
AND SO THE CLOT THICKENS! ANTICOAGULATION IN COVID-19

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NYSCHP CRITICAL CARE WEBINAR SERIES

AUGUST 24, 2021



DISCLOSURE STATEMENT

- Nothing to disclose

PHARMACIST OBJECTIVES

- Define thrombotic complications seen in patients infected with SARS-CoV-2
- Define various strategies used in patients with COVID-19
- Discuss supporting literature for anticoagulation dosing regimens in patients with COVID-19

PHARMACY TECHNICIAN OBJECTIVES

- Describe thrombotic complications seen in patients infected with SARS-CoV-2
- List medications used for anticoagulation in patients with COVID-19
- Describe the difference between prophylactic, intermediate, and full dose anticoagulation

CASE

- 71 year-old woman with PMH of hypothyroidism and osteoporosis presenting with hypoxemic respiratory failure requiring intubation in the setting of COVID-19 pneumonia
- ICU day 1:
 - CXR: no interval changes – low lung volumes, stable diffuse interstitial and airspace opacities in the bilateral lungs
 - Upper and lower extremities Doppler: negative for DVT bilaterally
 - TTE: LVEF 65-70%, RV size and function normal, trace pericardial effusion

Lab value	2 days prior to ICU	ICU admission
Procalcitonin, ng/mL	0.09	0.10
CRP, mg/L	99.12	60.38
Ferritin, ng/mL	535.2	486.8
ESR, mm/hr	57	41
D-dimer, mcg/mL	1.37	>20

AUDIENCE QUESTION

- Based on the available information which anticoagulation dosing strategy would you select for this patient:
 - a) Prophylactic dose anticoagulation
 - b) Intermediate dose anticoagulation
 - c) Therapeutic dose anticoagulation

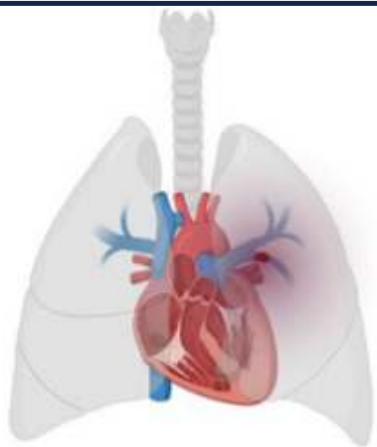
THROMBOSIS IN COVID-19

- Occurrence of thrombotic events in COVID-19 is associated with increasing disease severity and worsening clinical outcomes
- Thrombotic events occur in up to one-third of patients infected with COVID-19
- Higher rates are seen in patients admitted to the intensive care units (ICU)
- Thromboses have been identified both in the acute setting and in the weeks following critical illness suggesting that the pro-thrombotic could last several weeks

AUDIENCE QUESTION

- Which of the following thrombotic complications seen in COVID-19 patients has the **lowest** rate of incidence?
 - a) Deep vein thrombosis
 - b) Pulmonary embolism
 - c) Myocardial injury
 - d) Stroke

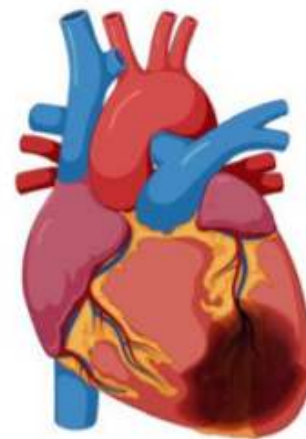
THROMBOTIC COMPLICATIONS



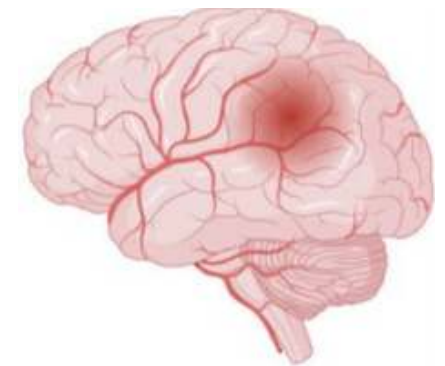
Pulmonary embolism
~13-20%



Deep vein
thrombosis
~14-20%



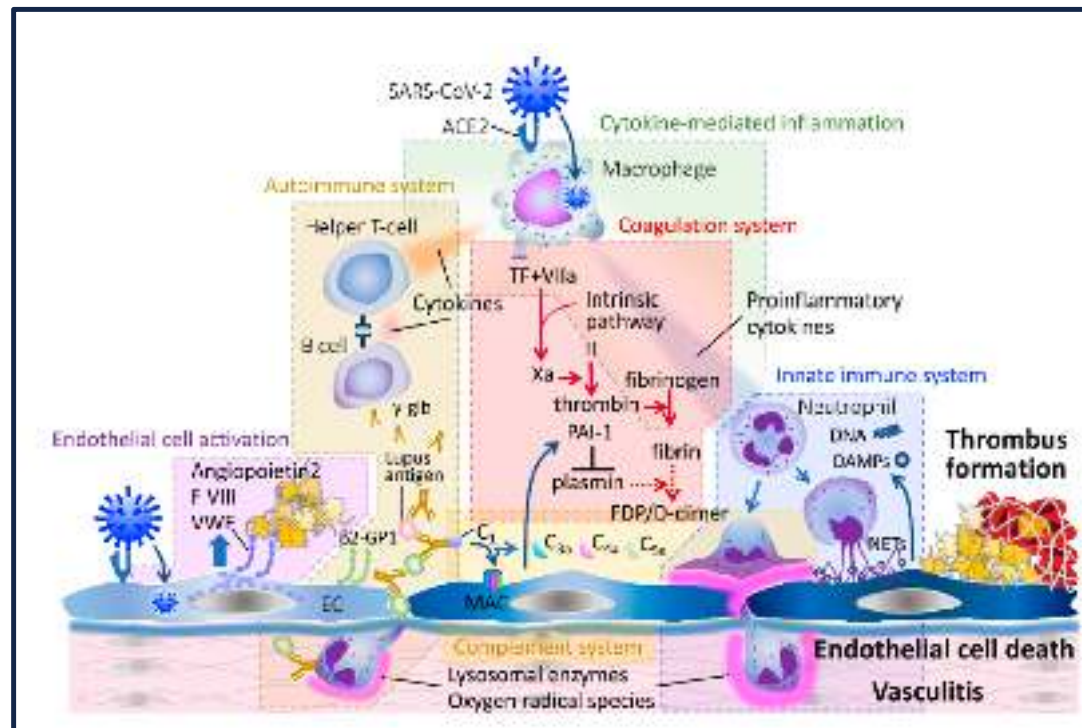
Myocardial injury
~20%



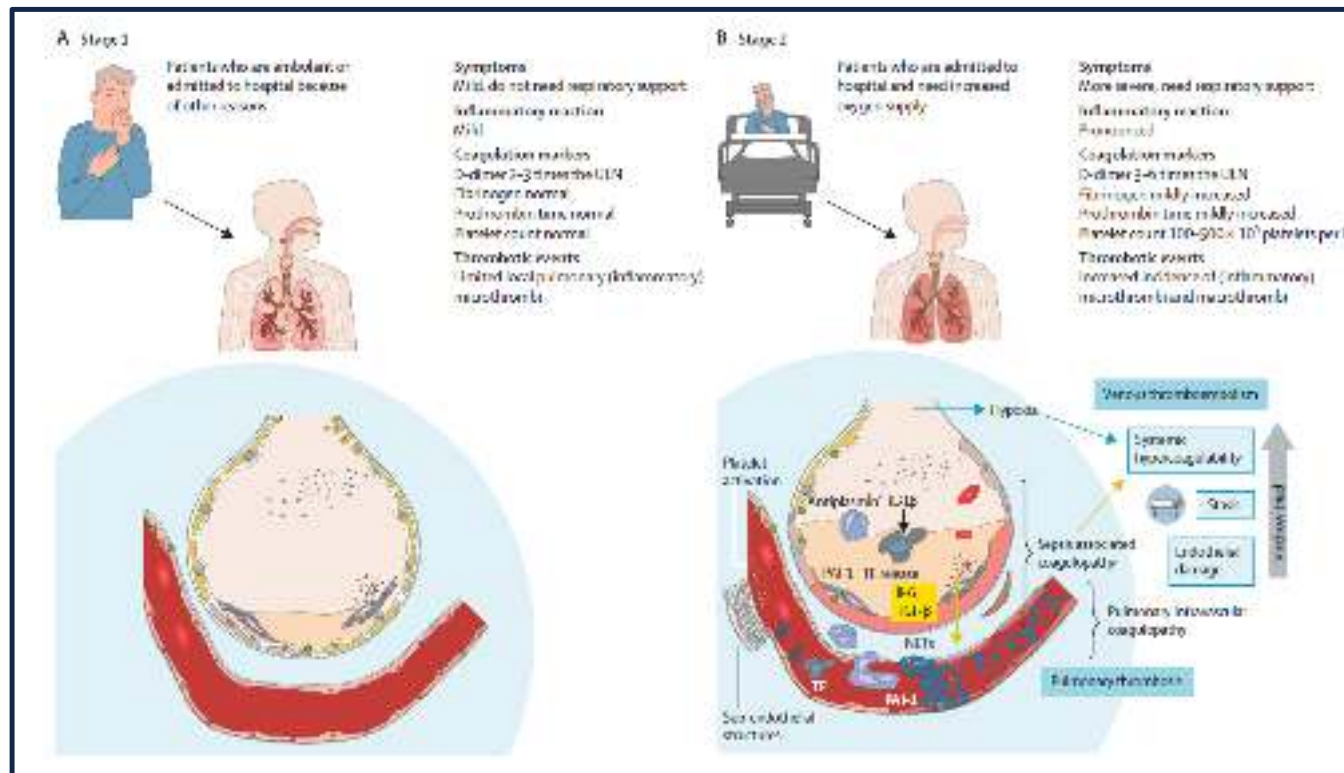
Stroke
<2%

Avila J, et al. *Am J Emerg Med.* 2021;39:213-281.
Sun YJ, et al. *Radiology*, 2021;298:E70-80.
Malas M, et al. *EClinicalMedicine.* 2020;29-30:100639.
Prasitlumkum N, et al. *Diseases.* 2020;8:40.
Qureshi AI, et al. *Stroke.* 2021;52:905-912.

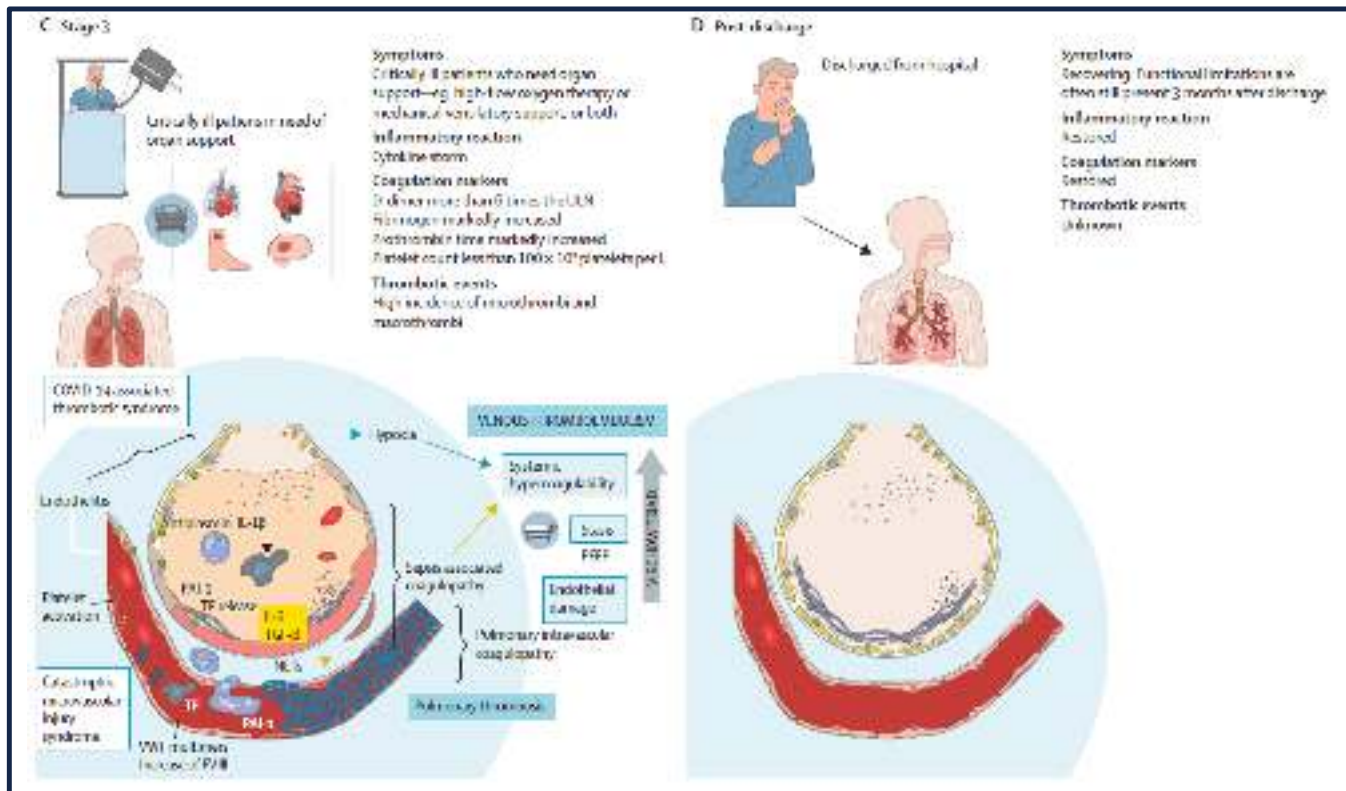
MECHANISM OF COVID-19 ASSOCIATED COAGULOPATHY



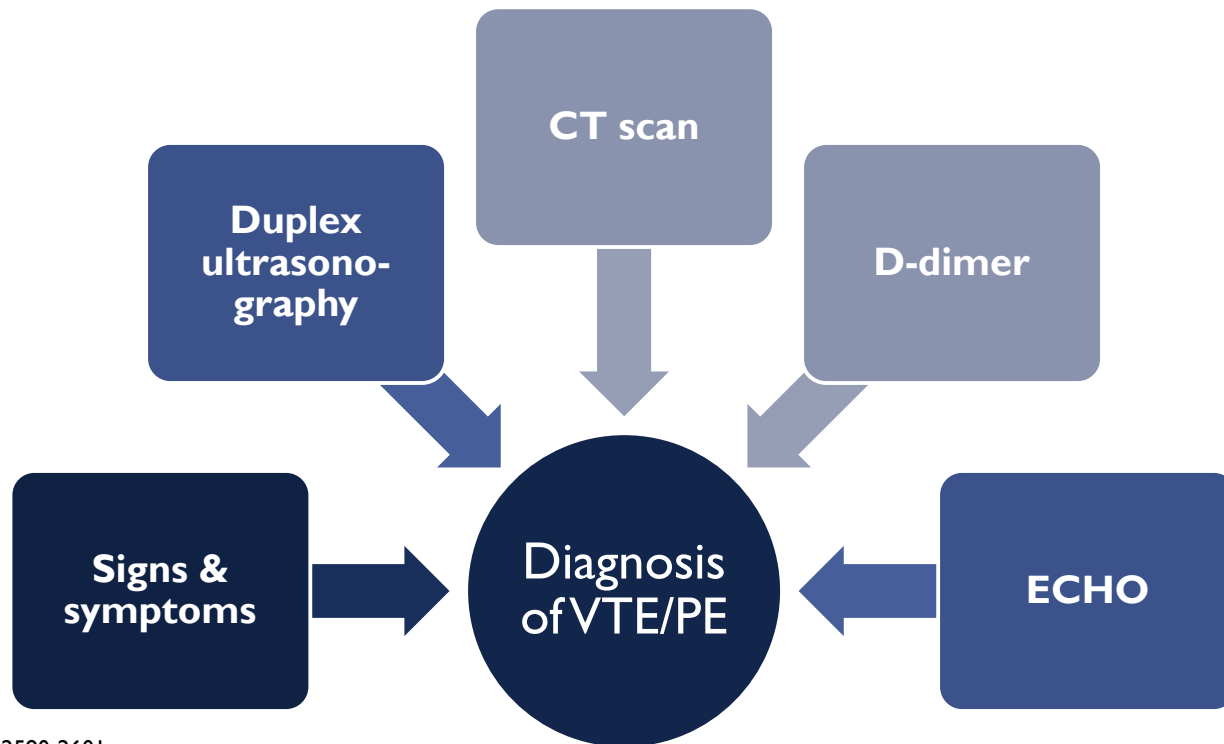
STAGES OF COVID-19 ASSOCIATED COAGULOPATHY



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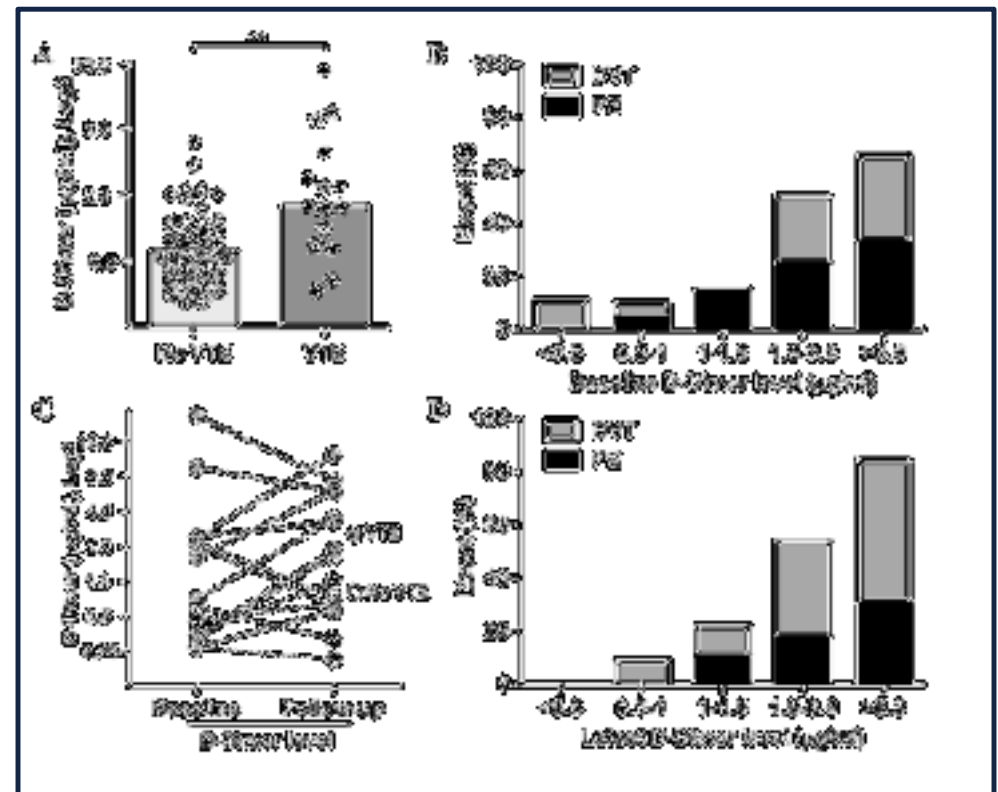


DIAGNOSIS OF THROMBOTIC COMPLICATIONS



THE ROLE OF D-DIMER

- Retrospective, cohort study of 71 patients with confirmed COVID-19 hospitalized for more than 48 hours
- Inclusion criteria included adequate thromboprophylaxis and available low limb venous duplex ultrasonography
- The incidence of venous thromboembolism was 23% and of PE was 10%
- Negative predictive value of baseline D-dimer was 90% for VTE and 98% PE
- Positive predictive value was VTE ranged from 44 to 67%



THE ROLE OF D-DIMER

- Multicenter, retrospective study of 400 hospital-admitted COVID-19 patients receiving standard-dose prophylactic anticoagulation
- Radiographically confirmed VTE rate was 5% and the overall thrombotic complication rate 10%
- The overall and major bleeding rates were 5% and 2%, respectively

Marker	No thrombotic or bleeding complications (n=347)	Thrombotic complications (n=38)	P-value (no complication vs thrombotic complication)	Bleeding complication (n=19)	P-value (no complication vs bleeding complication)
D-dimer, ng/mL					
- Initial	891 (568-1503)	1538 (953-3288)	0.0002	1189 (788-2577)	0.082
- Minimum	760 (494-1189)	1336 (833-1681)	0.0006	928 (605-1620)	0.17
- Peak	1377 (818-3052)	4001 (2896-8821)	<0.0001	3625 (2135-4783)	0.0004

Al-Samkari H, et al. *Blood*. 2020;136:489-500.

DIAGNOSTIC PARAMETERS ABNORMALITIES

- Retrospective analysis of 183 patients aimed to describe the coagulation features of patients with confirmed COVID-19
- On admission non-survivors has significantly higher D-dimer and fibrin degradation product levels, as well as longer prothrombin time and activated partial thromboplastin time (aPTT) compared to non-survivors
- Criteria for diagnosis of disseminated intravascular coagulation (DIC) was met by 71.1% of non-survivors and 0.6% of survivors

DISTINGUISHING LABORATORY FEATURES

Variable	SIC	DIC	Microangiopathy	CAC
Prothrombin time	↑	↑↑	↔	↑↑
aPTT	↑↑	↑↑ ↔ ↑	↔	↑
Fibrinogen	↓	↓	↔	↑↑
D-dimer	↑	↑ ↔	↔	↑↑ or ↑ +
Platelet count	↓	↓↓	↓	↑ or ↔
Von Willebrand factor	↑	↑↑	↔	↑↑
ADAMTS13	↔	↔	↓	↔
Antithrombin	↓	↓↓	↓	↑
Protein C	↓	↓	↔	+
Protein S	↓	↓	NA	↓
Factor VIII	↑	↑	NA	↑
Plasminogen	↓	↓	NA	↑

SIC, sepsis-induced coagulopathy; DIC, disseminated intravascular coagulation; CAC, COVID-19 associated coagulopathy

CAC THERAPEUTIC OPTIONS



Prophylactic Dose

Intermediate Dose

Full Anticoagulation

AUDIENCE QUESTION

- Which of the following is considered intermediate dose anticoagulation prophylaxis (patient weight = 70 kg)?
 - a) Enoxaparin 40 mg subcutaneously once daily
 - b) Heparin 5000 units subcutaneously every 8 hours
 - c) Enoxaparin 0.5 mg/kg subcutaneously every 12 hours
 - d) Enoxaparin 1 mg/kg subcutaneously every 12 hours

IS THE HEPARIN VIAL HALF EMPTY?



Prophylactic Dose

- UFH & LMWH at standard doses
- Adjusted for obesity
- Adjusted for renal dysfunction

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Intermediate Dose

- Enoxaparin
 - 1 mg/kg daily
 - 0.5 mg/kg q12h
 - 40 mg q12h
- UFH subcutaneous
 - 7500 units q8h

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Prophylactic Dose

- UFH & LMWH at standard doses
- Adjusted for obesity
- Adjusted for renal dysfunction



Intermediate Dose

- Enoxaparin
 - 1 mg/kg daily
 - 0.5 mg/kg q12h
 - 40 mg q12h
- UFH subcutaneous
 - 7500 units q8h



Full Anticoagulation

- Weight-based heparin infusion
- Enoxaparin 1 mg/kg q12h (adjusted for renal dysfunction)
- DOACs

IT'S BEEN A LONG YEAR

Clinical outcomes with the use of prophylactic versus therapeutic anticoagulation in Coronavirus Disease 2019

December 2020

Intermediate-dose anticoagulation, aspirin, and in-hospital mortality in COVID-19: A propensity score-matched analysis

January 2021

INSPIRATION Trial Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, ECMO, or mortality among patients with COVID-19 admitted to the ICU

March 2021

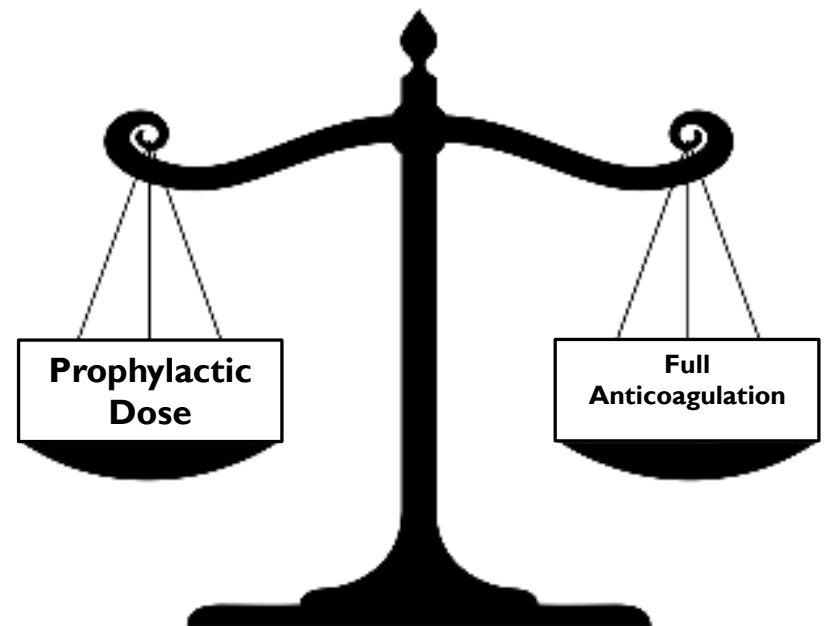
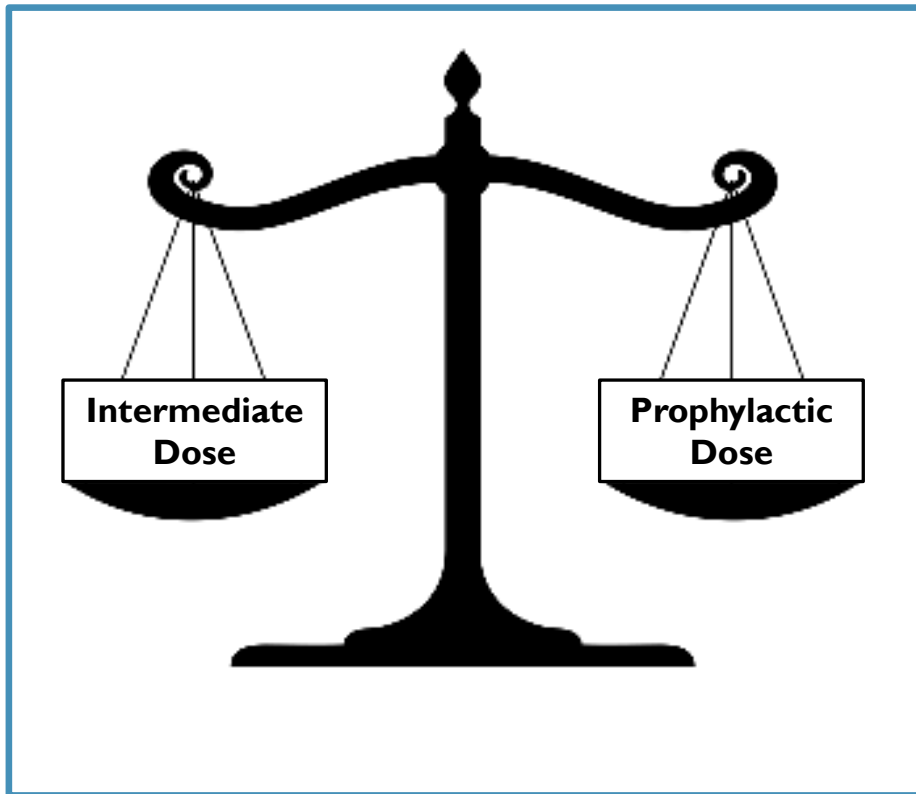
Thrombosis, bleeding, and the observational effect of early therapeutic anticoagulation on survival in critically ill patients with COVID-19

May 2021

REMAP-CAP, ACTIV-4a, and ATTACC Trials Therapeutic anticoagulation in critically ill and non-critically ill patients with COVID-19

August 2021

IS THE RIGHT DOSE STILL HANGING IN THE BALANCE?

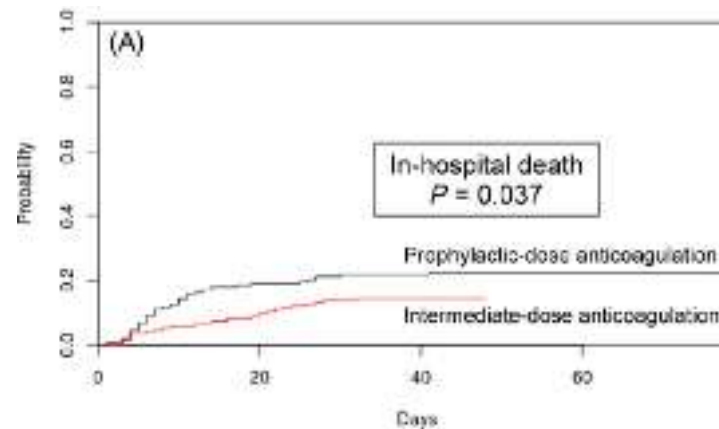


INTERMEDIATE DOSE ANTICOAGULATION

- Retrospective study hospitalized patients with COVID-19 that aimed to evaluate the effect of prophylactic dose and intermediate dose anticoagulation on in-hospital mortality
 - Anticoagulation strategy was chosen based on d-dimer level that was measured 1-2 times per day
- Dosing of anticoagulation:
 - Prophylactic dose
 - Enoxaparin 40 mg daily if BMI < 40 kg/m² or 40 mg every 12 hours if BMI ≥ 40 kg/m²
 - Subcutaneous heparin 5000 units every 8-12 hours or 7500 units every 8-12 hours if BMI ≥ 40 kg/m²
 - Intermediate dose
 - Enoxaparin 0.5 mg/kg every 12 hours
 - Subcutaneous heparin 7500 units every 8-12 hours

RESULTS

- Final propensity score-matched analysis included 382 patients
- Results showed that intermediate dose anticoagulation was associated with a significantly lower cumulative incidence of in-hospital death (HR 0.518 [0.308-0.872]; $p=0.013$)
- Other therapies with potential for disease-modifying effects were used but not included in the analysis



LET'S GET INSPIRED!

- Multicenter randomized clinical trial of 562 adult patients admitted to the ICU with COVID-19
- Primary efficacy outcome was a composite of adjudicated acute VTE, arterial thrombosis, treatment with ECMO, or all-cause mortality within 30 days of enrollment
- Dosing of anticoagulation:
 - Prophylactic dose
 - Enoxaparin 40 mg subcutaneously daily
 - Intermediate dose
 - Enoxaparin 1 mg/kg subcutaneously daily

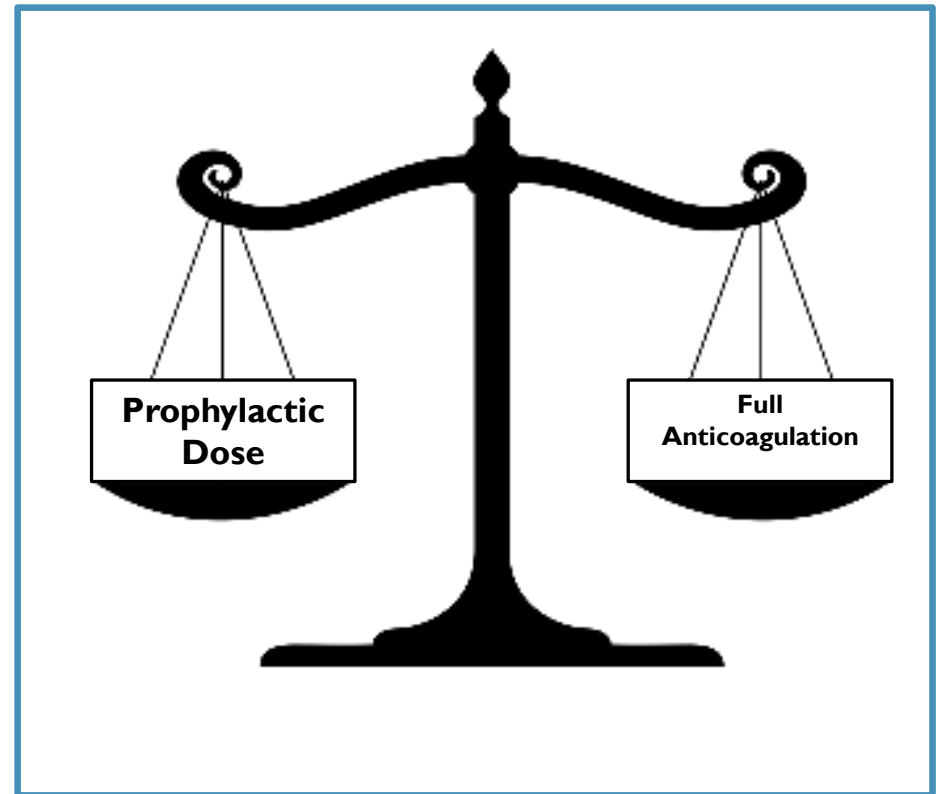
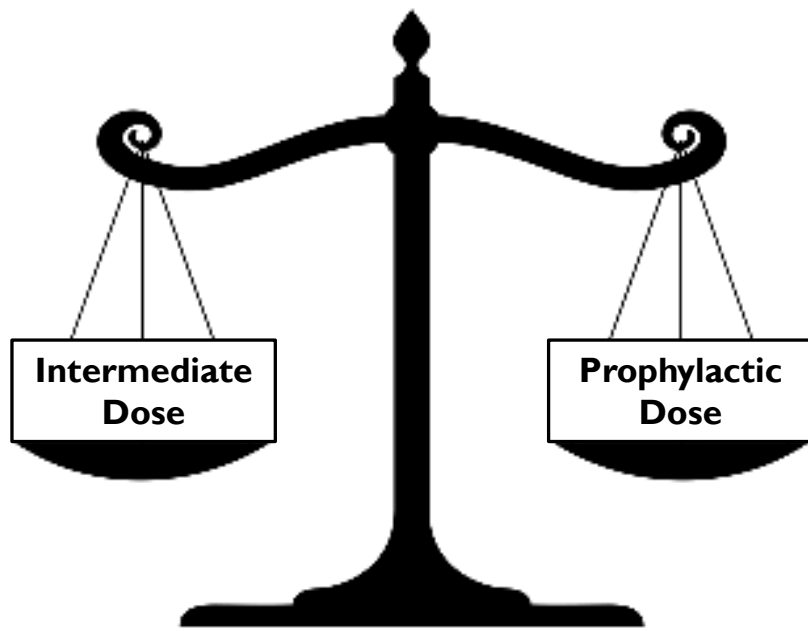
BASELINE CHARACTERISTICS

Characteristic	Intermediate dose n=276	Standard dose n=286
Age, year	62 (51-71)	61 (47-71)
Gender, men; No. (%)	162 (59)	163 (57)
Body mass index	27 (24-29)	27 (24-29)
Current smoker	35 (13)	21 (7)
Co-treatments, No. (%)		
- Remdesivir	168 (61)	170 (59)
- Corticosteroids	262 (95)	262 (92)
- Tocilizumab	34 (12)	40 (14)
D-dimer, ng/mL	1037 (460-3121)	910 (410-2380)
Prothrombin time	13.6 (12.6-15)	13.7 (12.6-15)
International normalized ratio	1.0 (1.1-1.2)	1.0 (1.1-1.2)
aPTT	32 (28-38)	31 (27-36)

RESULTS

Outcome, No. (%)	Intermediate n=276	Standard n=286	Absolute difference (95% CI), %	Odds ratio (95% CI)	P-value
Primary outcome					
Composite	126 (46)	126 (44)	1.5 (-6.6 - 9.8)	1.06 (0.76 -1.48)	0.70
Secondary outcomes					
All-cause mortality	119 (43)	117 (41)	2.2 (-5.9 -10.3)	1.09 (0.78 -1.53)	0.50
Adjudicated VTE	9 (3.3)	10 (3.5)	-0.2 (-3.2 - 2.7)	0.93 (0.97 -2.32)	0.87
Ventilator-free days, median (IQR)	30 (3 to 30)	30 (1 to 30)	0 (0 - 0)	NA	0.50

IS THE RIGHT DOSE STILL HANGING IN THE BALANCE?



PROPHYLAXIS VS FULL DOSE ANTICOAGULATION

- Retrospective cohort study of 374 patients (prophylactic n=299 vs therapeutic n=75)
- The objective of the study was to determine the impact of anticoagulation on in-hospital mortality among patients with diagnosis of COVID-19
- The primary outcome of the study was mortality and secondary outcome was mortality in patients with peak CRP \geq 200 mg/L

RESULTS

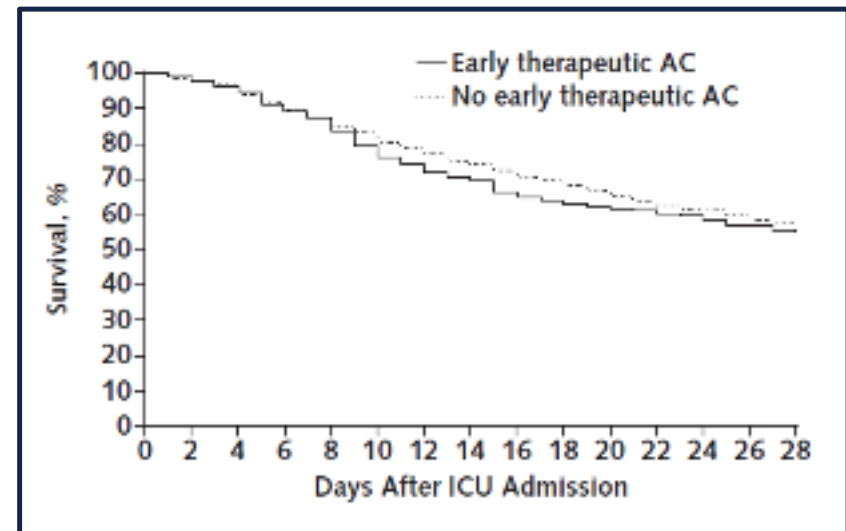
- The results showed a statistically significant increase in the risk of mortality in the therapeutic anticoagulation group compared with the prophylactic group
 - Absolute risk reduction=2.3; 95% CI=1.0-4.9; p=0.04
- Subgroup analysis of patients with greater severity of inflammation (CRP \geq 200 mg/L) did not show a significant mortality difference between the groups
- Significant bleeding requiring transfusion occurred in 0.3% of patients in the prophylaxis group and 2.7% of patients in the therapeutic group

THROMBOSIS, BLEEDING, AND EARLY ANTICOAGULATION

- Multicenter, cohort study of 3239 critically ill adult patients with COVID-19 that aimed to evaluate the incidence of VTE and major bleeding, as well as observe the effect of early therapeutic anticoagulation on survival
- Early therapeutic anticoagulation was defined as receiving therapeutic anticoagulation within 2 days of ICU admission
- A target trial emulation was performed to evaluate the effect of the early therapeutic anticoagulation

RESULTS

- A total of 2809 (87%) were included in the target trial with only 384 (12%) of patients receiving early therapeutic anticoagulation
- 47% of patients treated with early therapeutic anticoagulation died compared with 37% of patients not treated with early anticoagulation (HR 1.12 [CI 0.92-1.35])



BLEEDING RATES

- Major bleeding occurred in 3% of patients of whom 62% died within 28 days
- Most common sites of bleeding were gastrointestinal and intracranial
- 67% of patients with a major bleeding event were receiving therapeutic anticoagulation at the time of the event

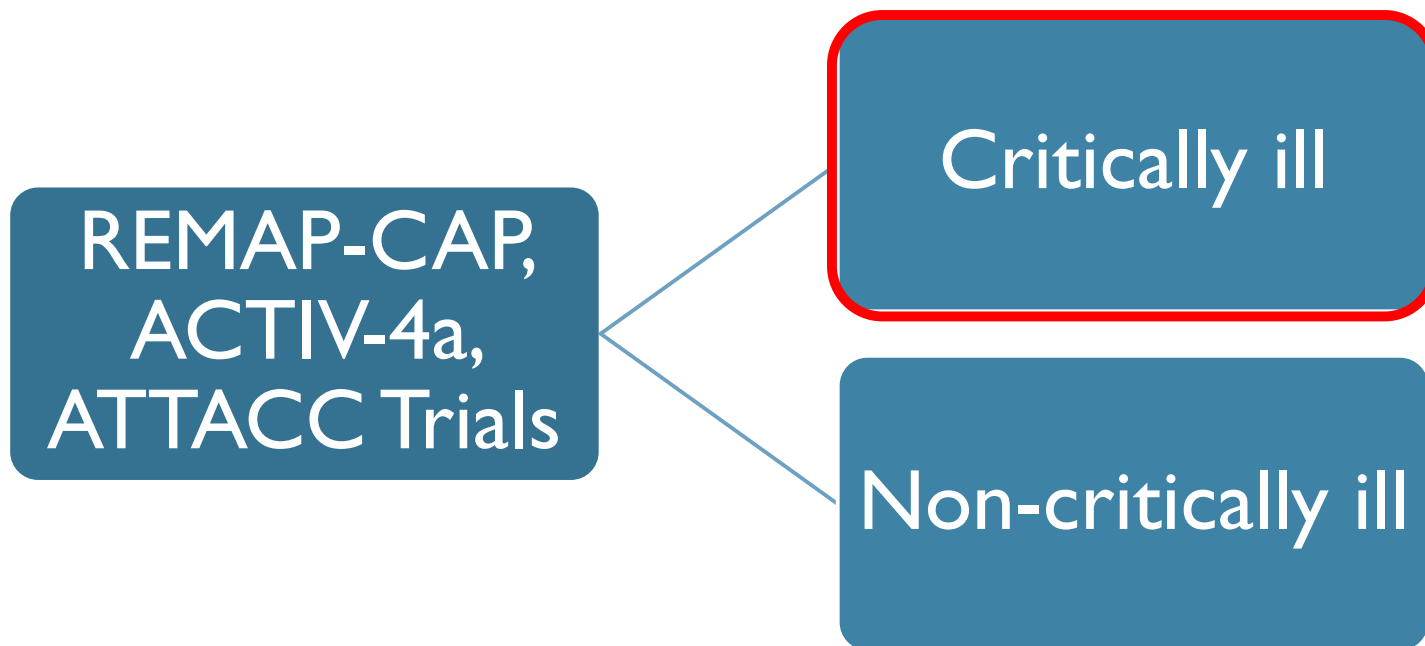
NEW KIDS ON THE BLOCK!

- REMAP-CAP, ACTIV-4a, and ATTACC trials are open-label, adaptive, multiplatform, randomized clinical trials that investigated whether a pragmatic strategy of therapeutic dose anticoagulation improves survival and reduces the duration of organ support compared with usual care pharmacological thromboprophylaxis in critically ill patients with COVID-19
- Evaluated the effect of therapeutic anticoagulation in four patient groups:
 - Severe COVID-19
 - Moderate COVID-19 – high D-dimer (baseline ≥ 2 local ULN)
 - Moderate COVID-19 – low D-dimer (baseline < 2 local ULN)
 - Moderate COVID-19 – unknown/missing D-dimer

OUTCOMES

- Primary outcome: **Organ support-free days** (OSFDs to day 21)
 - Ordinal scale combination of in-hospital mortality and organ support-free days
 - A higher value for OSFDs indicates a better outcome
- Secondary outcomes included survival to until discharge and major thrombotic events or death
- Safety outcomes included major bleeding (ISHT criteria) and confirmed heparin induced thrombocytopenia (HIT)

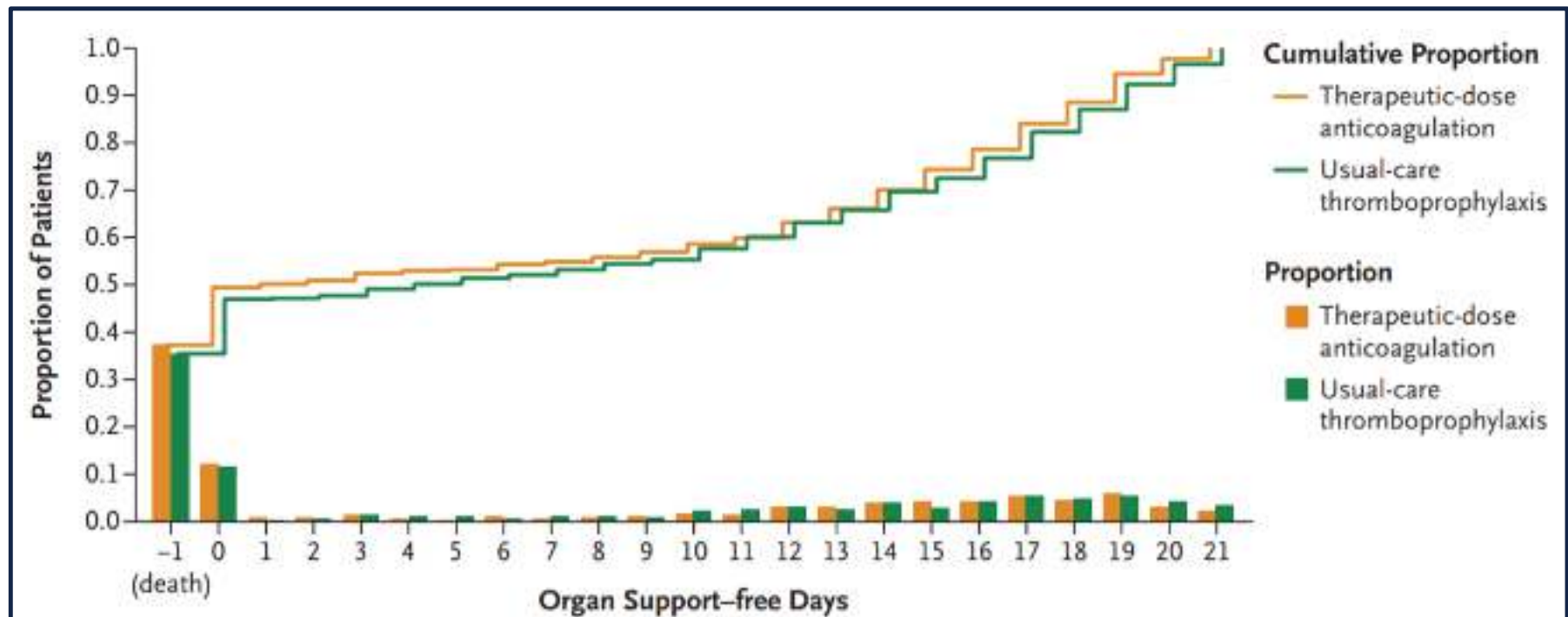
NEW KIDS ON THE BLOCK!



CRITICALLY ILL

Characteristic	Therapeutic Anticoagulation n = 536	Prophylactic Dose n = 567
Age, year; \pm SD	60 \pm 13	62 \pm 13
Male sex; No. (%)	387 (72)	385 (68)
Body mass index, IQR	30 (27-36)	30 (26-35)
Co-treatments, No. (%)		
- Remdesivir	174/532 (33)	172/564 (31)
- Corticosteroids	426/522 (82)	458/555 (83)
- Tocilizumab	11/532 (2)	9/564 (2)
Respiratory support, No. (%)		
- Low-flow nasal cannula or face mask or none	8 (2)	7 (1)
- High-flow nasal cannula	170 (32)	188 (33)
- Noninvasive mechanical ventilation	215 (40)	200 (35)
- Invasive mechanical ventilation	142 (27)	172 (30)
D-dimer level \geq 2x ULN, No. (%)	100/210 (48)	107/223 (48)

CRITICALLY ILL PATIENTS



SECONDARY OUTCOMES

Outcome	Therapeutic Dose*	Prophylaxis Dose*	Adjusted difference in risk (95% CI), %	Adjusted odds ratio (95% CI)
Survival until hospital discharge	335/534 (62)	364/564 (65)	-4.1 (-10.7 – 2.4)	0.83 (0.67 – 1.03)
Major thrombotic events or death	213/531 (40)	230/560 (41)	1.0 (-5.6 – 7.4)	1.04 (0.79 – 1.35)
Any thrombotic events or death	217/531 (41)	232/560 (41)	1.5 (-4.9 – 8.0)	1.06 (0.81 – 1.38)
Major bleeding	20/529 (4)	13/562 (2)	1.1 (-0.6 – 4.4)	1.48 (0.75 – 3.04)

* no. of patients/total patients, (%)

^ probability of futility of therapeutic anticoagulation

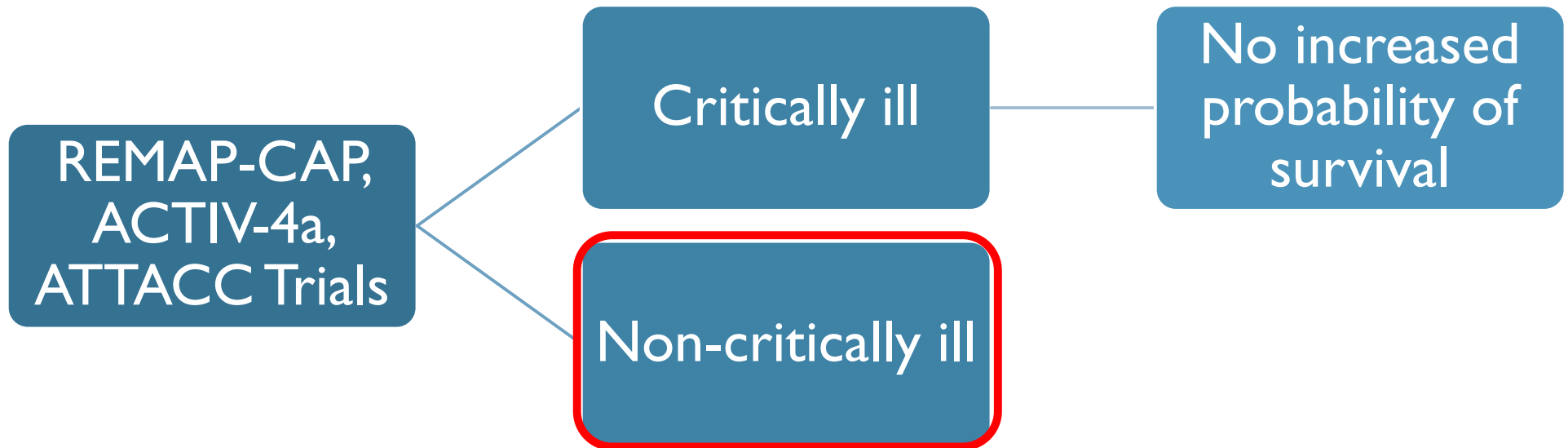
ANTICOAGULANTS AND DOSING

Anticoagulant drug, n (%)	Therapeutic anticoagulation n = 519	Prophylactic anticoagulation n = 551
Enoxaparin	252 (47)	287 (52)
Dalteparin	175 (34)	181 (33)
Subcutaneous UFH	7 (1)	25 (5)
Intravenous UFH	50 (10)	6 (1)
Fondaparinux	0 (0)	1 (0.2)
None	6 (1)	24 (4)
Other	1 (0.2)	4 (0.7)

ANTICOAGULANTS AND DOSING

Post randomization dosage equivalents	Therapeutic anticoagulation n = 469	Prophylactic anticoagulation n = 493
Low dose thromboprophylaxis	16 (3)	199 (40)
Intermediate dose thromboprophylaxis	50 (8)	255 (52)
Subtherapeutic dose anticoagulation	39 (8)	9 (2)
Therapeutic dose anticoagulation	364 (78)	30 (6)

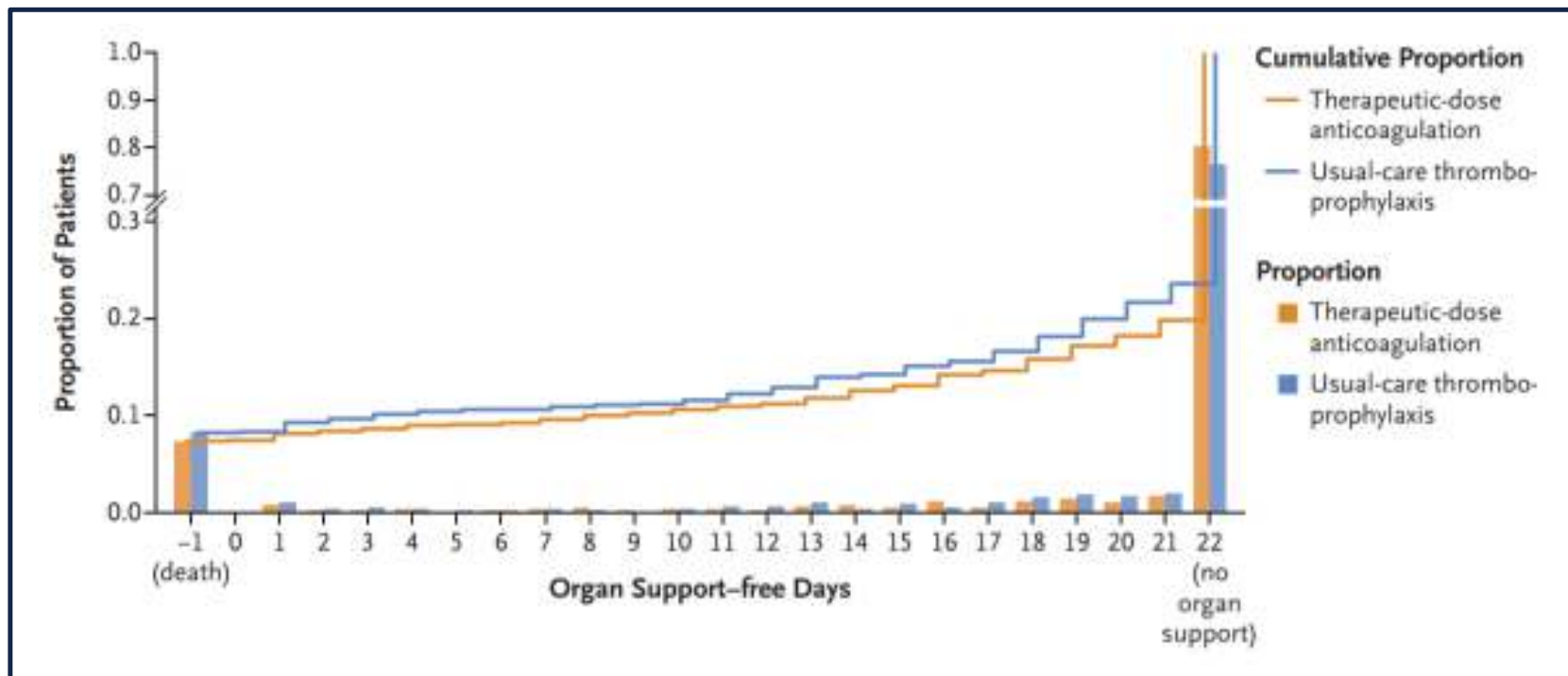
NEW KIDS ON THE BLOCK!



NON-CRITICALLY ILL PATIENTS

Characteristic	Therapeutic anticoagulation n = 1181	Prophylactic anticoagulation n = 1050
Age, year; \pm SD	59 \pm 14	59 \pm 14
Male sex; No. (%)	713 (60)	597 (57)
Body mass index, IQR	30 (26-35)	30 (27-35)
Co-treatments, No. (%)		
- Remdesivir	428/1178 (36)	383/1048 (37)
- Corticosteroids	479/791 (61)	415/656 (63)
- Tocilizumab	6/1178 (0.5)	7/1048 (0.7)
Respiratory support, No. (%)		
- None	156 (13)	123 (12)
- Low-flow nasal cannula or face mask	789 (69)	696 (66)
- High-flow nasal cannula	25 (2)	28 (3)
- Noninvasive mechanical ventilation	21 (20)	24 (2)
- Unspecified	190 (16)	179 (17)

NON-CRITICALLY ILL PATIENTS



PRIMARY OUTCOME BASED ON D-DIMER STRATIFICATION

Variable	Therapeutic anticoagulation*	Prophylactic anticoagulation*	Adjusted Odds Ratio (95% CI)
Overall group	939/1171 (80)	801/1048 (76)	1.27 (1.03-1.58)
D-dimer cohort			
- High level	264/339 (78)	210/291 (72)	1.31 (1.00-1.76)
- Low level	463/570 (81)	403/505 (80)	1.22 (0.93-1.57)
- Unknown	212/262 (81)	188/252 (75)	1.32 (1.00-1.86)

* no. of patients/total patients, (%)

^ probability of futility of therapeutic anticoagulation

SECONDARY OUTCOMES

Outcome	Therapeutic Dose*	Prophylactic Dose*	Absolute difference in risk (95% CI), %	Adjusted odds ratio (95% CI)	Probability of effect
Survival until hospital discharge	1085/1171 (93)	962/1048 (92)	1.3 (-1.1 – 3.2)	1.2 (0.87 – 1.68)	87
Survival without organ support at 28 days	932/1175 (79)	789/1046 (75)	4.5 (0.9 – 7.7)	1.3 (1.09 – 1.61)	99
Progression to intubation or death	129/1181 (11)	127/1050 (12)	-1.9 (-4.1 – 0.7)	0.82 (0.63 – 1.07)	92
Major thrombotic event or death	94/1180 (8)	104/1046 (10)	-2.6 (-4.4 – -0.2)	0.72 (0.53 – 0.98)	98
Major bleeding	22/1180 (2)	9/1047 (1)	0.7 (-0.1 – 2.3)	1.8 (0.9 – 3.74)	96

* no. of patients/total patients, (%)

^ probability of effect of therapeutic anticoagulation

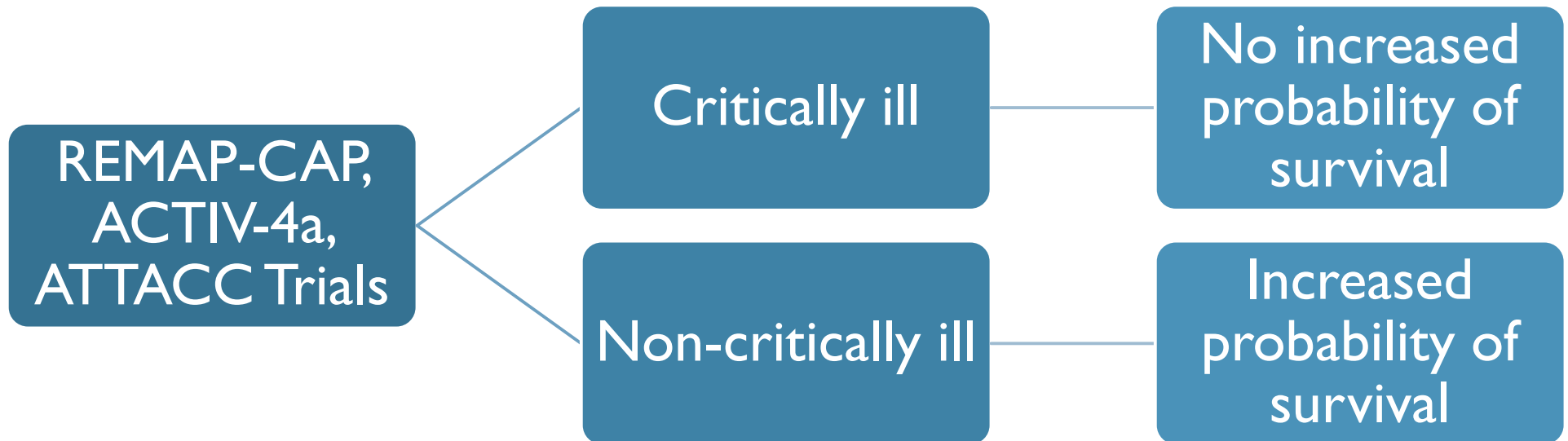
ANTICOAGULANTS AND DOSING

Anticoagulant drug, n (%)	Therapeutic anticoagulation n = 1181	Prophylactic anticoagulation n = 1050
Enoxaparin	921 (84)	629 (79)
Dalteparin	87 (8)	77 (10)
Tinzaparin	27 (3)	26 (3)
Subcutaneous UFH	11 (1)	49 (6)
Intravenous UFH	41 (4)	4 (0.5)
Direct oral anticoagulants	0 (0)	12 (2)
Other	6 (0.5)	2 (0.3)

ANTICOAGULANTS AND DOSING

Post randomization dosage equivalents	Therapeutic anticoagulation n = 1043	Prophylactic anticoagulation n = 855
Low dose thromboprophylaxis	61 (6)	613 (72)
Intermediate dose thromboprophylaxis	61 (6)	227 (27)
Subtherapeutic dose anticoagulation	91 (9)	7 (1)
Therapeutic dose anticoagulation	830 (80)	8 (1)

NEW KIDS ON THE BLOCK!



Lawler PR, et al. *N Engl J Med.* 2021. doi:10.1056/NEJMoa2105911.
Goligher EC, et al. *N Engl J Med.* 2022. doi:10.1056/NEJMoa2103417.

CONSIDERATIONS

- Open-label design
- Unclear reasons for protocol non-adherence
- Intermediate-dose prophylaxis used in standard thromboprophylaxis arm
- No screening logs kept

GUIDELINE RECOMMENDATIONS

Guideline	In-hospital	Intensive Care Unit
American Society of Hematology (ASH) March 2021	Prophylactic-intensity over intermediate intensity or therapeutic anticoagulation	Prophylactic-intensity over intermediate intensity or therapeutic anticoagulation
National Institutes of Health (NIH) February 2021	Routine dose prophylaxis	Routine dose prophylaxis
CHEST June 2020	Routine dose prophylaxis	Routine dose prophylaxis over intermediate-dose prophylaxis
International Society on Thrombosis and Haemostasis (ISTH) May 2020	Routine dose prophylaxis; intermediate dose may be considered	Routine dose prophylaxis; intermediate dose may be considered in high-risk patients
Anticoagulation Forum May 2020	Routine dose prophylaxis	Intermediate dose prophylaxis

CASE

- 71 year-old woman with PMH of hypothyroidism and osteoporosis presenting with hypoxemic respiratory failure requiring intubation in the setting of COVID-19 pneumonia
- ICU day 1:
 - CXR: no interval changes – low lung volumes, stable diffuse interstitial and airspace opacities in the bilateral lungs
 - Upper and lower extremities Doppler: negative for DVT bilaterally
 - TTE: LVEF 65-70%, RV size and function normal, trace pericardial effusion

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AUDIENCE QUESTION

- Based on the available information which anticoagulation dosing strategy would you select for this patient:
 - a) Prophylactic dose anticoagulation
 - b) Intermediate dose anticoagulation
 - c) Therapeutic dose anticoagulation

WHERE WILL THE PENDULUM SWING?

- All patients admitted to the hospital with COVID-19 should be initiated on prophylactic dose anticoagulation unless contraindicated
- Patients admitted with COVID-19 are at an increased risk of developing thrombosis and should be screened if clinically warranted
- Patients diagnosed or with high suspicion of VTE should be treated with therapeutic anticoagulation



AND SO THE CLOT THICKENS! ANTICOAGULATION IN COVID-19

KASIA GOSEK, PHARMD, BCCCP

NYSCHP CRITICAL CARE WEBINAR SERIES

AUGUST 24, 2021

