

# Anticoagulation for COVID-19

WEBINAR  
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**Mount  
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# Thrombosis in COVID

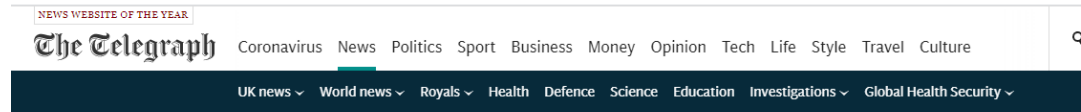
- Elevated markers and anecdote

- Autopsy data

- Hospital-acquired VTE

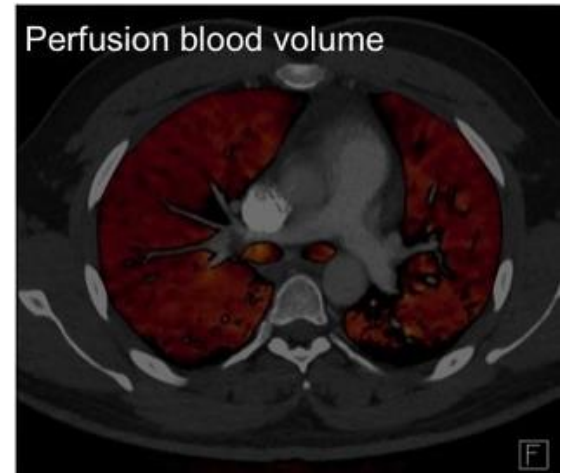
- Management challenging

- Poor evidence
- Testing often not done due to infectious risk
- Role of microthrombi



## Blood-thinning drugs can help save Covid-19 patients' lives

Hopes raised of breakthrough treatment as doctors hail anti-clot medicine as life saver



# Autopsy Data

**Hamburg, N=12**

**DVT 7/12 (58%)**

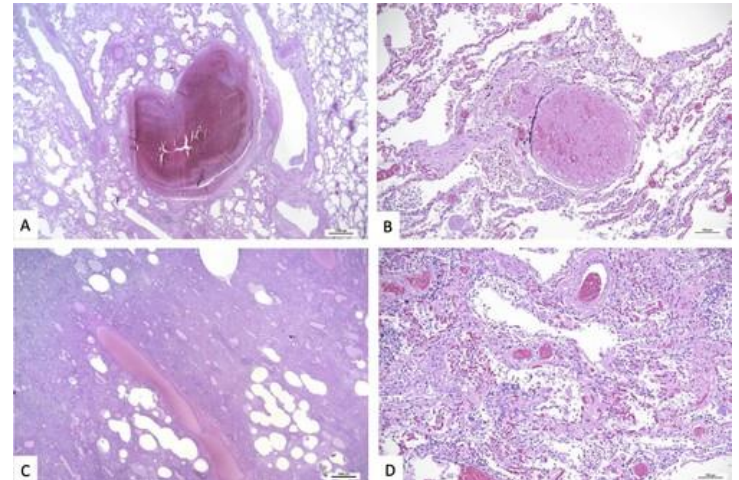
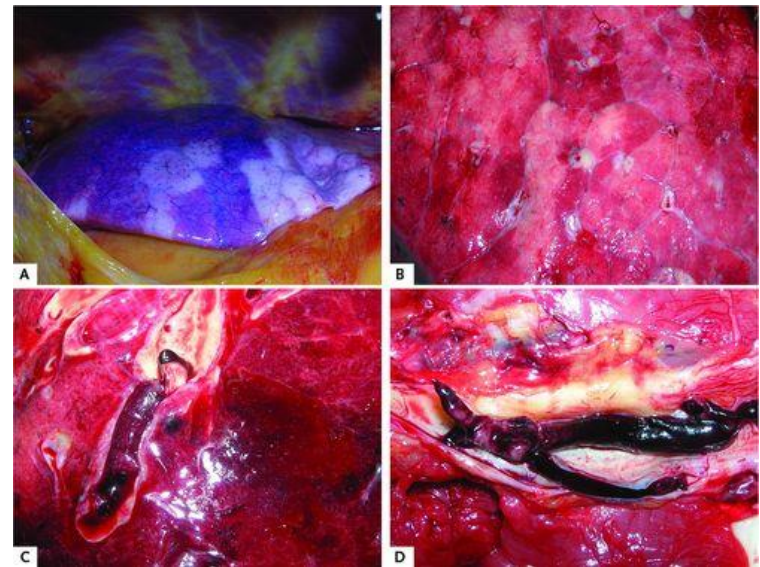
**PE cause of death 4/12 (33%)**

Diffuse alveolar damage, inflammatory infiltrates hyaline membranes, capillary congestion, interstitial edema, microvascular thromboemboli

**Austria, N=11**

**Pulm thrombi small/med 11/11 (100%)**

Diffuse alveolar damage (DAD), edema, hyaline membranes, pneumocytes and fibroblasts, thrombosis of small and mid-sized pulmonary arteries  
bronchopneumonia



Lax FA. *Ann Intern Med.* May 2020.

Wichmann D. *Ann Intern Med.* May 2020.

Menter T. *Histopathology.* May 2020.



# High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study

Julie Helms<sup>1,2</sup>, Charles Tacquard<sup>3</sup>, François Severac<sup>4</sup>, Ian Leonard-Lorant<sup>5</sup>, Mickaël Ohana<sup>5</sup>, Xavier Delabranche<sup>3</sup>, Hamid Merdji<sup>1,6</sup>, Raphaël Clere-Jehl<sup>1,2</sup>, Malika Schenck<sup>7</sup>, Florence Fagot Gandet<sup>7</sup>, Samira Fafi-Kremer<sup>2,8</sup>, Vincent Castelain<sup>7</sup>, Francis Schneider<sup>7</sup>, Lélia Grunebaum<sup>9</sup>, Eduardo Anglés-Cano<sup>10</sup>, Laurent Sattler<sup>9</sup>, Paul-Michel Mertes<sup>3</sup>, Ferhat Meziani<sup>1,6\*</sup> and CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis)

- ICU at 2 hospitals in France
- N=150, UFH/LMWH prophylaxis (80%) or treatment-dose (20%)
- Low threshold for testing

**Table 3 Outcomes of COVID-19 ARDS and non-COVID-19 ARDS**

	Population before matching (n = 383)				Population after matching (n = 222)			
	Non-COVID-19-ARDS (n = 233)	COVID-19-ARDS (n = 150)	OR [95% IC]	p-value	Non-COVID-19-ARDS (n = 145)	COVID-19-ARDS (n = 77)	OR [95% IC]	p-value
Thrombo-embolic complications—n (%)	14 (6)	27 (18)	3.4 [1.7–7.3]	<0.001	7 (4.8)	9 (11.7)	2.6 [1.1–6.1]	0.04
Pulmonary embolisms—n (%)	3 (1.3)	25 (16.7)	15.2 [4.5–80.4]	<0.001	3 (2.1)	9 (11.7)	6.2 [1.6–23.4]	0.01
Deep vein thrombosis—n (%)	3 (1.3)	3 (2)	1 [0.1–9.2]	1	2 (1.4)	0 (0)	–	–
Myocardial infarction—n (%)	6 (2.6)	0 (0)	0 [0–1.3]	0.09	2 (1.4)	0 (0)	–	–
Cerebral ischemic attack—n (%)	1 (0.4)	2 (1.3)	3.1 [0.2–185.5]	0.68	0 (0.0)	0 (0)	–	–
Limb ischemia—n (%)	0 (0)	1 (0.7)	Inf [0.0–Inf]	0.78	0 (0.0)	0 (0)	–	–
Mesenteric ischemia—n (%)	3 (1.3)	1 (0.7)	0.5 [0.0–6.5]	0.98	2 (1.4)	1 (1.3)	0.96 [0.09–9.8]	0.97
Nb of RRT filter per dialyzed patient—median, IQR	1 [2–1]	3 [2–7]	–	<0.001	2.0 [1.0–2.5]	3.0 [2.0–6]	–	0.03
Nb of RRT filter per day of RRT—median, IQR	0.3 [0.3; 0.5]	0.7 [0.5; 1]	–	<0.001	0.3 [0.3; 0.4]	0.7 [0.5; 1]	–	<0.001
ECMO oxygenator thrombosis—n (%)	1/10 (10)	2/12 (16.7)	–	0.59	1/7 (14.3)	0/4 (0)	–	–
Hemorrhagic complications—n (%)	1 (1.8)	4 (2.7)	2.4 [0.27–28.5]	0.6	2 (1.4)	0 (0)	–	–

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy

# VTE Incidence

## Extremely High Incidence of Lower Extremity Deep Venous Thrombosis in 48 Patients with Severe COVID-19 in Wuhan

Bin Ren, Feifei Yan, Zhouming Deng, Sheng Zhang, Lingfei Xiao, Meng Wu, and Lin Cai ✉

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## Extremely High Incidence of Lower Extremity Deep Venous Thrombosis in 48 Patients with Severe COVID-19 in Wuhan

**Running Title:** *Ren, Yan, Deng, Zhang, et al.; Incidence of DVT in Severe COVID-19*

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- ICU patients at 2 hospitals in Wuhan, China
- N=48, LMWH prophylaxis
- Screening LE US
- 41/48 DVT (85%)
- Most distal: 36/48 (75%); 5/48 (10%) proximal



# VTE Incidence

## Pulmonary Embolism or Pulmonary Thrombosis in COVID-19? Is the Recommendation to Use High-Dose Heparin for Thromboprophylaxis Justified?

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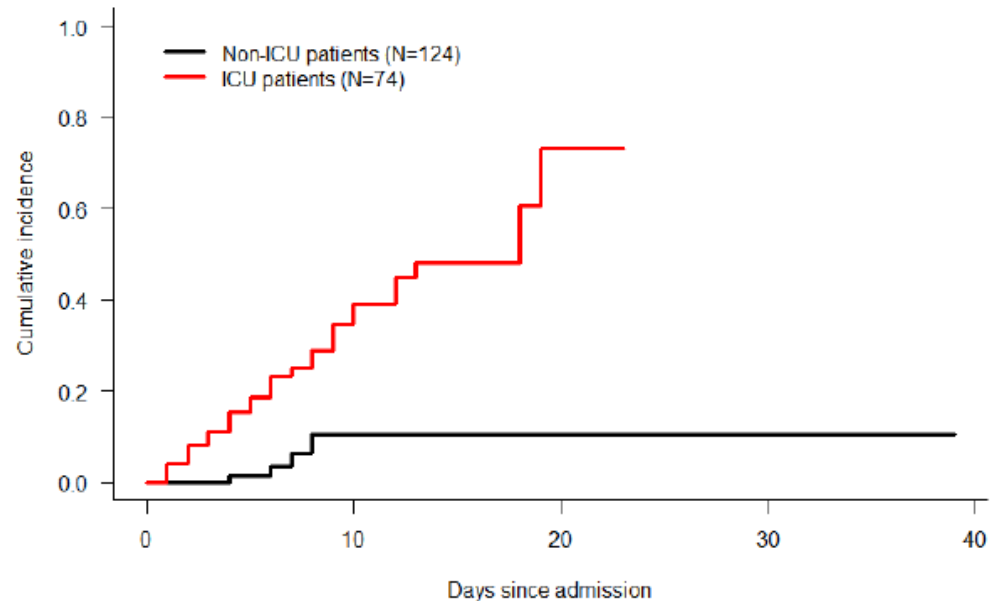
- Medical wards, N=388
- Received proph-dose LMWH
- No sx DVT
- Screening done on subset: 0/64 DVT

# VTE Incidence

N=198 patients; 123 wards, 75 ICU

- ✓ VTE 20%
- ✓ Symptomatic VTE 13%

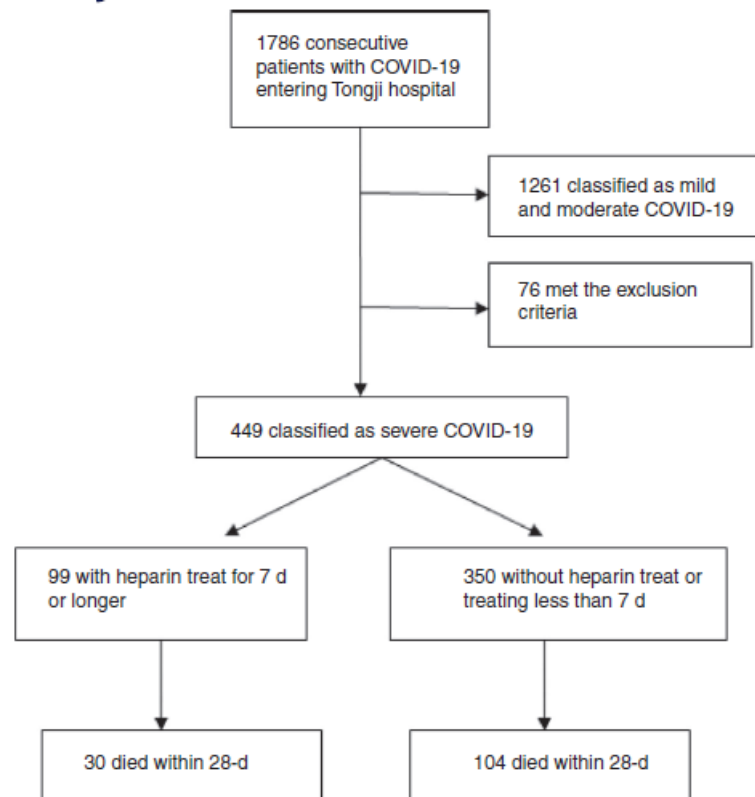
- VTE associated with death (HR, 2.4)
- Incidence higher in ICU than wards at 7 days (26% vs 6%)





# Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy

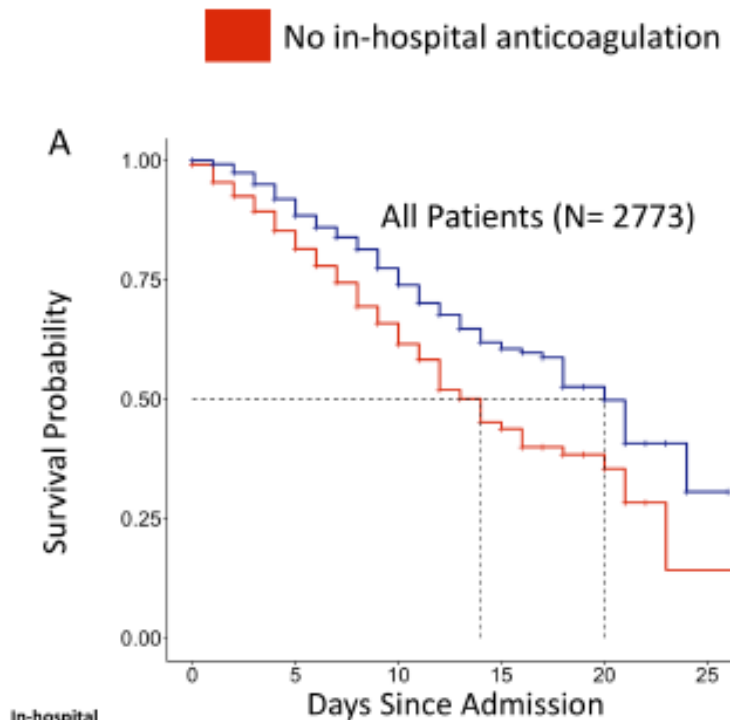
Ning Tang<sup>1</sup> | Huan Bai<sup>1</sup> | Xing Chen<sup>1</sup> | Jiale Gong<sup>1</sup> | Dengju Li<sup>2</sup> | Ziyong Sun<sup>1</sup>



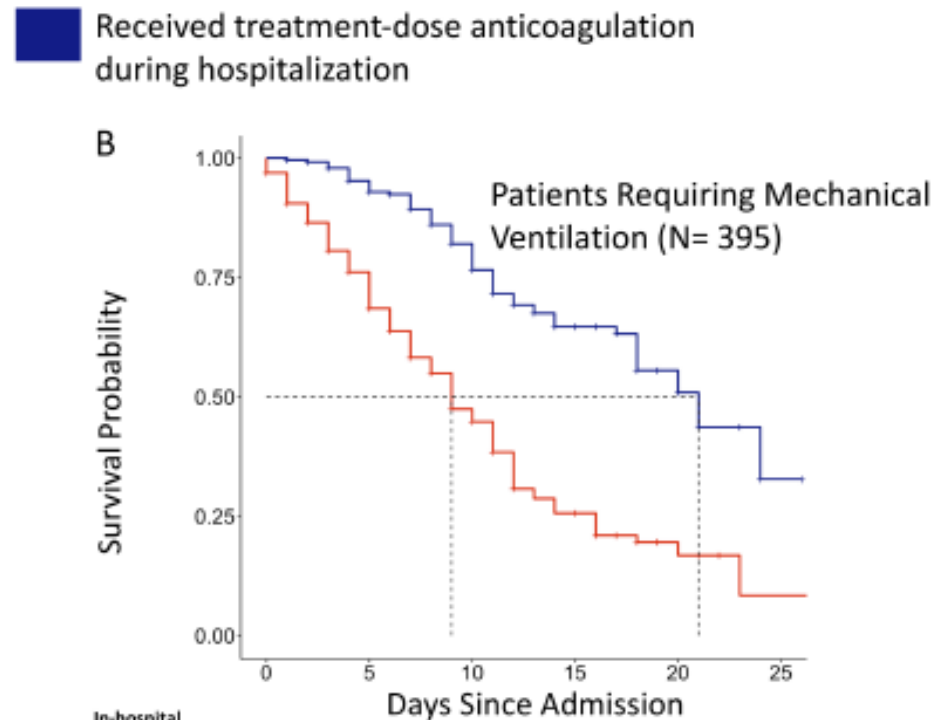
# Heparin and Mortality

Patients with	28-day mortality		Univariate analysis	
	Treating with heparin, %	Nontreating with heparin, %	Odds ratio (95% CI)	P value
SIC score $\geq$ 4 (n = 97)	40.0	64.2	0.372 (0.154-0.901)	.029
SIC score $\leq$ 4 (n = 352)	29.0	22.6	1.284 (0.700-2.358)	.419
D-dimer $\leq$ 1 ULN (n = 34)	33.3	9.7	4.667 (0.320-68.03)	.260
D-dimer > 1 ULN (n = 415)	30.2	32.7	0.934 (0.569-1.533)	.788
D-dimer > 2 ULN (n = 317)	32.1	36.9	0.810 (0.477-1.375)	.435
D-dimer > 3 ULN (n = 253)	31.1	42.5	0.611 (0.344-1.086)	.093
D-dimer > 4 ULN (n = 224)	33.3	44.5	0.623 (0.345-1.127)	.118
D-dimer > 5 ULN (n = 190)	34.9	48.8	0.563 (0.301-1.050)	.071
D-dimer > 6 ULN (n = 161)	32.8	52.4	0.442 (0.226-0.865)	.017
D-dimer > 8 ULN (n = 150)	33.3	54.8	0.412 (0.207-0.817)	.011

# Observational Study - JACC



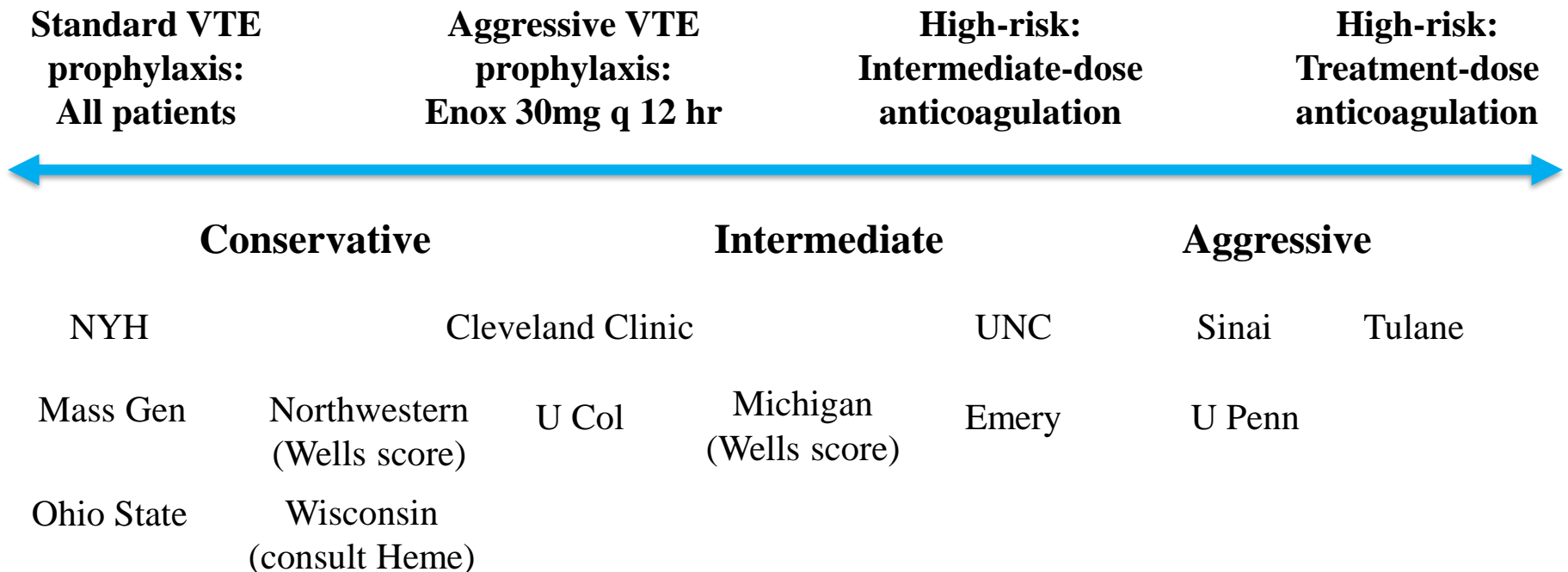
In-hospital Anticoagulation	Number at Risk					
Yes	786	538	266	90	19	3
No	1987	977	296	71	13	1



In-hospital Anticoagulation	Number at Risk					
Yes	234	197	137	65	14	3
No	161	100	54	25	7	1

# Academic Medical Centers – A Spectrum

- ▶ Academic med centers – Developed internal guidelines
- ▶ Spectrum - Based on severity: D-dimer, subjective assessment, ward/ICU



# Mount Sinai Protocol

## All admitted patients with COVID

- Assess VTE risk factors, signs/symptoms of DVT/PE, severity, bleeding risk
- Severity - based on clinician judgment
  - symptoms (worsening dyspnea)
  - signs (e.g., RR >24)
  - oxygen requirement (e.g.,  $\geq 6$ L O<sub>2</sub> NC)
  - biomarkers (e.g., D-dimers >1.5 or increasing)
- Increased risk for bleeding - active bleeding, PLT <50K, or INR >1.8

# Mount Sinai Protocol - Medicine wards

## Without evidence of severe respiratory compromise - Aggressive VTE prophylaxis

- BMI <40
  - CrCl >30: Enoxaparin 30 mg SQ Q12H
  - CrCl ≤30: Enoxaparin 30 mg SQ daily; Alternative - heparin 5,000 units SQ Q8hrs
- BMI ≥40
  - CrCl >30: Enoxaparin 40 mg SQ Q12H
  - CrCl ≤30: Enoxaparin 40 mg SQ daily; Alternative - heparin 7,500 units SQ Q8hrs

# Mount Sinai Protocol - Medicine wards

## Severe respiratory compromise or worsening respiratory status - Intermediate-dose AC

- Intermediate-dose AC: Enoxaparin 1mg/kg SC q 24hr
- CKD
  - CrCl <30, not on RRT – No dose change
  - RRT – Consider substituting apixaban 2.5mg PO BID



# Mount Sinai Protocol - ICU

## ICU - Treatment dose anticoagulation

- Enoxaparin 1mg/kg SC q 12hr
- CrCl <30 - IV heparin
- Duration – Treatment-dose anticoagulation for 2 weeks after transfer from ICU

# Mount Sinai Protocol – Confirmed VTE

## Confirmed VTE - positive diagnostic test

- Treatment dose anticoagulation
  - Treatment-dose apixaban/rivaroxaban - no need to transition from LMWH to oral agent
    - Apixaban dose: 10mg PO BID for 7 days then 5mg PO BID
    - Rivaroxaban dose: 15mg PO BID for 21 days then 20mg daily
  - CrCl <30, including RRT: No adjustment to apixaban needed. Alternative - IVH/warfarin
- Duration – Minimum of 3 months. Total duration based on risk of recurrent VTE and bleeding.

# Mount Sinai Protocol – Post-hospitalization

## VTE not documented

- If treated empirically with intermediate or treatment-dose anticoagulation - Treatment dose apixaban (5mg PO BID) or rivaroxaban (20mg PO once daily) for 2 weeks
- CKD – If CrCl <30 or RRT, consider apixaban 2.5mg PO BID

# Take Home Points

- There is an increased incidence of VTE and likely a role of microthrombi in COVID
- Aggressive VTE prophylaxis is warranted
- Consider intermediate-dose or treatment-dose AC for highest risk patients (decompensating, ICU)
- First, minimize the harm
  - ✓ Identify patients at increased risk for bleeding
  - ✓ Select based on greatest possible benefit
- Better data is coming!

**THANK YOU!**