all-cause mortality (30 days)
CORIMMUNO-COAG	Randomized, open-label, multicenter, clinical trial	Non-ICU patients requiring oxygen (group 1) or ICU patients requiring mechanical ventilation (group 2)	Therapeutic LMWH or UFH	Prophylactic LMWH or UFH	Group 1: survival without ventilation (14 days) or group 2: ventilator free survival (28 days)
ACOVACT	Randomized, multifactorial, adaptive, open-label, multicenter, platform trial	Non-ICU and ICU patients	Rivaroxaban 5 mg twice daily	Local standard thromboprophylaxis	Sustained improvement (>48h) of one point on the World Health Organization Scale (29 days)
Perepu et al.	Randomized, open-label, multicenter, clinical trial	Non-ICU and ICU patients with modified ISTH DIC score ≥3	Intermediate-dose LMWH	BMI-adjusted prophylactic dose LMWH	All-cause mortality (30 days)

Trial designs:

1. LMWH/Heparin as an add-on treatment approach in reducing severity/morbidity of COVID-19 pneumonia

2. LMWH/Heparin as a classic antithrombotic agent in reducing TE complications/mortality from thrombosis

Tritchler T et al JTH 2020

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INSPIRATION Randomized Trial:

Intermediate vs Standard-dose Heparin in ICU COVID Pts

Table 2. Primary, Secondary, and Exploratory Outcomes Within 30 Days of Enrollment in the Prespecified Primary Analysis in a Study of the Effect of Intermediate- vs Standard-Dose Prophylactic Anticoagulation Among Patients With COVID-19 Admitted to the Intensive Care Unit (ICU)

Outcome	No. (%)		Absolute difference (95% CI), %	Odds ratio (95% CI)	*P* value
	Intermediate dose (n = 276)	Standard dose (n = 286)			
Primary outcome					
Composite of adjudicated acute venous thromboembolism, arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all-cause mortality[a]	126 (45.7)	126 (44.1)	1.5 (−6.6 to 9.8)	1.06 (0.76 to 1.48)	.70
Secondary outcomes					
All-cause mortality	119 (43.1)	117 (40.9)	2.2 (−5.9 to 10.3)	1.09 (0.78 to 1.53)	.50
Adjudicated venous thromboembolism	9 (3.3)	10 (3.5)	−0.2 (−3.2 to 2.7)	0.93 (0.37 to 2.32)	.87
Ventilator-free days, median (IQR)[b]	30 (3 to 30)	30 (1 to 30)	0 (0 to 0)	NA	.50[c]
Safety outcomes					
Major bleeding[c]	7 (2.5)	4 (1.4)	1.1 (−1.1 to 3.4)	1.83 (0.53 to 5.93)	.33

Inspiration Investigators JAMA 2021

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ACTION Trial: Efficacy Outcomes (N=615)
Therapeutic AC (Rivaroxaban 20mg)* vs SOC prophylaxis

Efficacy Outcome	Therapeutic (N=310)	Prophylactic (N=304)	Effect Measure	Effect (95% CI)
Composite thromboembolic outcome*	23/310 (7.4%)	30/304 (9.9%)	Relative Risk	0.75 (0.45–1.26)
Myocardial infarction	13/310 (4.2%)	14/304 (4.6%)	Relative Risk	0.91 (0.44–1.91)
Venous thromboembolism†	11/310 (3.5%)	18/304 (5.9%)	Relative Risk	0.60 (0.29–1.25)
Deep vein thrombosis	5/310 (1.6%)	5/304 (1.6%)	Relative Risk	0.98 (0.29–3.35)
Pulmonary embolism	7/310 (2.3%)	13/304 (4.3%)	Relative Risk	0.53 (0.21–1.31)
Stroke	1/310 (0.3%)	0/304 (0.0%)	---	---
Major adverse limb event	0/310 (0.0%)	1/304 (0.3%)	---	---
Composite thrombotic outcome and all-cause mortality	46/310 (14.8%)	44/304 (14.5%)	Relative Risk	1.03 (0.70–1.50)
All-cause mortality	35/310 (11.3%)	23/304 (7.6%)	Relative Risk	1.49 (0.90–2.46)

*Composite thromboembolic outcome is defined as any venous thromboembolism, myocardial infarction, stroke, systemic embolism and major adverse events of the extremities.
†One patient had one episode of deep vein thrombosis, followed six days later by a pulmonary embolism.

*Rivaroxaban Inpatient +30 days PostDdischarge

Lopez R et al Lancet 2021

RAPID Trial: Moderately Ill

Outcomes	No (%) of patients		Odds ratio or geometric mean ratio (95% CI)	P value
	Therapeutic heparin (n=228)	Prophylactic heparin (n=237)		
Primary outcome				
Primary composite outcome*	37 (16.2)	52 (21.9)	0.69 (0.43 to 1.10)	0.12
Secondary outcomes				
Death from any cause	4 (1.8)	18 (7.6)	0.22 (0.07 to 0.65)	0.006
Invasive mechanical ventilation	11 (4.8)	16 (6.8)	0.70 (0.32 to 1.55)	0.38
Any mechanical ventilation†	21 (9.2)	26 (11.0)	0.82 (0.45 to 1.51)	0.53
ICU admission	33 (14.5)	42 (17.7)	0.79 (0.48 to 1.29)	0.34
Death or any mechanical ventilation	23 (10.1)	38 (16.0)	0.59 (0.34 to 1.02)	0.06
Death or ICU admission	36 (15.8)	50 (21.1)	0.70 (0.44 to 1.13)	0.14
Mean (SD) ventilator-free days	26.5 (5.6)	24.7 (8.5)	1.77 (1.02 to 3.08)	0.042
Mean (SD) organ support-free days	25.8 (6.2)	24.1 (8.8)	1.41 (0.90 to 2.21)	0.13
Mean (SD) ICU-free days	26.0 (6.1)	24.2 (8.8)	1.51 (0.94 to 2.41)	0.087
Mean (SD) hospital-free days	19.8 (7.3)	18.4 (9.2)	1.09 (0.79 to 1.50)	0.59
Renal replacement therapy‡	2 (0.9)	5 (2.1)	0.41 (0.08 to 2.15)	0.29
Thromboembolism§:				
Venous	2 (0.9)	6 (2.5)	0.34 (0.07 to 1.71)	0.19
Arterial	0 (0.0)	1 (0.4)	-	-
Bleeding:				
ISTH major bleeding¶	2 (0.9)	4 (1.7)	0.52 (0.09 to 2.85)	0.69
Red blood cell transfusion (≥1 unit)	3 (1.3)	9 (3.8)	0.34 (0.09 to 1.27)	0.14
Transfusion of other blood components or products**	1 (0.4)	0 (0.0)	-	-
Heparin induced thrombocytopenia	0 (0.0)	0 (0.0)	-	-
Geometric mean (SD) D-dimer ratio (D-dimer×ULN)††	1.9 (0.7)	2.4 (0.9)	0.88 (0.78 to 0.99)	0.032

Scholzberg M et al BMJ 2021; 375:n2400

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Multiplatform Randomized Trials: Critically Ill

ATTACC, ACTIV-IVa, REMAP-CAP

Table 2. Primary and Secondary Outcomes.

Outcome	Therapeutic-Dose Anticoagulation (N=536)	Usual-Care Thromboprophylaxis (N=567)	Adjusted Difference in Risk (95% Credible Interval)	Adjusted Odds Ratio (95% Credible Interval)*	Probability of Superiority	Probability of Futility	Probability of Inferiority
	median no. (IQR)		*percentage points*		%	%	%
Organ support–free days up to day 21†‡	1 (–1 to 16)	4 (–1 to 16)	—	0.83 (0.67 to 1.03)	5.0	99.9	95.0
	no. of patients/total no. (%)						
Survival to hospital discharge‡	335/534 (62.7)	364/564 (64.5)	–4.1 (–10.7 to 2.4)	0.84 (0.64 to 1.11)	10.8	99.6	89.2
Major thrombotic events or death§	213/531 (40.1)	230/560 (41.1)	1.0 (–5.6 to 7.4)	1.04 (0.79 to 1.35)	40.3	—	59.7
Major thrombotic events¶	34/530 (6.4)	58/559 (10.4)	—	—	—	—	—
Death in hospital	199/534 (37.3)	200/564 (35.5)	—	—	—	—	—
Any thrombotic events or death§	217/531 (40.9)	232/560 (41.4)	1.5 (–4.9 to 8.0)	1.06 (0.81 to 1.38)	33.4	—	66.6
Any thrombotic events‖	38/530 (7.2)	62/559 (11.1)	—	—	—	—	—
Death in hospital	199/534 (37.3)	200/564 (35.5)	—	—	—	—	—
Major bleeding§	20/529 (3.8)	13/562 (2.3)	1.1 (–0.6 to 4.4)	1.48 (0.75 to 3.04)	12.8	—	87.2

The REMAP-CAP,ACTIVE-IVa, ATTACC Investigators NEJM 2021; Aug 5

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Multiplatform Randomized Trials: Non-Critically Ill

ATTACC, ACTIV-IVa, REMAP-CAP

Table 2. Primary Outcome of Organ Support–Free Days.*

Variable	Therapeutic-Dose Anticoagulation	Usual-Care Thromboprophylaxis	Adjusted Difference in Risk (95% Credible Interval)†	Adjusted Odds Ratio (95% Credible Interval)‡	Probability of Superiority of Therapeutic-Dose Anticoagulation
	no. of patients/total no. (%)		*percentage points*		%
Patients with moderate disease					
Overall group§	939/1171 (80.2)	801/1048 (76.4)	4.0 (0.5 to 7.2)	1.27 (1.03–1.58)	98.6
D-dimer cohort¶					
High level	264/339 (77.9)	210/291 (72.2)	5.1 (0.0 to 9.9)	1.31 (1.00–1.76)	97.3
Low level	463/570 (81.2)	403/505 (79.8)	3.0 (–1.2 to 6.3)	1.22 (0.93–1.57)	92.9
Unknown level	212/262 (80.9)	188/252 (74.6)	4.9 (0.00 to 9.9)	1.32 (1.00–1.86)	97.3

Table 3. Secondary Outcomes among All Patients with Moderate Disease.*

Outcome	Therapeutic-Dose Anticoagulation	Usual-Care Thromboprophylaxis	Adjusted Difference in Risk (95% Credible Interval)†	Adjusted Odds Ratio (95% Credible Interval)‡	Probability of Effect of Therapeutic-Dose Anticoagulation
	no. of patients/total no. (%)		*percentage points*		%
Survival until hospital discharge	1085/1171 (92.7)	962/1048 (91.8)	1.3 (–1.1 to 3.2)	1.21 (0.87 to 1.68)§	87.1¶
Survival without organ support at 28 days‖	932/1175 (79.3)	789/1046 (75.4)	4.5 (0.9 to 7.7)	1.30 (1.05 to 1.61)	99.1¶
Progression to intubation or death**	129/1181 (10.9)	127/1050 (12.1)	–1.9 (–4.1 to 0.7)	0.82 (0.63 to 1.07)	92.2¶
Major thrombotic event or death	94/1180 (8.0)	104/1046 (9.9)	–2.6 (–4.4 to –0.2)	0.72 (0.53 to 0.98)	98.0¶
Major thrombotic event	13/1180 (1.1)	22/1046 (2.1)			
Death in hospital	86/1180 (7.3)	86/1046 (8.2)			
Major bleeding	22/1180 (1.9)	9/1047 (0.9)	0.7 (–0.1 to 2.3)	1.80 (0.90 to 3.74)	95.5††

Usual care thromboprophylaxis: 71.7% low dose; 26.5% intermediate dose

The REMAP-CAP,ACTIVE-IVa, ATTACC Investigators NEJM 2021; Aug 5

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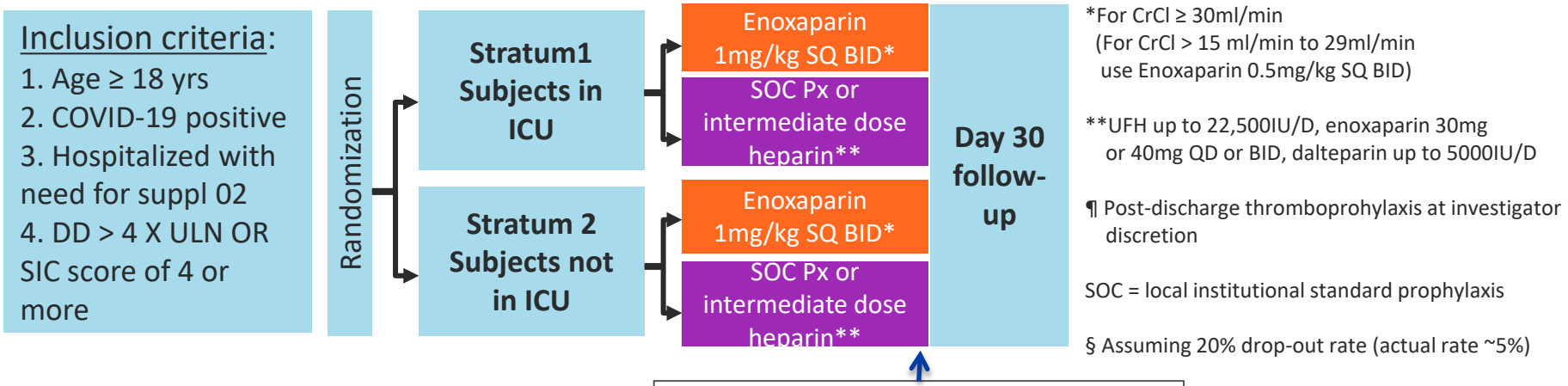
HEP-COVID Trial

Multicenter, pragmatic, randomized, pseudo-blinded active control trial

Screening Phase Up to 72hrs

Pseudo-blinded Treatment Phase In-Hospital

Post-treatment Phase¶



*For CrCl ≥ 30ml/min
(For CrCl > 15 ml/min to 29ml/min use Enoxaparin 0.5mg/kg SQ BID)

**UFH up to 22,500IU/D, enoxaparin 30mg or 40mg QD or BID, dalteparin up to 5000IU/D

¶ Post-discharge thromboprohylaxis at investigator discretion

SOC = local institutional standard prophylaxis

§ Assuming 20% drop-out rate (actual rate ~5%)

Day 10 + 4 or hospital D/C screening LE Compression Ultrasound

Executive Committee
Independent Data Safety Monitoring Board
Patient and Investigator blinded to study drug
Local adjudication with central quality oversight

Sample size §	Control	RRR	Power for superiority	2 sided α
308	42%	40%	80%	5%

Primary analysis: mITT population and PP population

NCT: 04401293 IND Exempt #150026

Goldin M et al Thromb Haemost 2021

Primary Efficacy Outcomes at 30-Days Post Randomization
mITT Population (N=253)

Outcome	Therapeutic Dose (N=129)	Standard Dose (N=124)	RR (95% CI)	P Value†
	Number (percent)			
Primary efficacy outcome				
Composite VTE, ATE, ACM	**37/129 (28.7)**	**52/124 (41.9)**	**0.68 (0.49-0.96)**	**0.0273**
Non-ICU Stratum	**14/84 (16.7)**	**31/86 (36.1)**	**0.46 (0.27-0.81)**	**0.0042**
ICU Stratum	23/45 (51.1)	21/38 (55.3)	0.92 (0.62-1.39)	
VTE+ATE	**14/129 (10.9)**	**36/124 (29.0)**	**0.37 (0.21-0.66)**	**0.0003**
ACM	25/129 (19.4)	31/124 (25.0)	0.78 (0.49-1.23)	

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Secondary Efficacy Outcomes at 30-Days Post Randomization
mITT Population (N=253)

Outcome	Therapeutic Dose (N=129)	Standard Dose (N=124)	RR (95% CI)	P Value†
	Number (percent)			
Secondary efficacy outcomes				
Primary Efficacy Outcome at Day 14	**30/129 (23.3)**	**45/124 (36.3)**	**0.64 (0.43-0.95)**	**0.0232**
Progression to ARDS	11/127 (8.7)	6/121 (5.0)	1.75 (0.67-4.58)	
Rehospitalization	1/129 (0.8)	3/124 (2.4)	0.32 (0.03-3.03)	
Need for intubation	17/122 (13.9)	21/121 (17.4)	0.80 (0.45-1.45)	
Need for ECMO	1/129 (0.8)	1/124 (0.8)	0.96 (0.06-15.2)	
Non-fatal cardiac arrest	0/129 (0.0)	2/124 (1.6)	0.19 (0.01-3.97)	
Acute Kidney Injury	17/129 (13.2)	12/124 (9.7)	1.36 (0.68-2.73)	
New Onset Atrial Fibrillation	4/129 (3.1)	5/124 (4.0)	0.77 (0.21-2.80)	

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Principal Safety Outcome at 30-Days Post Randomization
mITT Population (N=253)

Outcome	Therapeutic Dose (N=129)	Standard Dose (N=124)	RR (95% CI)	P Value†
	Number (percent)			
In non-ICU population using therapeutic-dose LMWH, NNT of 5 to prevent one major TE event and death and NNH of ~2000 to incur one MB				
Non-ICU Stratum	2/84 (2.38)	2/86 (2.33)	1.02 (0.15-7.10)	
ICU Stratum	4/45 (8.9)	0/38 (0.0)	7.62 (0.42-137.03)	

*ISTH Definition

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Mechanisms of the Dampening of COVID-19 Coagulopathy by LMWH

What have we learned from the randomized trial data of anticoagulation in hospitalized COVID-19 patients?

1. Pleiotrophic/anti-inflammatory effects of therapeutic dose LMWH/Heparin only helpful "early" in the course of disease (non-ICU or ward setting) before hyper-inflammatory state/cytokine storm
   - In critically ill patients – too late
   - Heparins possibly beneficial in reducing microvascular thrombosis/intravascular coagulopathy
   - Very elevated Dd exquisite biomarker for poor outcomes YET modifiable disease in non-ICU patients "just in time" paradigm
   - Use optimal (i.e. therapeutic) doses of heparins for thromboprophylaxis in these thrombotic patient groups

2. Small molecule DOACs do not have pleiotrophic/anti-inflammatory effects – likely inferior to heparins IP

3. Populations studied and trial designs?
   - Mortality or disease severity too high a bar?
   - Traditional antithrombotic trial design best chance of success (prevent macrovessel TE disease)

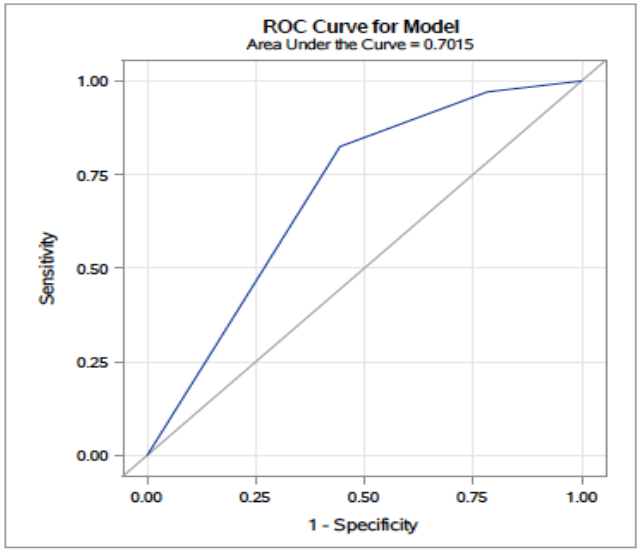
4. Better clarity once a WHO prospective meta-analysis and a Bayesian network meta-analysis (INVENT network) completed

Spyropoulos AC et al Lancet 2022

Validation of IMPROVE-DD for VTE in Hospitalized COVID-19 Patients (N= 9407)

Table of IMPROVE_DD by vte			
	vte		
IMPROVE_DD	No	Yes	Total
0-1, Low Risk	1988 99.60	8 0.40	1996
2-3, Moderate Risk	3093 98.72	40 1.28	3133
4-12, High Risk	4052 94.72	226 5.28	4278
Total	9133	274	9407

Factor	Points
Previous VTE	3
Known thrombophilia	2
Current lower-limb paralysis	2
Current cancer	2
Immobilized ≥ 7 days	1
ICU or CCU stay	1
Age > 60 years	1
D-dimer ≥ 2 × ULN	2



Spyropoulos AC et al Res Pract Thromb Haemost 2021

High Rates of Post-Discharge Thrombosis and Death in COVID-19 Patients

Ongoing prospective registry (CORE-19)[1]

11,249 consecutive hospitalized patients with COVID-19 from March 1, 2020 to May 31, 2020

- Complete follow-up in 4906 patients

Post-discharge prophylaxis: LMWH, direct oral anticoagulants (rivaroxaban/apixaban) or baby aspirin

Results:

- All-cause mortality rate - 4.83%
- Overall VTE rate - 1.55% (PE –0.85%)
- ATE rate - 1.71%
- Major bleeding rate - 1.73%
- Rehospitalization rate - 15.5%

Predictors of Post-Discharge Thrombosis and Death: Advanced age, cardiovascular risk factors, CKD, IMPROVE–DD VTE score ≥4, and ICU stay

- In multivariate analysis, post-discharge extended thromboprophylaxis decreased thrombosis and ACM by 46% (OR 0.54, 95% CI 0.47 - 0.81, p =.003)

Study (N)	Patients receiving post-discharge anticoagulation n (%)	Patients with VTE, n (%)	Type of VTE, (n)
Giannis (4907)[1]	12.7	76 (1.55)	DVT (44), PE (42)
Roberts (1877)[2]	0	9 (0.5)	DVT (2), PE (7)
Engelen (102)[3]	8 (8)	1 (0.98)	Asymptomatic DVT (1)
Patell (163)[4]	13 (8)	1 (0.6)	PE (1)

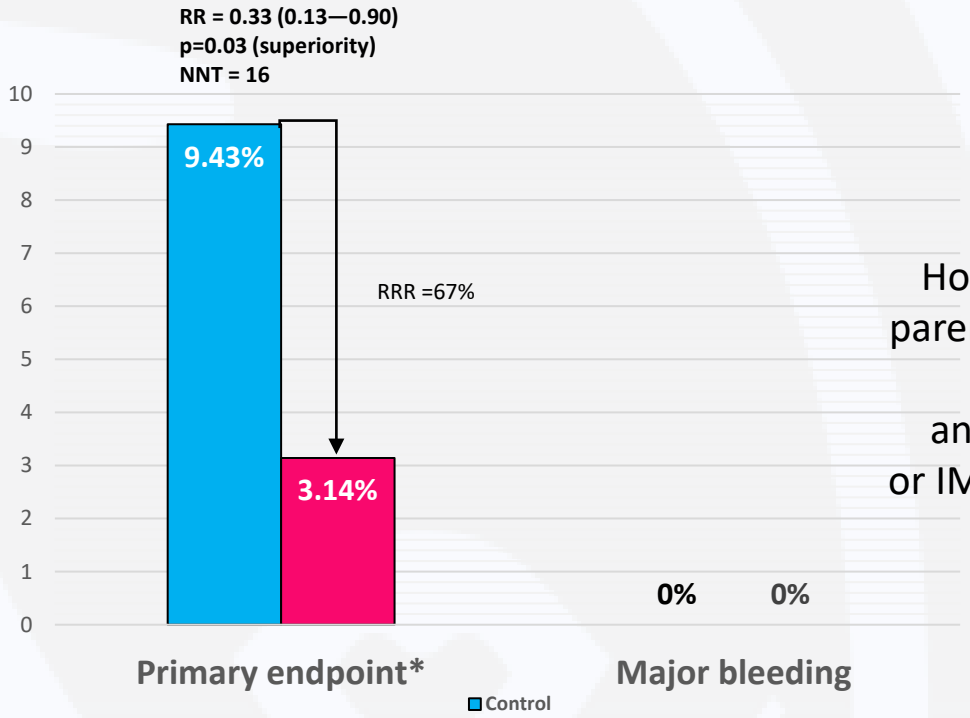
ATE: arterial thromboembolism; COVID-19: coronavirus disease 2019; DVT: deep vein thrombosis; LMWH: low molecular weight heparin; NR: not reported; PE: pulmonary embolism; VTE: venous thromboembolism.

1. Giannis D et al Blood 2021. **2.** Roberts LN, et al. *Blood*. 2020;136:1347-1350. **3.** Engelen MM, et al. Presented at: International Society on Thrombosis and Hemostasis 2020 Congress; July 12-14, 2020; LB/CO01.3. **4.** Patell R, et al. *Blood*. 2020;136:1342-1346.

MICHELLE Trial: Post-discharge thromboprophylaxis*

Primary efficacy and safety outcomes (N=320)

*Rivaroxaban 10mg QD x 30d
Vs
No Anticoagulation



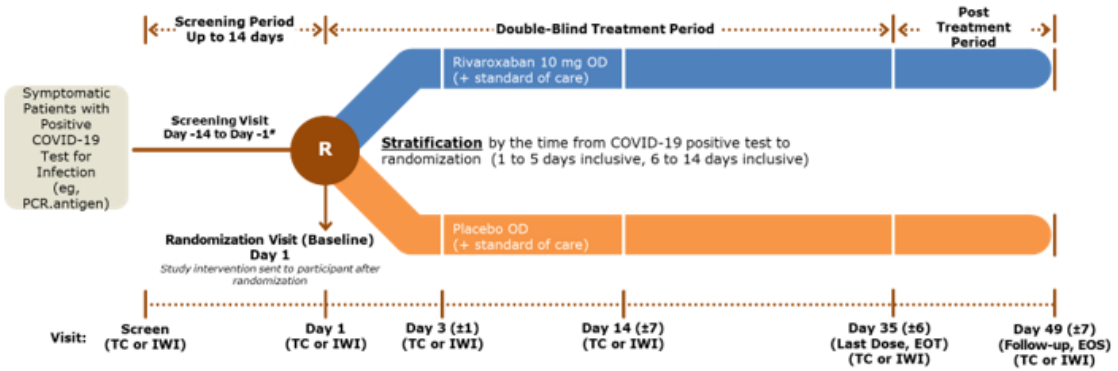
*Composite of composite of symptomatic VTE, VTE-related death, asymptomatic VTE (Doppler and AngioCT scan) and symptomatic ATE, MI, non-hemorrhagic stroke, (MALE), and cardiovascular death at day 35.

Inclusion criteria:
Hospitalized COVID-19 with parenteral thromboprophylaxis
AND
an IMPROVE VTE score ≥ 4
or IMPROVE VTE score 2-3 and DD > 2XULN

Rammacciotti E et al Lancet 2022

Role of Primary Thromboprophylaxis in Outpatient Settings?

1. OVID Trial [NCT04400799]: enoxaparin 40mg QD or Pb, N=1000
2. NIH ACTIVE IVb [NCT04498273]: apixaban 2.5 or 5mg BID or ASA or Pb, N= 7000
3. PREVENT-HD (Janssen-sponsored) [NCT04508023] N= 4000 - 5000
   - Reduction of VTE, ATE, ACM, hospitalization using rivaroxaban 10mg QD in high risk COVID-19 outpatients



Presence of at least 1 additional risk factor:

Age ≥60 years
Prior history of VTE
History of thrombophilia
History of CAD
History of PAD
History of cerebrovascular disease or ischemic stroke
History of cancer (other than basal cell carcinoma)
History of diabetes requiring medication
History of heart failure
Body Mass Index ≥35 kg/m2
D-dimer > upper limit of normal for local laboratory

Capell W et al Am Heart J 2021

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ACTIVE IVB Randomized Trial: COVID-19 Outpatients

	No. (%)			
	Aspirin (81 mg once daily) (n = 144)	Apixaban (2.5 mg twice daily) (n = 135)	Apixaban (5 mg twice daily) (n = 143)[a]	Placebo (n = 136)[a]
Suspected outcomes				
Composite primary end point[b]	1 (0.7)	1 (0.7)	2 (1.4)	1 (0.7)
Risk difference (in percentage points) vs placebo (95% CI)	0.0 (-3.4 to 3.2)	0.0 (-3.4 to 3.4)	0.7 (-2.8 to 4.3)	
Components of primary end point				
Cardiopulmonary hospitalizations	0	1 (0.7)	2 (1.4)	1 (0.7)
Deep vein thrombosis or pulmonary embolism	1 (0.7)	0	0	0
Myocardial infarction, stroke or other arterial embolism	0	0	0	0
Death	0	0	0	0
Any acute medical event[c]	6 (4.2)	8 (5.9)	13 (9.1)	7 (5.2)
Risk difference (in percentage points) vs placebo (95% CI)	-1.0 (-6.6 to 4.3)	0.8 (-5.1 to 6.7)	4.0 (-2.4 to 10.4)	
Adjudicated hemorrhagic events[f]				
Major bleeding	0	0	0	0
Clinically relevant nonmajor bleeding	0	1 (0.7)	1 (0.7)	0

Connors JM et al JAMA 2021 Oct 11

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Updated Northwell Guidance Documents for Managing COVID-19 Coagulopathy in Hospitalized Patients

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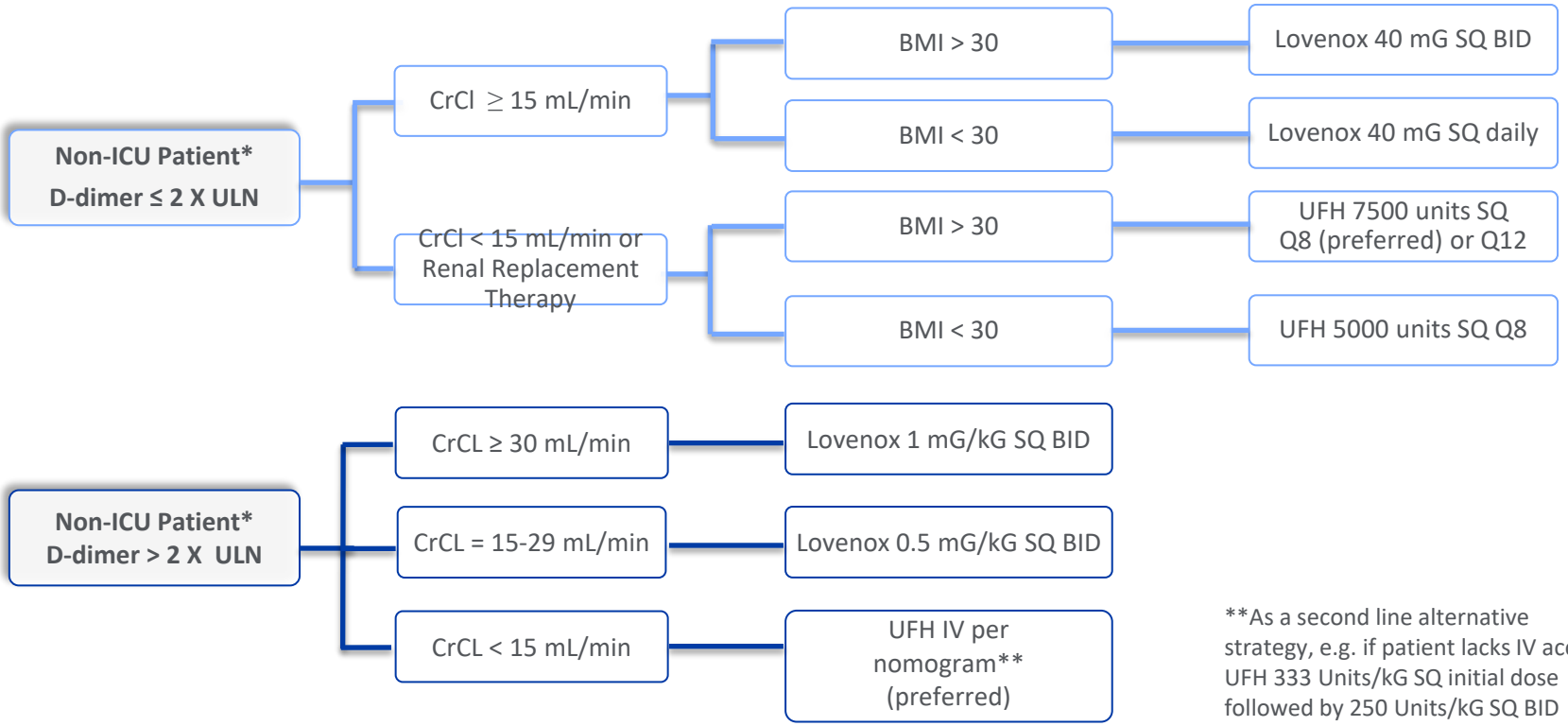
VTE Prophylaxis for Hospitalized COVID-19 Patients Receiving non-ICU level of care*



**As a second line alternative strategy, e.g. if patient lacks IV access, UFH 333 Units/kG SQ initial dose followed by 250 Units/kG SQ BID

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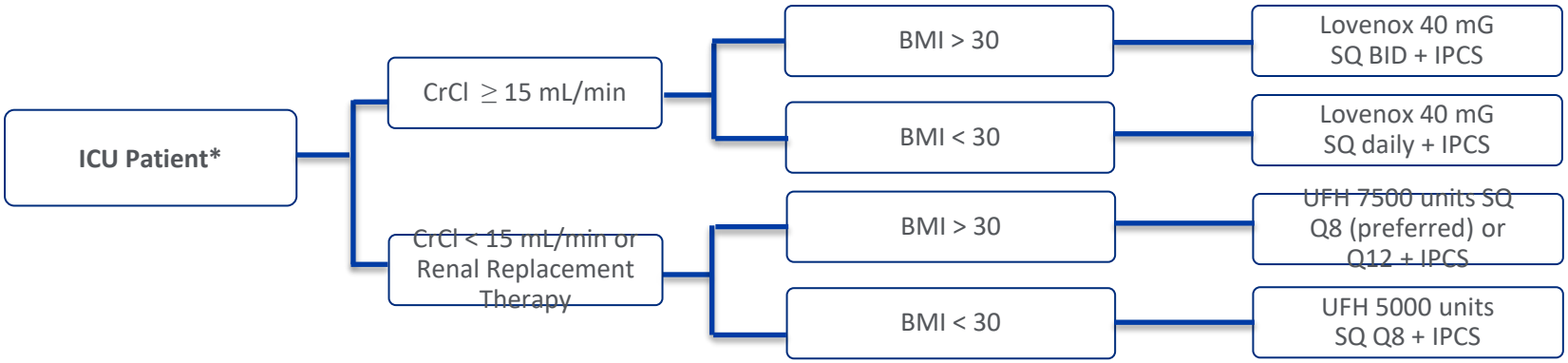
VTE Prophylaxis for Hospitalized COVID-19 Patients Receiving ICU level of care*



IPCS= intermittent pneumatic compression stockings

***ICU level of care include patients receiving:**

- **high-flow nasal cannula OR**
- **noninvasive positive pressure ventilation OR**
- **vasoactive infusion OR**
- **mechanical ventilation**

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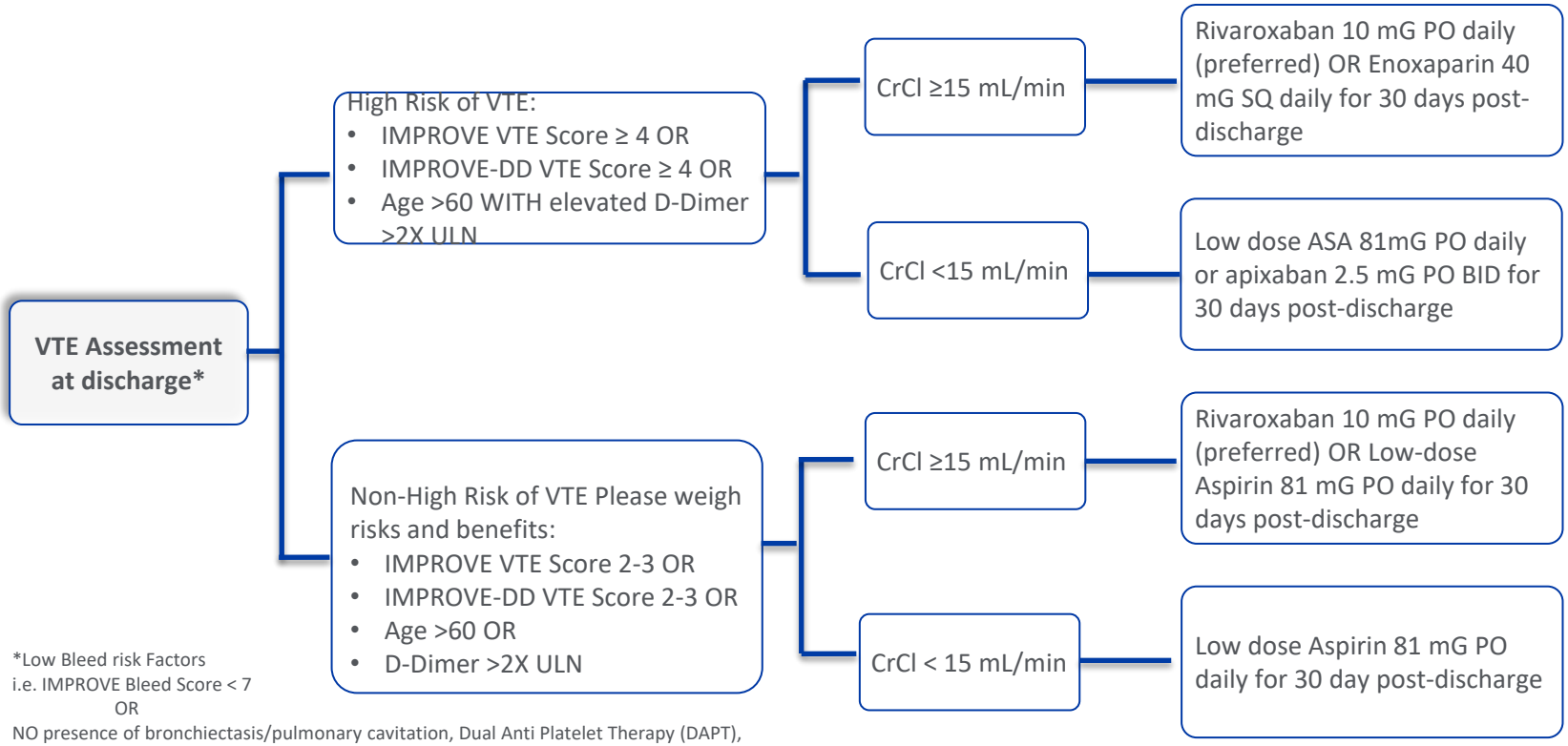
Extended VTE Prophylaxis of Hospitalized COVID-19 Patients



*Low Bleed risk Factors
i.e. IMPROVE Bleed Score < 7
OR
NO presence of bronchiectasis/pulmonary cavitation, Dual Anti Platelet Therapy (DAPT), active cancer with high bleeding risk (such as gastrointestinal cancer, GU cancer, neurologic and brain cancer), history of recent bleed (within 3 months), active gastroduodenal ulcer

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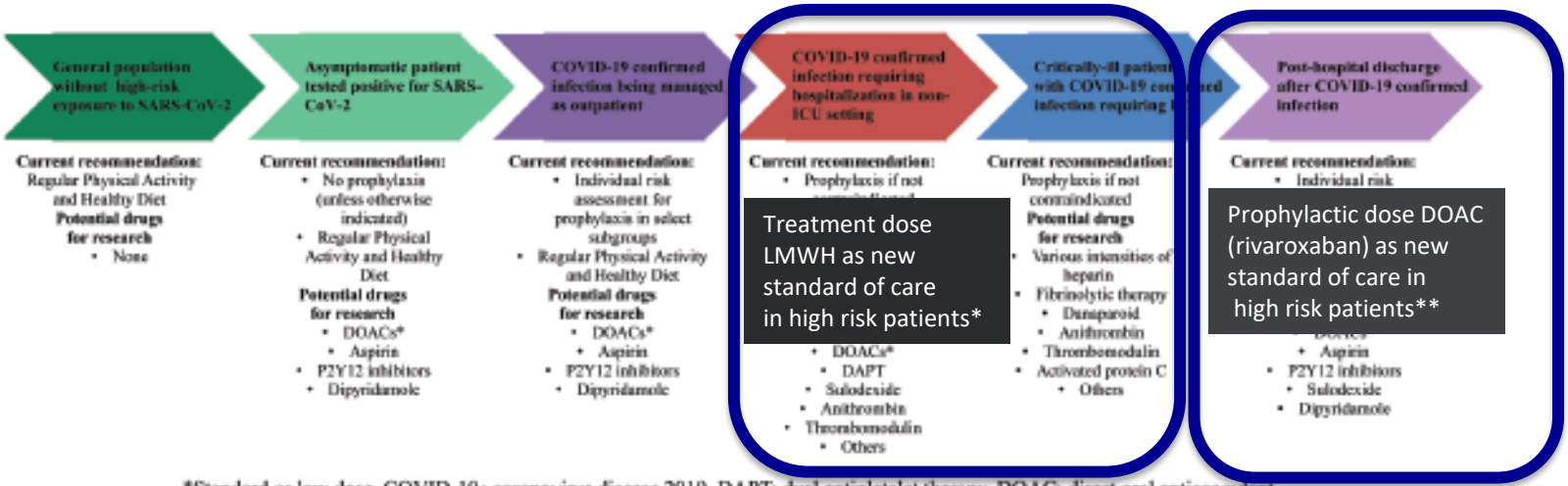
Conclusions: Future Antithrombotic Strategies in COVID-19



*Standard or low dose. COVID-19: coronavirus disease 2019. DAPT: dual antiplatelet therapy. DOAC: direct oral anticoagulant.

*DD based strategy, +/- 02 requirements
(**2022 NIH Guidelines, 2022 ASH Guidelines, 2022 ISTH Guidelines**)
**IMPROVE VTE or IMPROVE-DD VTE score ≥ 4 or score of 2-3 with DD > 2X ULN
(**2021 ASH Guidelines, 2022 ISTH Guidelines**)

Bikedeli B et al Thromb Haemost 2020

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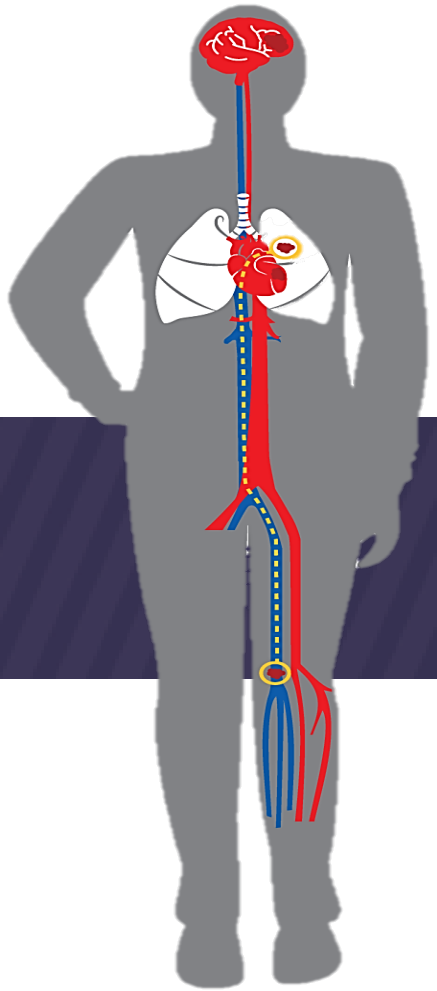

WORLD THROMBOSIS DAY
13 OCTOBER

THROMBOSIS: KNOW THE RISK AND REDUCE THE BURDEN

KNOW THROMBOSIS

KNOW VTE, Protect Your Health

www.WorldThrombbosisDay.org

Interactive Discussion: Speakers, Panelists, Attendees

- What challenges might you anticipate for smaller hospitals implementing a thromboprophylaxis protocol for their high-risk COVID-19 patients?
- What additional sources do you recommend for learning more about this topic?

Please Submit Additional Questions in Chat!

Key Takeaways

- In this randomized clinical trial, therapeutic-dose LMWH reduced major thromboembolism and death compared with institutional standard heparin thromboprophylaxis among inpatients with COVID-19 with very elevated D-dimer levels
- The treatment effect was not seen in ICU patients
- Low-molecular-weight heparin is a relatively accessible and cost-effective treatment
- Positive outcomes have also been seen in high-risk COVID-19 inpatients who receive post-discharge anticoagulant therapy using Direct Oral Anticoagulants (DOACs)(ex. Rivaroxaban)

Tools & Resources

From Today's Speaker:

- Article - *Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19*
- National Institutes of Health guidelines
- American Society of Hematology guidelines

Additional Resources:

- HQIC Anticoagulant ADEs Change Path - *coming soon*

Register for the Next HQIC Collaborative Event!

Save the Date!

Adverse Drug Events Webinar:

Exploring Strategies to Prevent Opioid Morbidity and Mortality

Tuesday, March 8, 2022

12:00 p.m. - 1:00 p.m. CT

Register Here

Thank you for Attending Today's Event

We value your input!

Please complete the brief survey posted in chat.

Contact Us

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