GRAND ROUNDS JOURNAL CLUB

HEPCOVID TRIAL

Peter F. Weinberg MD, MSc

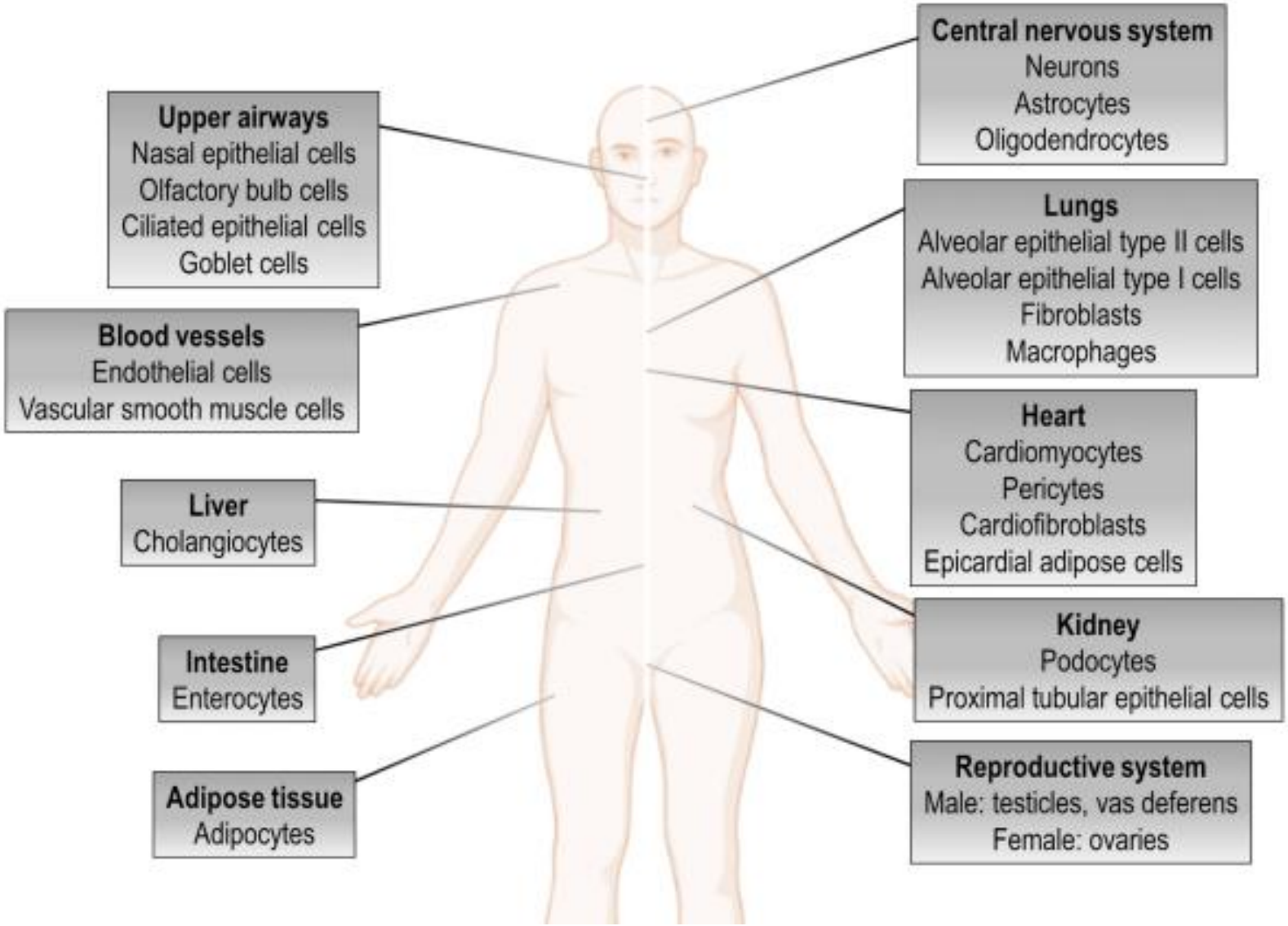
DISCLOSURES

I am a proud parent and grandparent

EARLY 2020

OUR RESPONSE HAS MARKEDLY CHANGED

COVID IS A MULTISYSTEM DISEASE



COVID COAGULOPATHY

Early COVID data

- Thromboembolism in critically ill ICU patients
  - Incidence ~ 25%
  - Mortality ~ 40%
- Increased incidence despite thromboprophylaxis
- 50% diagnosed within 24 hours of admission
- Autopsy data
  - 58% had PE
  - Thought to be direct cause of death in 33%

More recent COVID data

- **Incidence of VTE has decreased to 8-14%**
- **Due to decreased severity of hospital admissions, early treatment interventions, vaccines, etc.**

COVID COAGULOPATHY

Is a prothrombotic state

PE > DVT

Venous > Arterial

Has both macro- and microvascular thrombosis

Is associated with an elevated D-Dimer

D-Dimer elevations are associated with an increased risk of VTE as well as mortality

Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

The REMAP-CAP, ACTIV-4a, and ATTACC Investigators*

N Engl J Med 2021;385:777-89

CONCLUSIONS

In critically ill patients with Covid-19, an initial strategy of therapeutic-dose anticoagulation with heparin did not result in a greater probability of survival to hospital discharge or a greater number of days free of cardiovascular or respiratory organ support than did usual-care pharmacologic thromboprophylaxis. (REMAP-CAP, ACTIV-4a, and ATTACC ClinicalTrials.gov numbers, NCT02735707, NCT04505774, NCT04359277, and NCT04372589.)

Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

The ATTACC, ACTIV-4a, and REMAP-CAP Investigators*

N Engl J Med 2021;385:790-802

CONCLUSIONS

In noncritically ill patients with Covid-19, an initial strategy of therapeutic-dose anticoagulation with heparin increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support as compared with usual-care thromboprophylaxis. (ATTACC, ACTIV-4a, and REMAP-CAP ClinicalTrials.gov numbers, NCT04372589, NCT04505774, NCT04359277, and NCT02735707.)

JAMA Internal Medicine | Original Investigation

Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19

The HEP-COVID Randomized Clinical Trial

Alex C. Spyropoulos, MD; Mark Goldin, MD; Dimitrios Giannis, MD, MSc; Wassim Diab, MD; Janice Wang, MD; Sameer Khanijo, MD; Andrea Mignatti, MD; Eugenia Gianos, MD; Marc Cohen, MD; Gulru Sharifova, MD; Jeet M. Lund, DO; Alfonso Tafur, MD, MSc, RPVI; Paul A. Lewis, MD, CPE; Kevin P. Cohoon, DO; Husneara Rahman, PhD; Cristina P. Sison, PhD; Martin L. Lesser, PhD; Kanta Ochani, MBBS; Nirav Agrawal, MBBS; Judith Hsia, MD; Victoria E. Anderson, MPH; Marc Bonaca, MD, MPH; Jonathan L. Halperin, MD; Jeffrey I. Weitz, MD; for the HEP-COVID Investigators

Question Does thromboprophylaxis with therapeutic-dose low-molecular-weight heparin reduce the incidence of major thromboembolism and death compared with prophylactic/intermediate-dose heparins in inpatients with high-risk COVID-19?

JAMA 2021; 181: 1612-1620

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Inclusion criteria:

(1) Requirement for supplemental oxygen per investigator judgment

(2) Plasma D-dimer level greater than 4 times the upper limit of normal based on local laboratory criteria or a sepsis-induced coagulopathy score of 4 or greater

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Study Design:

Multicenter (12 U.S. Centers)
Randomized control trial
Modified intention-to-treat
Nonpregnant pts aged 18 or older
Inclusion dates: May 8, 2020 – May 14, 2021
Pts screened w/in 72 hrs of admission or transfer
COVID-19 dxed by nasal swab or serologic testing
Written informed consent in all patients

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Outcome Measures

(w/in 30 ± 2 days after randomization)

Primary

VTE (symptomatic UE or LE DVT, asymptomatic LE proximal DVT, symptomatic PE, splanchnic vein thrombosis, or cerebral sinus thrombosis)

ATE (myocardial infarction, ischemic stroke, peripheral or systemic ATE)

Death from any cause

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Outcome Measures

(w/in 30 ± 2 days after randomization)

Secondary

Composite primary outcome within 14 days after admission

Progression to ARDS

New-onset AF

Acute kidney injury

Nonfatal cardiac arrest

Endotracheal intubation

Extracorporeal membrane oxygenation,

Rehospitalization within 30 ± 2 days

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Therapeutic Heparin Dosing

Patients in the therapeutic dose group received enoxaparin at a dose of 1 mg/kg subcutaneously twice daily if CrCl was 30 mL/min/1.73 m^2 or greater or 0.5 mg/kg twice daily if CrCl was 15-29 mL/min/1.73 m^2.

JAMA 2021; 181: 1612-1620

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Standard Heparin Dosing

Patients in the standard-dose group received prophylactic or intermediate-dose heparin regimens per local institutional standard and could include UFH, up to 22,500 IU subcutaneously (divided twice or thrice daily); enoxaparin, 30 mg or 40 mg subcutaneously once or twice daily (weight-based enoxaparin 0.5 mg/kg subcutaneously twice daily was permitted but strongly discouraged); or dalteparin, 2500 IU or 5000 IU subcutaneously daily. If CrCl fell below 15 mL/ min/1.73 m^2, enoxaparin was converted to treatment-dose intravenous UFH until kidney function improved to CrCl greater than 15 mL/min/1.73 m^2 , when blinded-dose subcutaneous enoxaparin was resumed.

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Exclusion criteria:

(1) Physician determined need for full-dose anticoagulation or dual antiplatelet therapy

(2) Bleeding within the past month

(3) Active gastrointestinal or intracranial cancer

(4) Bronchiectasis or pulmonary cavitation

(5) Hepatic dysfunction with baseline INR greater than 1.5

(6) Creatinine clearance (CrCl) less than 15mL/min/1.73m^2

(7) Platelet count less than 25,000/µL

(8) History of heparin-induced thrombocytopenia (HIT) w/in 100 d

(9) Hypersensitivity/intolerance to study drug or components

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Study Design (cont'd):

Patients w/o diagnosed VTE underwent laboratory and screening lower extremity compression ultrasonography testing at hospital day 10 + 4, because asymptomatic proximal deep vein thrombosis diagnosed by ultrasonography is associated with death in medically ill inpatients, including those with pneumonia and sepsis.

Postdischarge anticoagulation was allowed at the discretion of treating physicians.

Primary efficacy, principal safety, and secondary outcomes were assessed in clinic or by telephone 30 ± 2 days after randomization

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Outcome Measures

(w/in 30 ± 2 days after randomization)

Safety

The principal safety outcome was major bleeding based on International Society on Thrombosis and Haemostasis criteria within 30 ± 2 days after randomization.

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Outcome Measures

(w/in 30 ± 2 days after randomization)

Outcomes were adjudicated locally by blinded investigators via imaging, laboratory, and other objective health record data. Serious adverse events included hypersensitivity reactions to study drug, hepatotoxicity, HIT as per major professional society definitions, and bone marrow toxicity. Locally adjudicated events underwent central quality review.

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Statistical Analysis

O’Brien-Fleming design

Bonferroni-adjusted subgroup analysis

Twain-Disraeli analysis

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PATIENTS

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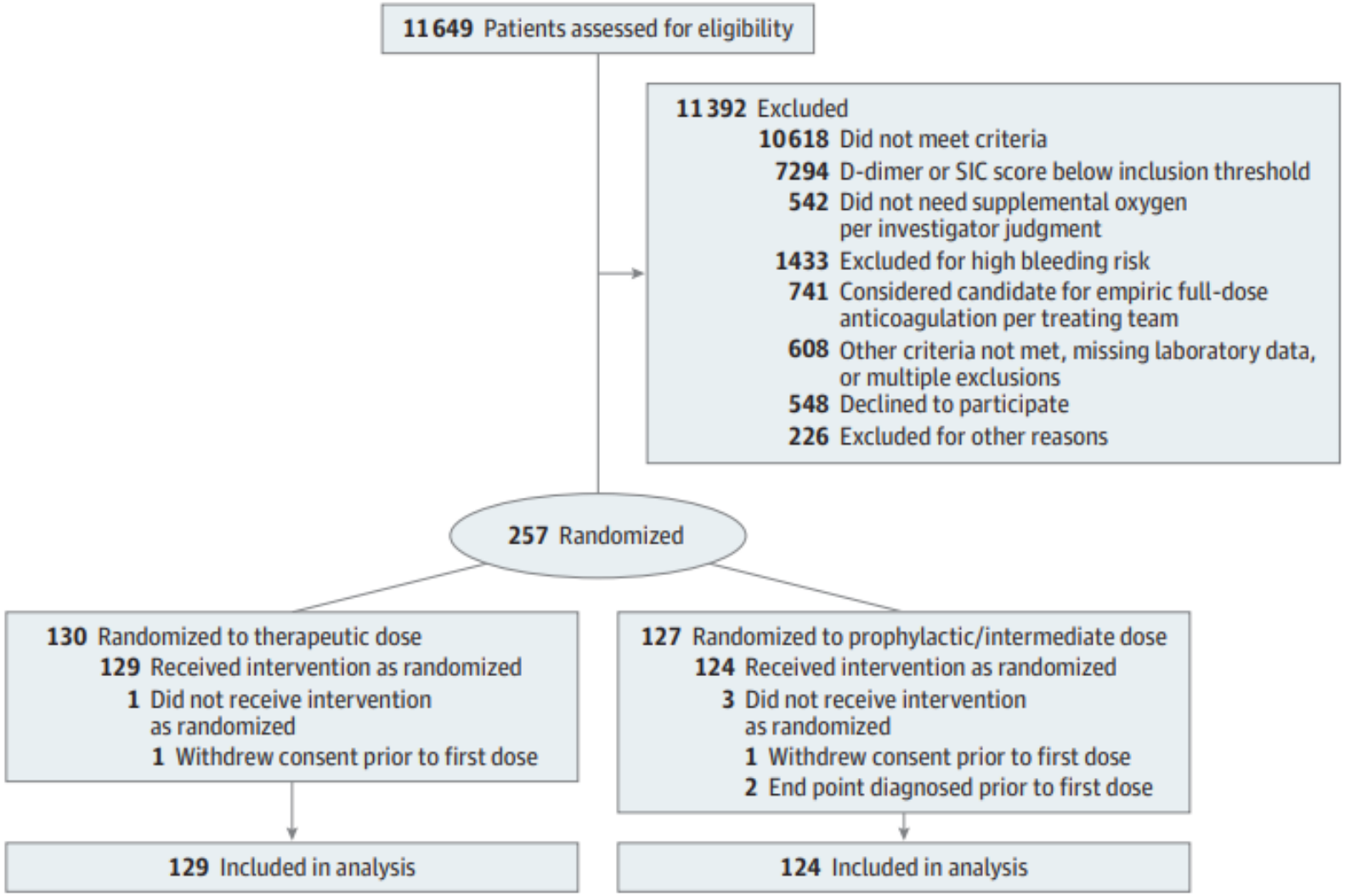

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HEP-COVID TRIAL

Table 1. Characteristics of Randomized Patients at Baseline[a]

Characteristic	No./total No. (%)		Standardized difference
	Therapeutic dose (n = 129)	Standard dose (n = 124)	
Age, mean (SD), y	65.8 (13.9)	67.7 (14.1)	−0.135
Sex, No. (%)			
Male	68 (52.7)	68 (54.8)	−0.043
Female	61 (47.3)	56 (45.2)	0.043
BMI, mean (SD)	31.2 (9.3)	29.8 (13.6)	0.116
Race and ethnicity, No. (%)[b]			
Asian	11 (8.5)	14 (11.3)	−0.093
Black	33 (25.6)	37 (29.8)	−0.095
White	56 (43.4)	46 (37.1)	0.129
Multiracial/unknown	29 (22.5)	27 (21.8)	0.017
ICU	45/129 (34.9)	38/124 (30.6)	0.090

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HEP-COVID TRIAL

Table 1. Characteristics of Randomized Patients at Baseline[a]

Characteristic	No./total No. (%)		Standardized difference
	Therapeutic dose (n = 129)	Standard dose (n = 124)	
Comorbidities			
Hypertension	81/129 (62.8)	70/123 (56.9)	0.120
Heart failure	0	2/124 (1.6)	NA
Diabetes mellitus	51/128 (39.8)	43/124 (34.7)	0.107
Dyslipidemia	48/129 (37.2)	39/124 (31.5)	0.121
Coronary artery disease	7/129 (5.4)	11/124 (8.9)	−0.134
Valvular heart disease	1/129 (0.8)	3/124 (2.4)	−0.131
History of ischemic stroke	5/129 (3.9)	3/124 (2.4)	0.084
History of carotid occlusive disease	0	0	NA
Peripheral arterial disease	4/129 (3.1)	1/124 (0.8)	0.166
Chronic kidney disease	5/129 (3.9)	4/124 (3.2)	0.035
Chronic lung disease	9/129 (7.0)	8/124 (6.5)	0.021
Chronic liver disease/cirrhosis	2/129 (1.6)	1/124 (0.8)	0.069
Pulmonary hypertension	1/127 (0.8)	2/124 (1.6)	−0.076

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HEP-COVID TRIAL

Table 1. Characteristics of Randomized Patients at Baseline[a]

Characteristic	No./total No. (%)		Standardized difference
	Therapeutic dose (n = 129)	Standard dose (n = 124)	
VTE risk factors			
Personal history of VTE	6/129 (4.7)	2/124 (1.6)	0.175
History of cancer	16/129 (12.4)	10/124 (8.1)	0.144
Active cancer	1/129 (0.8)	4/124 (3.2)	−0.176
Autoimmune disease	1/128 (0.8)	2/124 (1.6)	−0.077
Hormonal therapy/oral contraceptives	1/129 (0.8)	1/124 (0.8)	−0.004
Known thrombophilia	0	0	NA
Recent stroke with paresis	1/129 (0.8)	1/124 (0.8)	−0.004

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HEP-COVID TRIAL

Table 1. Characteristics of Randomized Patients at Baseline[a]

Characteristic	No./total No. (%)		Standardized difference
	Therapeutic dose (n = 129)	Standard dose (n = 124)	
Clinical scores, mean (SD)			
IMPROVEDD VTE risk score	4.33 (1.48)	4.22 (1.36)	0.076
Sepsis-induced coagulopathy score	2.35 (0.73)	2.31 (0.85)	0.043
Laboratory parameters, mean (SD)			
White blood cell count, /μL	9600 (5800)	9800 (8200)	−0.032
Platelets, $\times 10^3$/μL	287.7 (119.8)	269.7 (108.2)	0.158
Serum creatinine, mg/dL	0.94 (0.45)	1.00 (0.50)	−0.117
Prothrombin time, s	13.5 (1.6)	13.6 (2.6)	−0.033
D-dimer, ng/mL			
Mean (SD)	3837 (6166)	3183 (5409)	0.113
Lower quartile	1045	1072	
Median	1451	1700	
Upper quartile	3393	2942	

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HEP-COVID TRIAL

Table 1. Characteristics of Randomized Patients at Baseline[a]

Characteristic	No./total No. (%)		Standardized difference
	Therapeutic dose (n = 129)	Standard dose (n = 124)	
Medications prior to randomization			
Low-molecular-weight heparin	106/128 (82.8)	97/124 (78.2)	0.116
Unfractionated heparin	18/127 (14.2)	23/121 (19.0)	−0.130
Remdesivir	93/129 (72.1)	85/124 (68.6)	0.078
Glucocorticoids	111/127 (87.4)	93/123 (75.6)	0.307
Antiplatelets	40/129 (31.0)	24/124 (19.4)	0.271
Oxygen therapy			
Nasal cannula	80/129 (62.0)	83/124 (66.9)	−0.103
Nonrebreather mask	12/129 (9.3)	11/124 (8.9)	0.015
Ventilation mask	4/129 (3.1)	2/124 (1.6)	0.098
High-flow or noninvasive positive-pressure ventilation	20/129 (15.5)	19/124 (15.3)	0.005
Invasive mechanical ventilation	8/129 (6.2)	5/124 (4.0)	0.099
Length of hospital stay, mean (SD), d	12.2 (9.3)	11.6 (8.2)	0.073

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RESULTS

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HEP-COVID TRIAL

Table 2. Clinical Outcomes During the 30-Day Postrandomization Phase

Outcome	No./total No. (%)		RR (95% CI)	*P* value[a]
	Therapeutic dose (n = 129)	Standard dose (n = 124)		
Primary efficacy outcome				
VTE, ATE, or death	37/129 (28.7)	52/124 (41.9)	0.68 (0.49-0.96)	.03
Non-ICU stratum	14/84 (16.7)	31/86 (36.1)	0.46 (0.27-0.81)	.004
ICU stratum	23/45 (51.1)	21/38 (55.3)	0.92 (0.62-1.39)	.71
VTE + ATE	14/129 (10.9)	36/124 (29.0)	0.37 (0.21-0.66)	<.001
Death	25/129 (19.4)	31/124 (25.0)	0.78 (0.49-1.23)	.28

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HEP-COVID TRIAL

Table 2. Clinical Outcomes During the 30-Day Postrandomization Phase

Outcome	No./total No. (%)		RR (95% CI)	*P* value[a]
	Therapeutic dose (n = 129)	Standard dose (n = 124)		
Secondary efficacy outcomes				
Primary efficacy outcome at day 14	30/129 (23.3)	45/124 (36.3)	0.64 (0.43-0.95)	.02
Progression to ARDS	11/127 (8.7)	6/121 (5.0)	1.75 (0.67-4.58)	.25
Rehospitalization	1/129 (0.8)	3/124 (2.4)	0.32 (0.03-3.04)	.36
Intubation	17/122 (13.9)	21/121 (17.4)	0.80 (0.45-1.45)	.46
ECMO	1/129 (0.8)	1/124 (0.8)	0.96 (0.06-15.20)	>.99
Nonfatal cardiac arrest	0	2/124 (1.6)	0.19 (0.01-3.97)	.24
Acute kidney injury[b]	17/129 (13.2)	12/124 (9.7)	1.36 (0.68-2.73)	.38
New-onset atrial fibrillation	4/129 (3.1)	5/124 (4.0)	0.77 (0.21-2.80)	.75

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HEP-COVID TRIAL

Table 2. Clinical Outcomes During the 30-Day Postrandomization Phase

Outcome	No./total No. (%)		RR (95% CI)	*P* value[a]
	Therapeutic dose (n = 129)	Standard dose (n = 124)		
Principal safety outcome				
Major bleeding	6/129 (4.7)	2/124 (1.6)	2.88 (0.59-14.02)	.28
Non-ICU stratum	2/84 (2.4)	2/86 (2.3)	1.02 (0.15-7.10)	>.99
ICU stratum	4/45 (8.9)	0	7.62 (0.42-137.03)	.12

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HEP-COVID TRIAL

Table 3. Clinical Outcome Components During the 30-Day Postrandomization Phase in the Modified Intention-to-Treat Population

Outcome	No./total No. (%)		RR (95% CI)	*P* value[a]
	Therapeutic dose (n = 129)	Standard dose (n = 124)		
VTE				
Symptomatic DVT	7/129 (5.4)	19/124 (15.3)	0.35 (0.15-0.81)	.01
Asymptomatic proximal DVT	2/129 (1.6)	3/124 (2.4)	0.64 (0.11-3.77)	.68
Symptomatic pulmonary embolism	4/129 (3.1)	10/124 (8.1)	0.38 (0.12-1.19)	.08
Other VTE[a]	2/129 (1.6)	3/124 (2.4)	0.64 (0.11-3.77)	.68

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HEP-COVID TRIAL

Table 3. Clinical Outcome Components During the 30-Day Postrandomization Phase in the Modified Intention-to-Treat Population

Outcome	No./total No. (%)		RR (95% CI)	*P* value[a]
	Therapeutic dose (n = 129)	Standard dose (n = 124)		
ATE				
Myocardial infarction	0	3/124 (2.4)	0.14 (0.01-2.63)	.12
Stroke	1/129 (0.8)	1/124 (0.8)	0.96 (0.06-15.20)	>.99
Major adverse limb event	2/129 (1.6)	0	4.81 (0.23-99.13)	.50
Other ATE[b]	1/129 (0.8)	0	2.88 (0.12-70.13)	>.99

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HEP-COVID TRIAL

Table 3. Clinical Outcome Components During the 30-Day Postrandomization Phase in the Modified Intention-to-Treat Population

Outcome	No./total No. (%)		RR (95% CI)	*P* value[a]
	Therapeutic dose (n = 129)	Standard dose (n = 124)		
Death, No./total No. (%)				
Cardiovascular	10/129 (7.8)	15/124 (12.1)	0.64 (0.30-1.37)	.25
Infectious/sepsis	12/129 (9.3)	8/124 (6.5)	1.44 (0.61-3.41)	.40
Other	3/129 (2.3)	8/124 (6.5)	0.36 (0.10-1.33)	.11

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HEP-COVID TRIAL

Table 3. Clinical Outcome Components During the 30-Day Postrandomization Phase in the Modified Intention-to-Treat Population

Outcome	No./total No. (%)		RR (95% CI)	*P* value[a]
	Therapeutic dose (n = 129)	Standard dose (n = 124)		
Bleeding, No./total No. (%)				
Decrease in hemoglobin ≥2 g/dL within 24 h	4/129 (3.1)	1/124 (0.8)	3.85 (0.44-33.93)	.37
Transfusion of ≥2 U of packed red blood cells	0	1/124 (0.8)	0.32 (0.01-7.79)	.49
Critical site bleeding	2/129 (1.6)	0	4.81 (0.23-99.13)	.50
Fatal bleeding	0	0	NA	NA

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HEP-COVID TRIAL

Number Needed to Treat (NNT)

Primary Outcome

VTE+ATE+Death	NNT=8
VTE+ATE	NNT=6
VTE	NNT=6
Death (if stats validated)	NNT=18

Note: Number Needed to Harm (NNH) 2,000

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HEP-COVID TRIAL STRENGTHS

- Multicenter study
- Randomized patients consecutively
- Diverse patient population
- Outcomes were patient-oriented
- Performed intention to treat and per-protocol analysis
- Actively screened VTE in all patients which can eliminate some bias that may have occurred by unblinding
- No patients were lost to follow up

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HEP-COVID TRIAL LIMITATIONS I

Study design changed twice (D-Dimer elevation from 6x to 4x ULN; hypoxemia criterion changed from RR>20 breaths/min and SpO_2<92% on RA to any perceived need for supplemental oxygen as per investigator judgment)

Primary outcome was a composite of VTE, ATE, and death (not all outcomes are equal)

Study not powered for mortality benefit

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HEP-COVID TRIAL LIMITATIONS II

Increased nonanticoagulant COVID therapies in the treatment group may have contributed to the results

Intermediate anticoagulant dosing in control group may introduce a level of bias

Intermediate anticoagulant dosing in control group may dilute results

Variable heparin prophylactic dosing may have slightly muddied the results (although this may represent the “real world”)

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HEP-COVID TRIAL LIMITATIONS III

Discretionary post hospitalization anticoagulation may have affected results

The 72 hr study entry window may have affected results and increased overall VTE/ATE

No hard criteria for supplemental oxygen use

Generalizability may be limited because of small size

Nonmajor bleeding not reported

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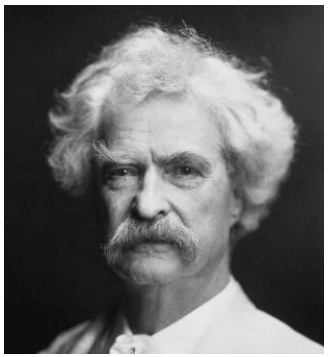
STATISTICAL CLARIFICATION

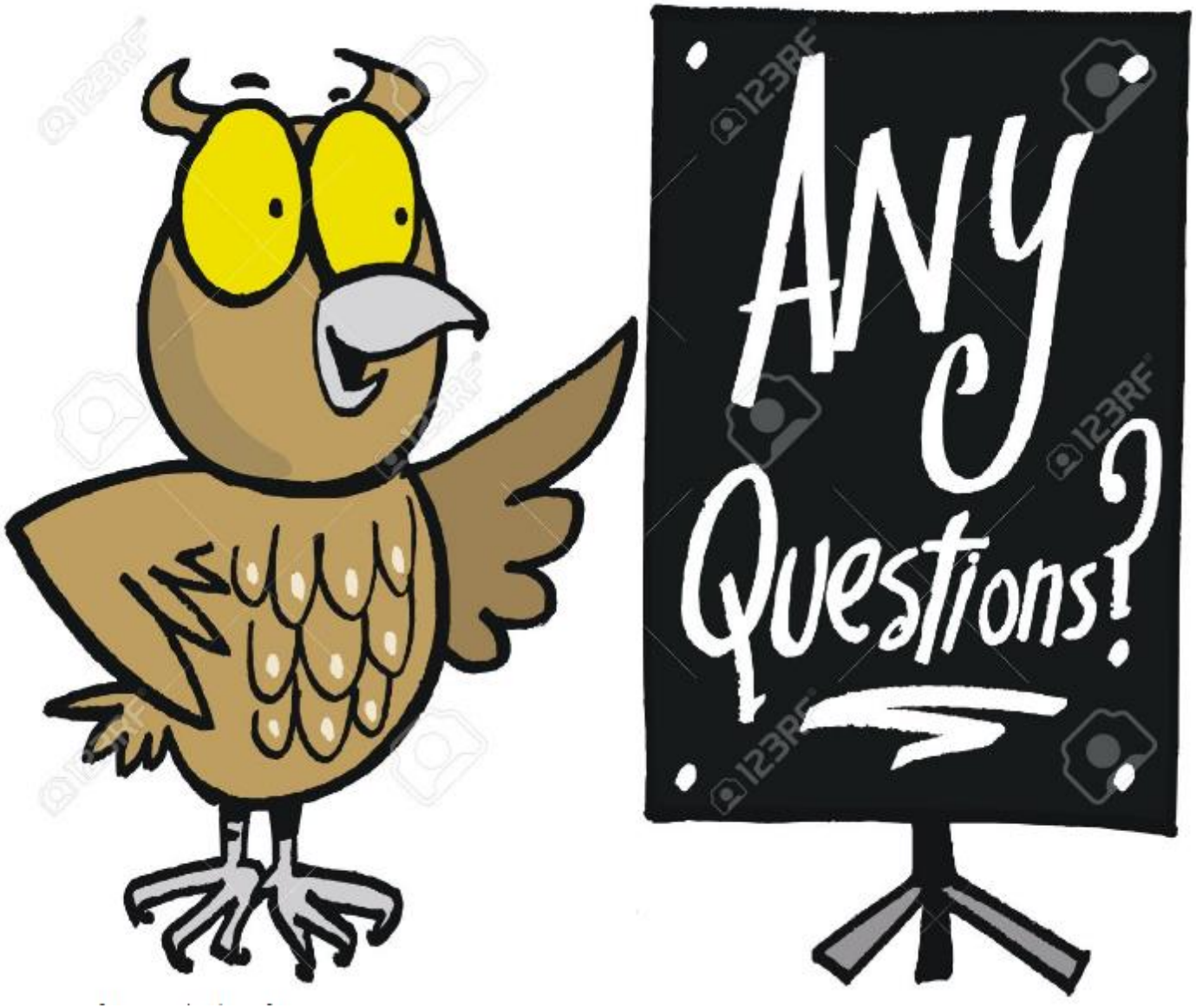
Twain-Disraeli analysis

There are three kinds of lies: lies, damn lies, and statistics.

Originated by Benjamin Disraeli and popularized by Mark Twain



THANK YOU FOR LISTENING


ANY
Questions?

SUPPLEMENTAL SLIDES/COMMENTS

IF ALL YOU HAVE IS A HAMMER, EVERYTHING LOOKS LIKE A NAIL

COVID COAGULOPATHY

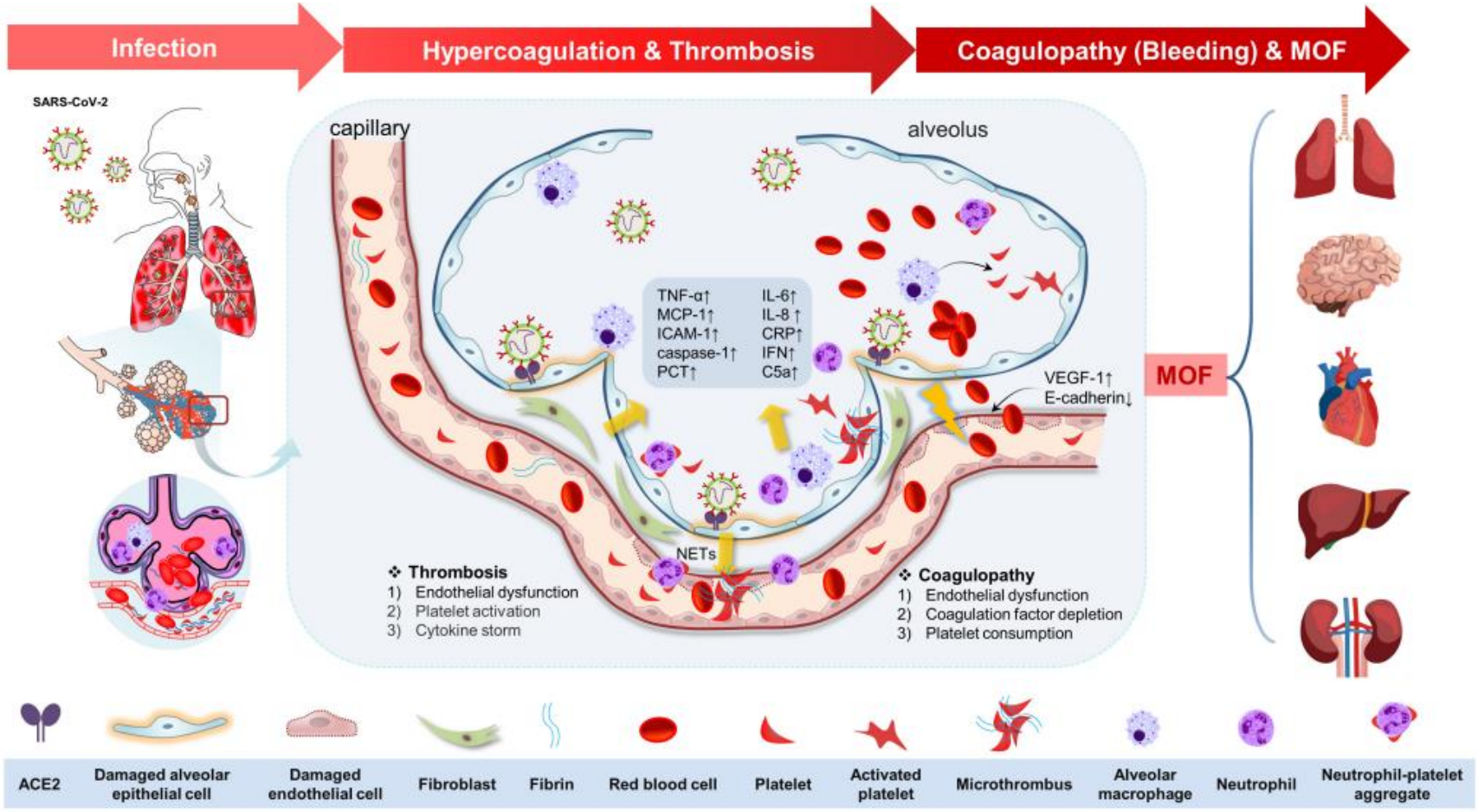
In COVID-19, this is not due to a single pathway that is overstimulated

It is primarily an endothelialopathy

There are several pathways involved that may prove to be variable

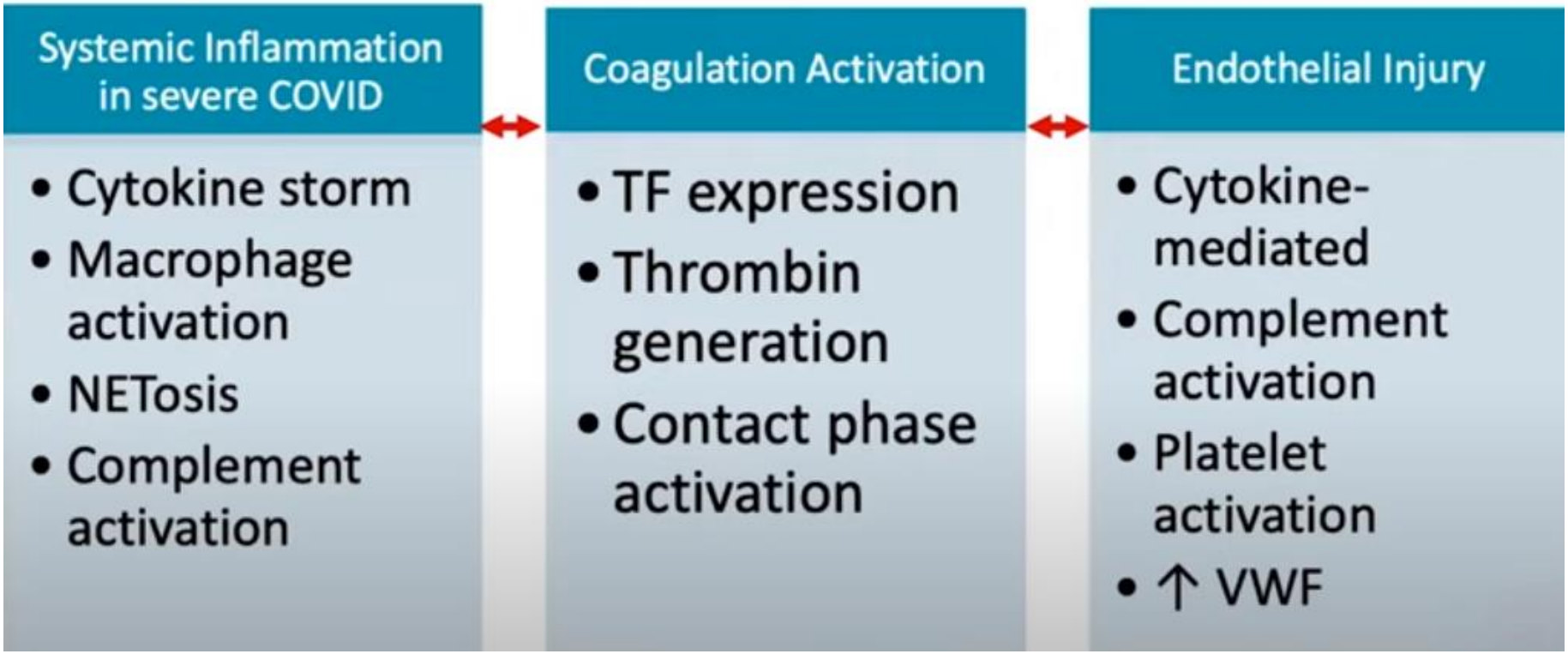
Immunothrombosis is a major factor

COVID COAGULOPATHY PATHOGENESIS



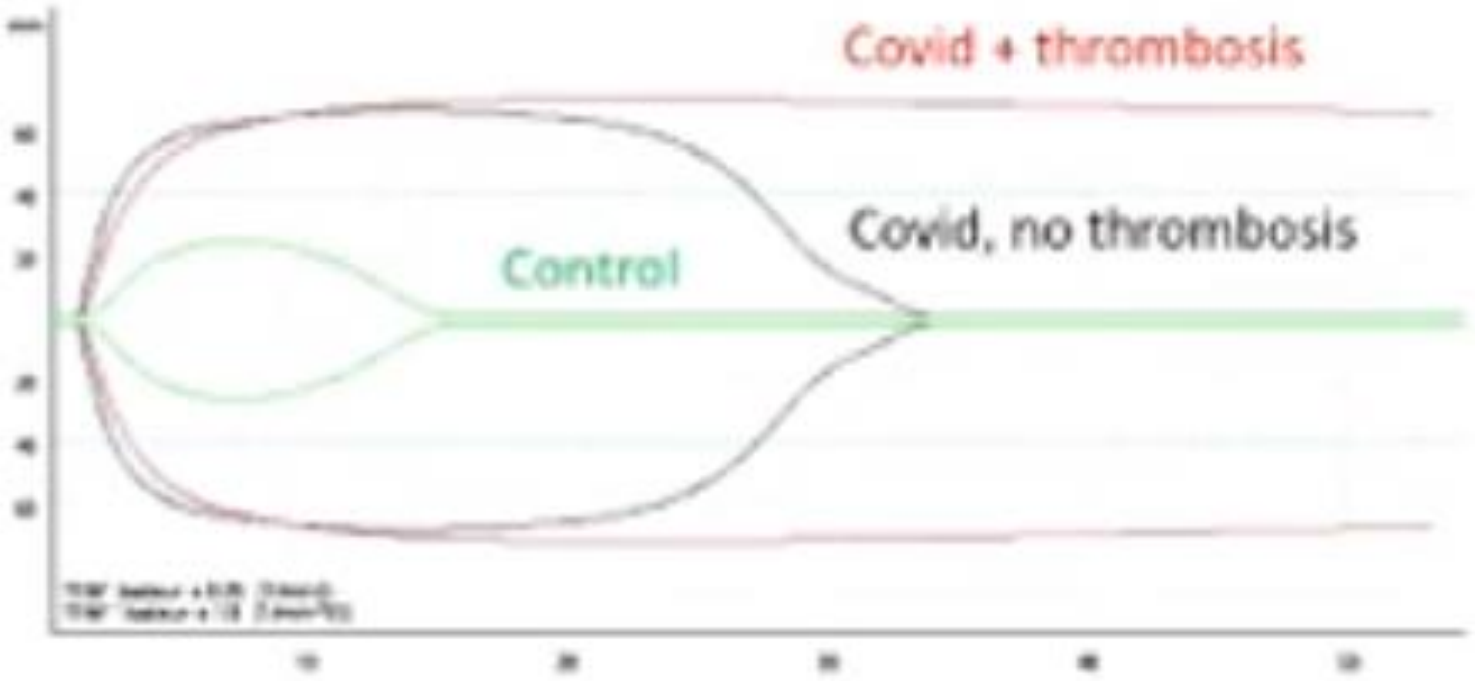
Front. Cardiovasc. Med. 7: 599334

COVID-19 and Immunothrombosis Multiple Mechanisms



slide courtesy Dr. Caroline Berube

DECREASED FIBRINOLYSIS IN COVID-19



slide courtesy Dr. Julie Helms

ISICEM Conference September 2, 2021

RIGHT DRUG

RIGHT DOSE

RIGHT TIME

RIGHT PATIENT

HEPARIN PROPERTIES

Antithrombotic

Antiinflammatory

Antiviral

Immunomodulatory

ANTICOAGULANT PATHOPHYSIOLOGY

UFH inhibits Xa, inhibits IIa, inhibits PAI

LMWH inhibits Xa, min IIa inhibition, less PAI inhibition

Fondaparinux inhibits Xa

Apixaban, Rivaroxaban, Edoxaban inhibit Xa

Dabigatran inhibits IIa

COVID COAGULOPATHY RX

CASE REPORTS, SMALL SERIES

TPA

Iloprost

Antiplatelet agents

Anticytokine agents

Combinations

IMPROVEDD VTE RISK SCORE

IMPROVEDD VTE Risk Score Calculator

Variable	Score	
Prior episode of VTE	3	☐
Thrombophilia	2	☐
Paralysis of the lower extremity during the hospitalization	2	☐
Current malignancy	2	☐
Immobilization for at least 7 days	1	☐
ICU or CCU admission	1	☐
Age more than 60 years	1	☐
D-dimer ≥2× upper limit of normal (or ≥1.0 µg/mL)	2	☐

Original study (Score/Risk):
0 0.4%; 1 0.6%; 2 0.8%; 3 1.2%; 4 1.6%; ≥5 2.2%
Validation study (Score/Risk):
0-1 Low 0.4%; 2-3 Moderate 1.3%; 4-12 High 5.3%

SEPSIS-INDUCED COAGULOPATHY SCORE

Sepsis Induced Coagulopathy (SIC) score

Test	0 points	1 point	2 points
INR	INR ≤1.2	INR 1.2-1.4	INR >1.4
Platelets	>150,000/uL	100,000-150,000/uL	<100,000/uL
SOFA score*	0	1	≥2

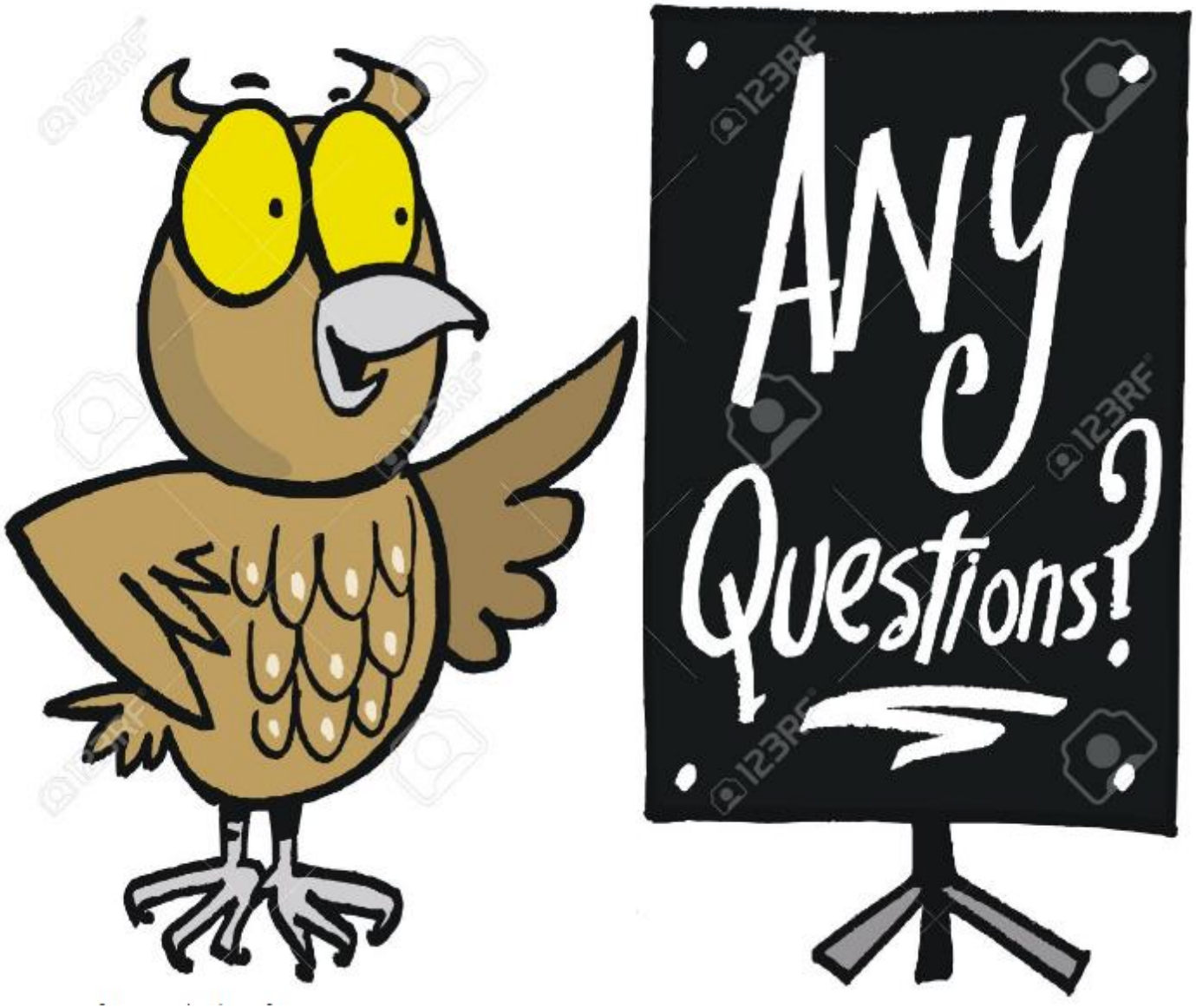
Interpretation of total score:

- ≥4 points: Positive for SIC
- <4 points: Negative for SIC

*SOFA score table reproduced below 👇 for rapid referencing.

Iba T et al. 2019 PMID 31410983

THANK YOU AGAIN FOR LISTENING


ANY
Questions?