Exploring the Coagulopathic Nature of COVID-19

Midwest Medication Safety Symposium COVID Clinical Pearls

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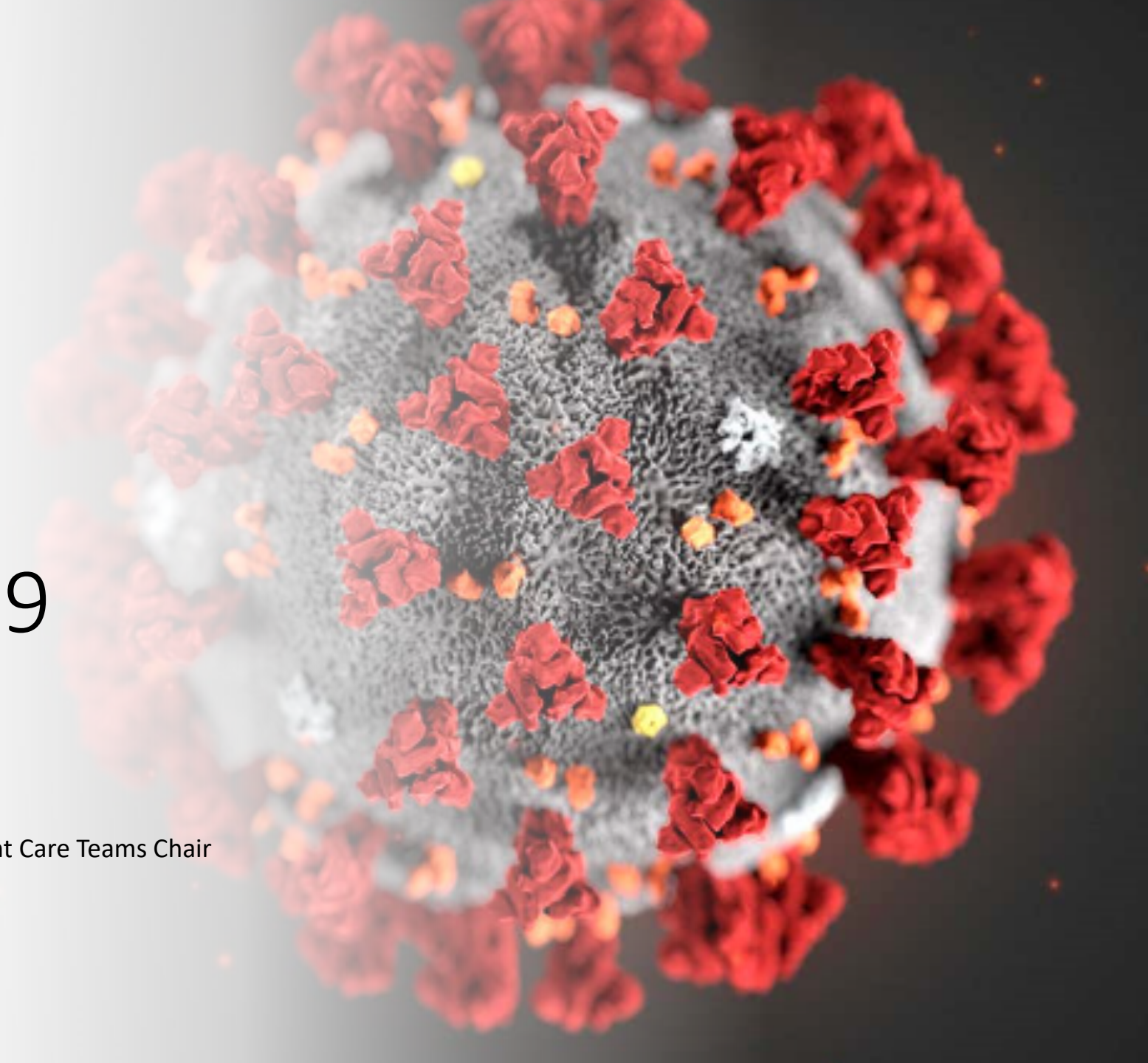
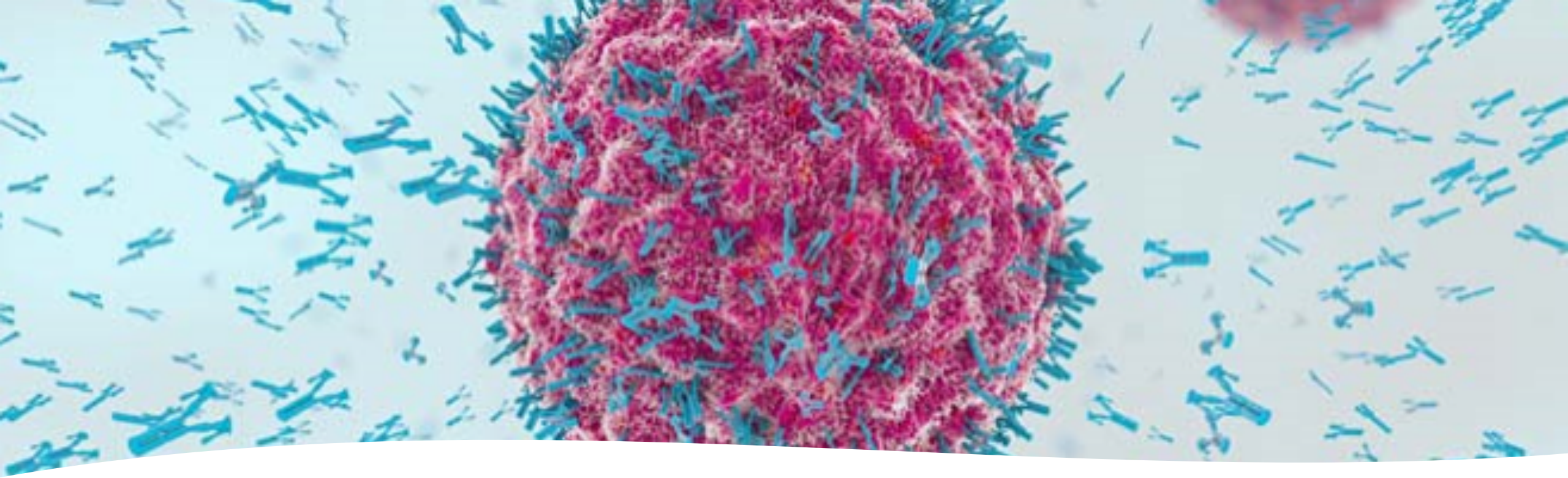




Learning Objective

Explain the coagulopathic nature of COVID-19, and identify key strategies to safely decrease the widespread propagation of microthrombi and tame the ensuing cytokine storm.

- Develop an algorithm for appropriate anticoagulation in all COVID-19 patients
- Understand when it is prudent to either escalate or deescalate anticoagulation
- Learn how to avoid bleeding complications in COVID-19 patients
- Develop a COVID-specific heparin drip dosing strategy (with lower drip rates and goal aPTTs than in non-COVID patients)

- TEG (thromboelastography)➔use in COVID is off-label
- General information: represent ongoing research

COAGULOPATHIES

ESC European Society of Cardiology

Cardiovascular Research (2020) **00**, 1–8
doi:10.1093/cvr/cvaa230

REVIEW

Endothelial dysfunction in COVID-19: a position paper of the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science

Paul C. Evans [1]*, G. Ed Rainger [2], Justin C. Mason [3], Tomasz J. Guzik [4], Elena Osto [5], Zania Stamataki [6], Desley Neil [2], Imo E. Hoefer [7], Maria Fragiadaki [1], Johannes Waltenberger [8], Christian Weber [9], Marie-Luce Bochaton-Piallat [10], and Magnus Bäck [11]*

Vascular Endotheliitis:
central feature of COVID-19

Key driver of
-cytokine dysregulation
-systemic coagulopathies

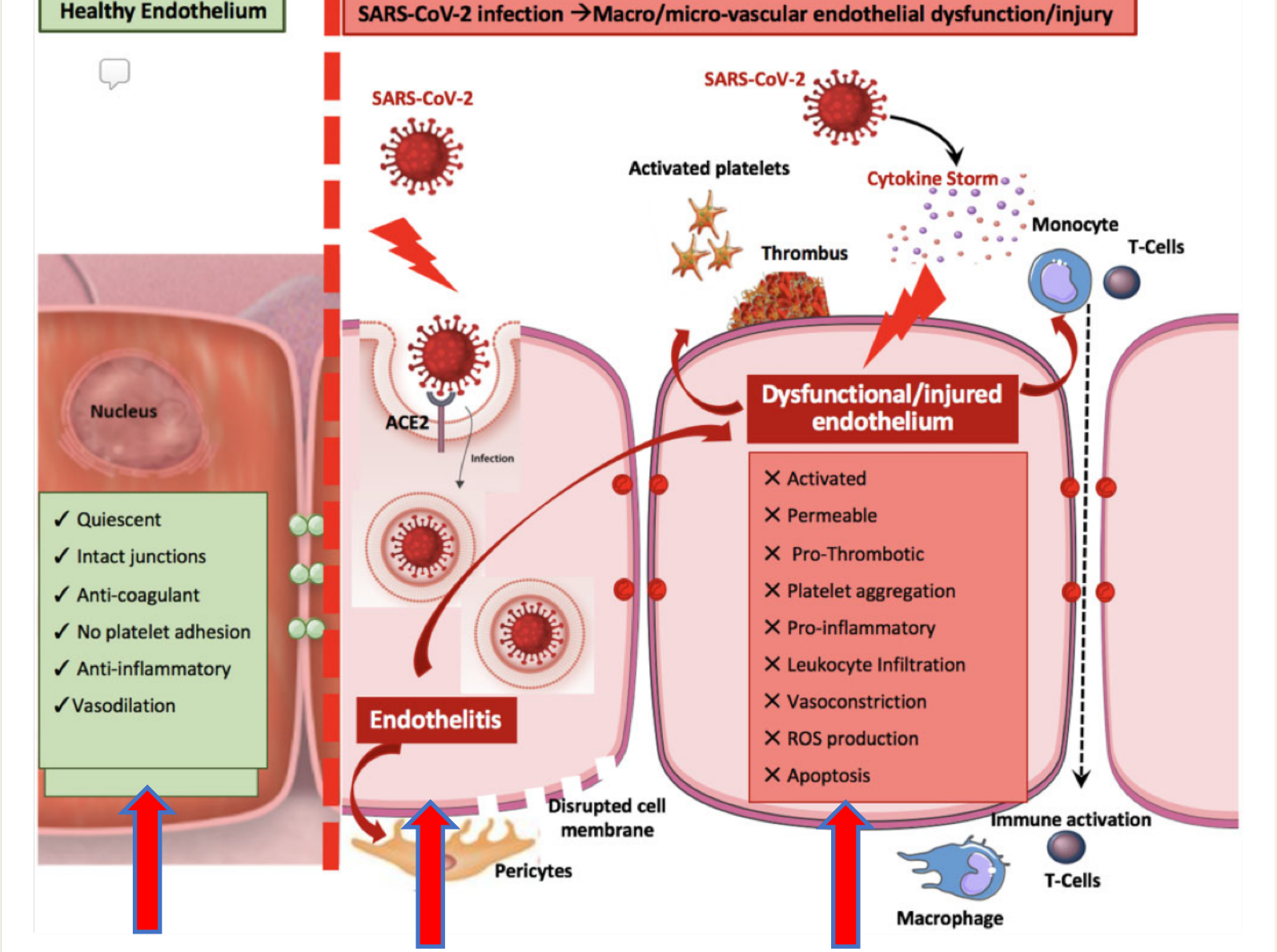
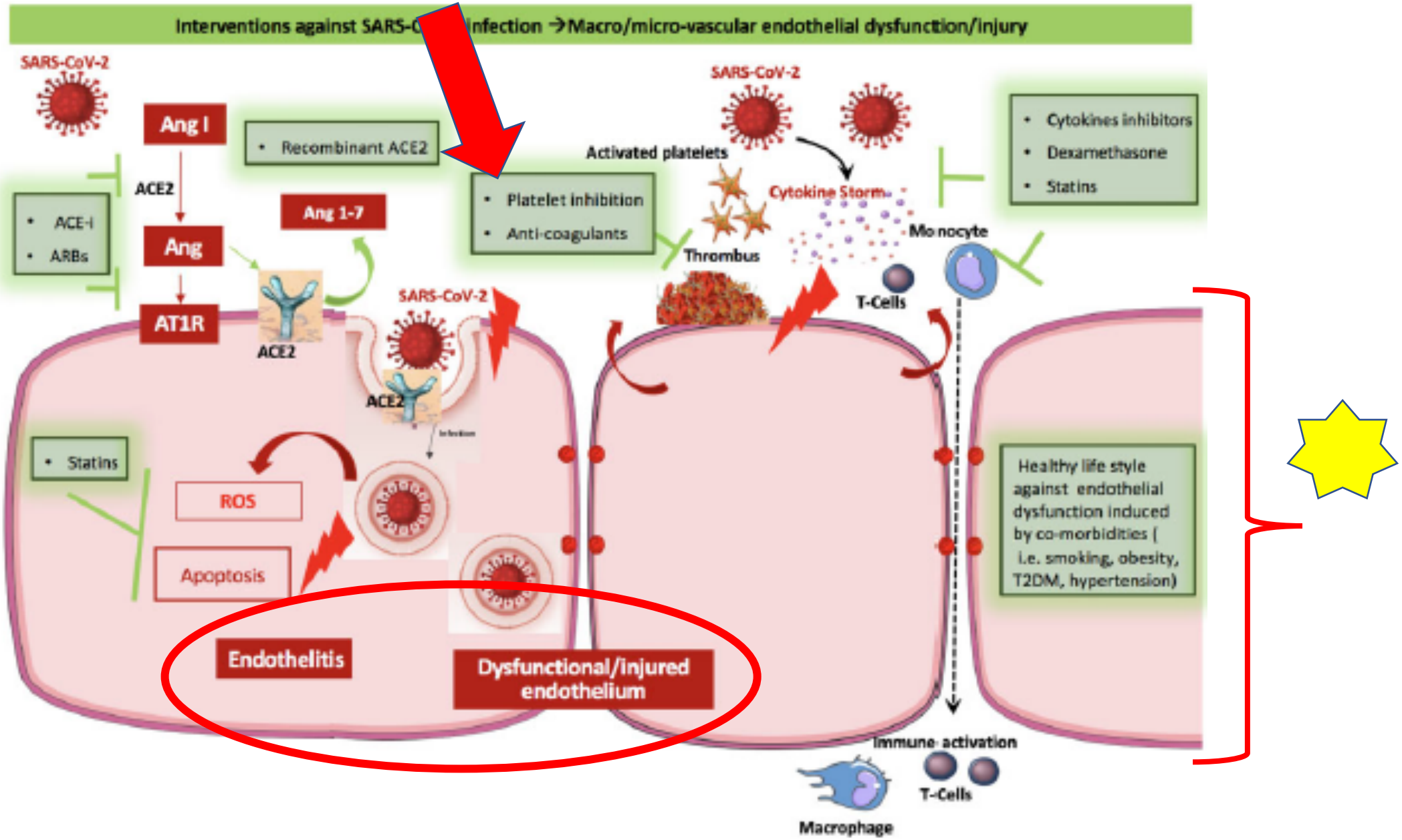
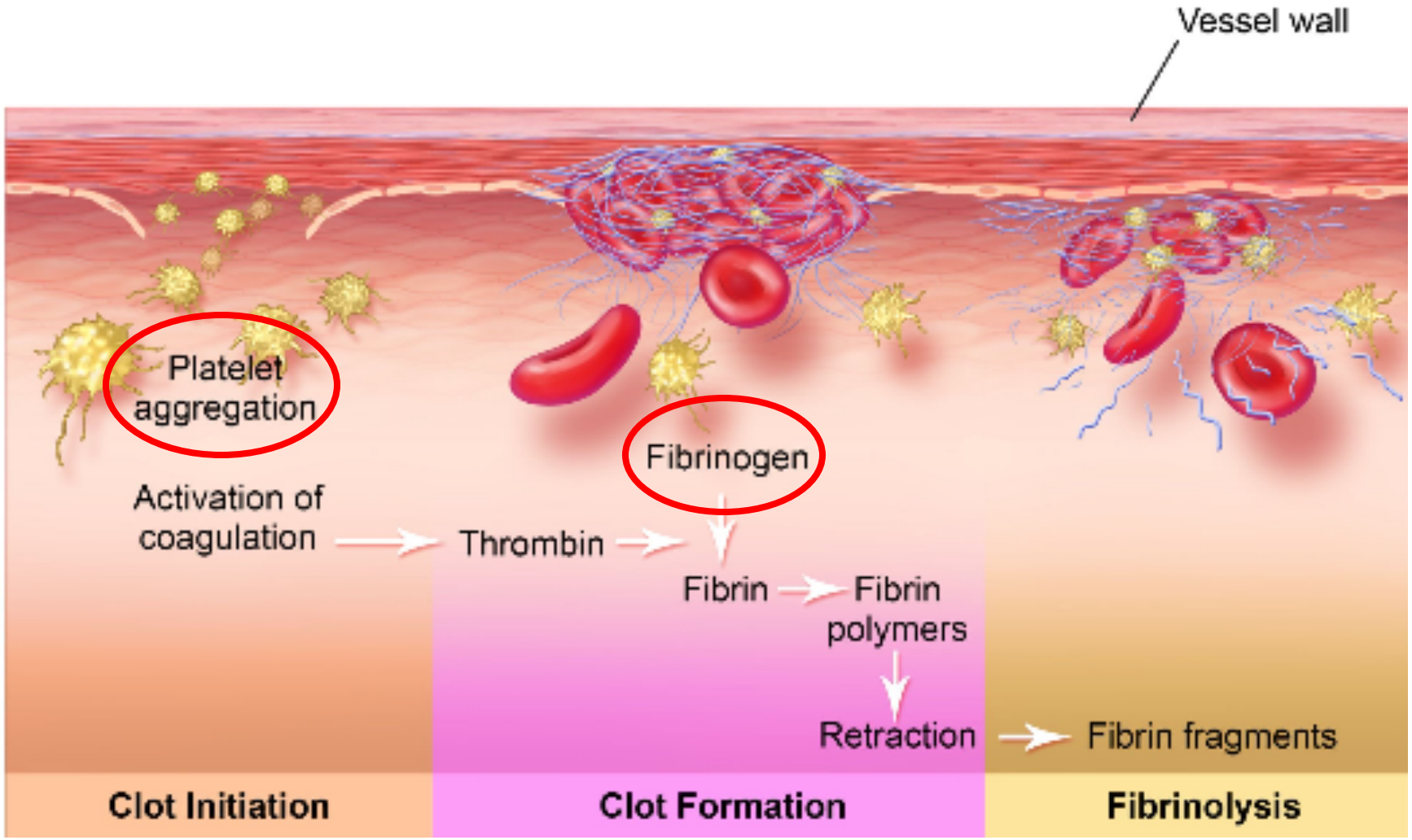


Figure 1 Endothelial dysregulation by SARS-CoV-2. Healthy endothelium (left) is characterized by quiescence, intact junctions, anticoagulant anti-inflammatory phenotype, and an intact vasodilation phenotype. The cell in the centre (endothelitis) is infected with SARS-CoV-2, whereas the cells to the right have been activated as a result of cytokine release and activation of prothrombotic pathways. Infection with SARS-CoV-2 is via ACE2 which is subsequently endocytosed, potentially reducing ACE2-mediated regulation of vascular tone. SARS-CoV-2 infection causes endothelial dysfunction at multiple levels including inflammatory activation, cytokine storm, leucocyte infiltration, increased permeability, thrombosis, platelet aggregation, vasoconstriction, production of reactive oxygen species (ROS), and apoptosis.


Interventions against SARS-C infection →Macro/micro-vascular endothelial dysfunction/injury
SARS-CoV-2
Ang I
ACE2
Ang
AT1R
Ang 1-7
ACE2
• ACE-i
• ARBs
• Recombinant ACE2
• Platelet inhibition
• Anti-coagulants
Activated platelets
Thrombus
SARS-CoV-2
Cytokine Storm
Mo nocyte
T-Cells
• Cytokines inhibitors
• Dexamethasone
• Statins
SARS-CoV-2
ACE2
• Statins
ROS
Apoptosis
Endothelitis
Dysfunctional/injured endothelium
Healthy life style against endothelial dysfunction induced by co-morbidities (i.e. smoking, obesity, T2DM, hypertension)
Immune activation
T-Cells
Macrophage

Fibrinogen and the clotting cascade



COVID-19 Labs

- Lab Markers Indicating "Severe COVID" Disease:
  - d-dimer >1,
  - creatine kinase (CK) >2X ULN (>600),
  - CRP >100,
  - LDH >245,
  - increased troponin,
  - ferritin >300,
  - absolute lymphocyte count (ALC) <0.8
- Other Important Labs:
  - *Fibrinogen-prothrombotic
  - *D-dimer-fibrin degradation product (coagulation activation marker)
  - IL-6
  - Hgb, plts

Cytokine Storm:

-Cytokine-normal immune response

-Large amount cytokines all at once

➔ harmful (kills tissues / damages organs)

-↑ Inflammatory Labs

COVID-19 VTE Algorithm

➢Rationale for early anticoagulation

- Pathophysiology of COVID-19 associated respiratory disease is consistent with pulmonary vascular thromboemboli
- Autopsy studies have demonstrated venous thromboembolism in deceased coronavirus patients
- Early anticoagulation is necessary to prevent propagation of microthrombi at disease presentation
- Thrombotic complications➔strong determinant of high mortality rate
  - Strategies to prevent thrombosis central to treatments / critical importance (decreased mortality??)

*Not just a disease of the lungs!!

COVID-19 VTE Algorithm

➢Rationale for use of heparins (LMWH/UFH)

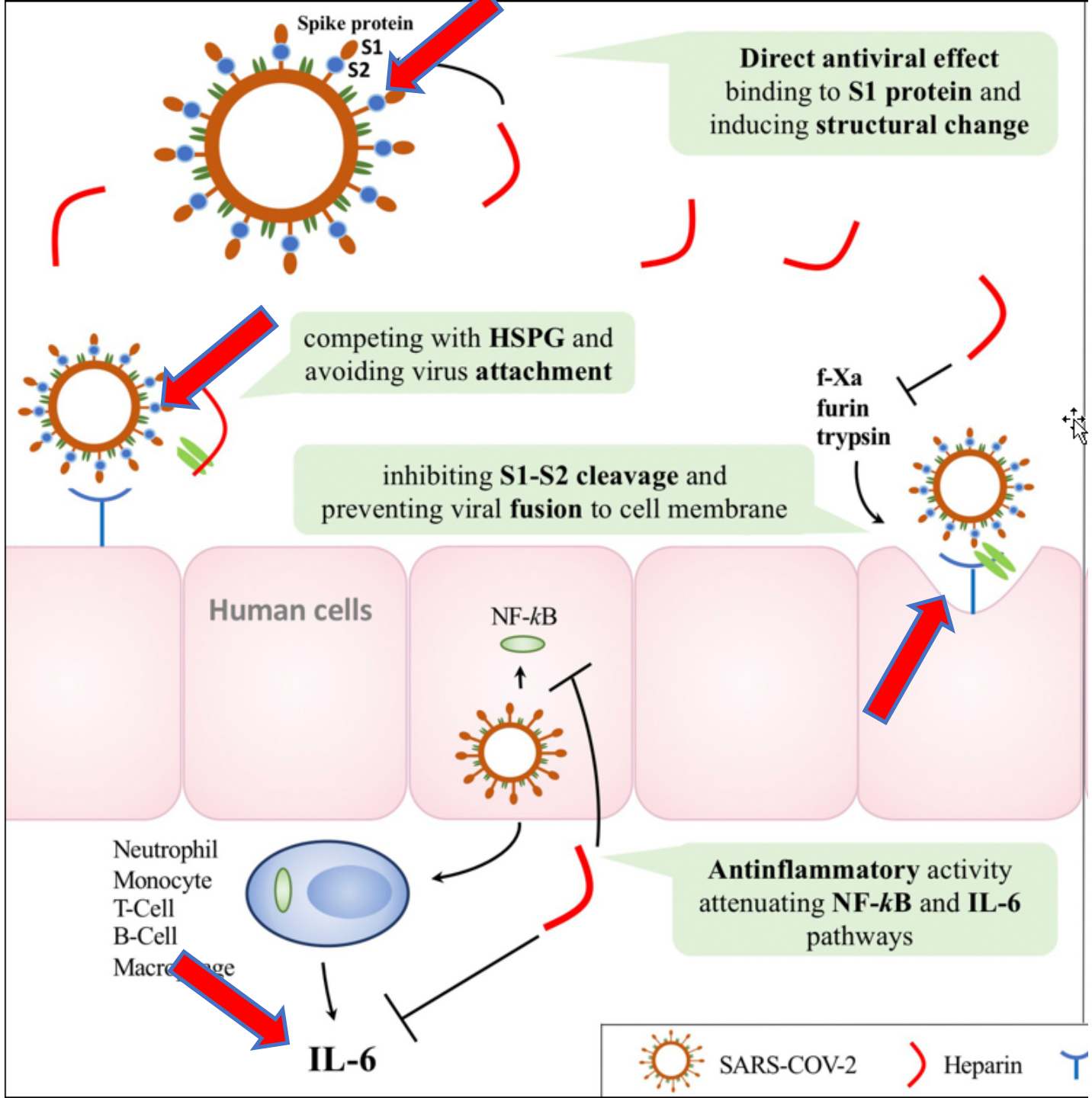
- Anticoagulation: ↓es widespread microthrombi (found deceased coronavirus patients) ➔ ↓ed mortality
- Antiinflammatory: Heparins down regulate inflammatory responses (IL-6, nuclear factor-kB); directly dampen immune activation
- Antiviral: Heparins inhibit cell entry via multiple mechanisms

Non-heparin anticoagulant recommendations:

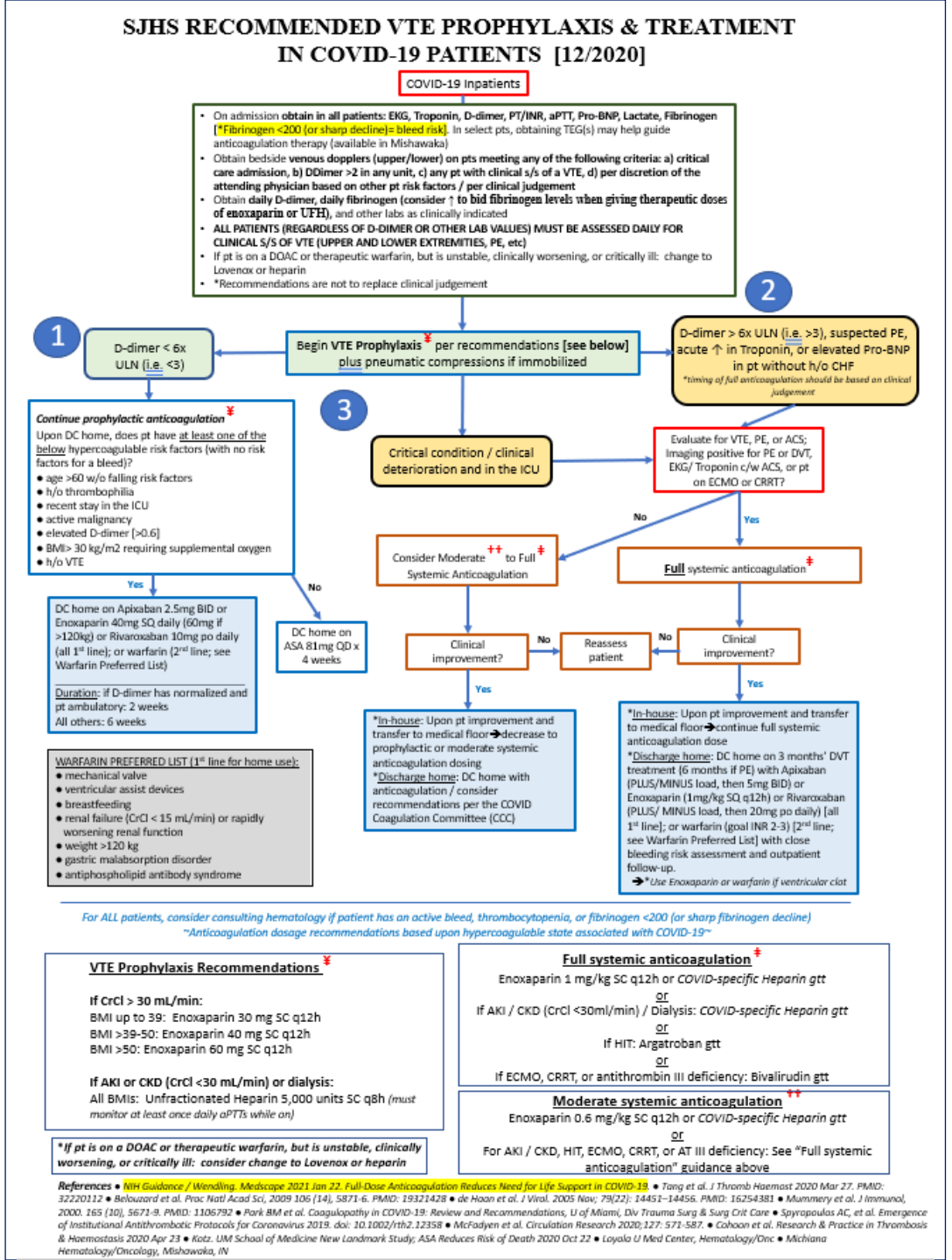
DOACs/warfarin do not appear to have these anti-viral /inflammatory properties

➔DOACs /warfarin (therapeutic) can be utilized in COVID hospitalized patients who are not in, or going into, a cytokine storm (Never in ICU patients)

Heparins and anti-viral, immune modulating /inflammatory effects



SJHS VTE Prophylaxis and Treatment Algorithm



Obtaining Dopplers (UE/LE):

Number of VTEs found per location (updated as of 11/3/20):

- Cephalic: 12
- Brachial: 9
- Femoral: 10
- Basilic: 8
- Axillary: 4
- IJV: 4
- Iliac: 3
- Popliteal: 3
- Subclavian: 1
- Peroneal: 1
- Tibial: 1

Total 56: Upper (68%), lower (32%)

*3 COVID pts who have complained re: LE pain have had UE VTEs

COVID VTE Update as of 11/3/2020:

-58 affected pts (32: Sept thru Nov 3)

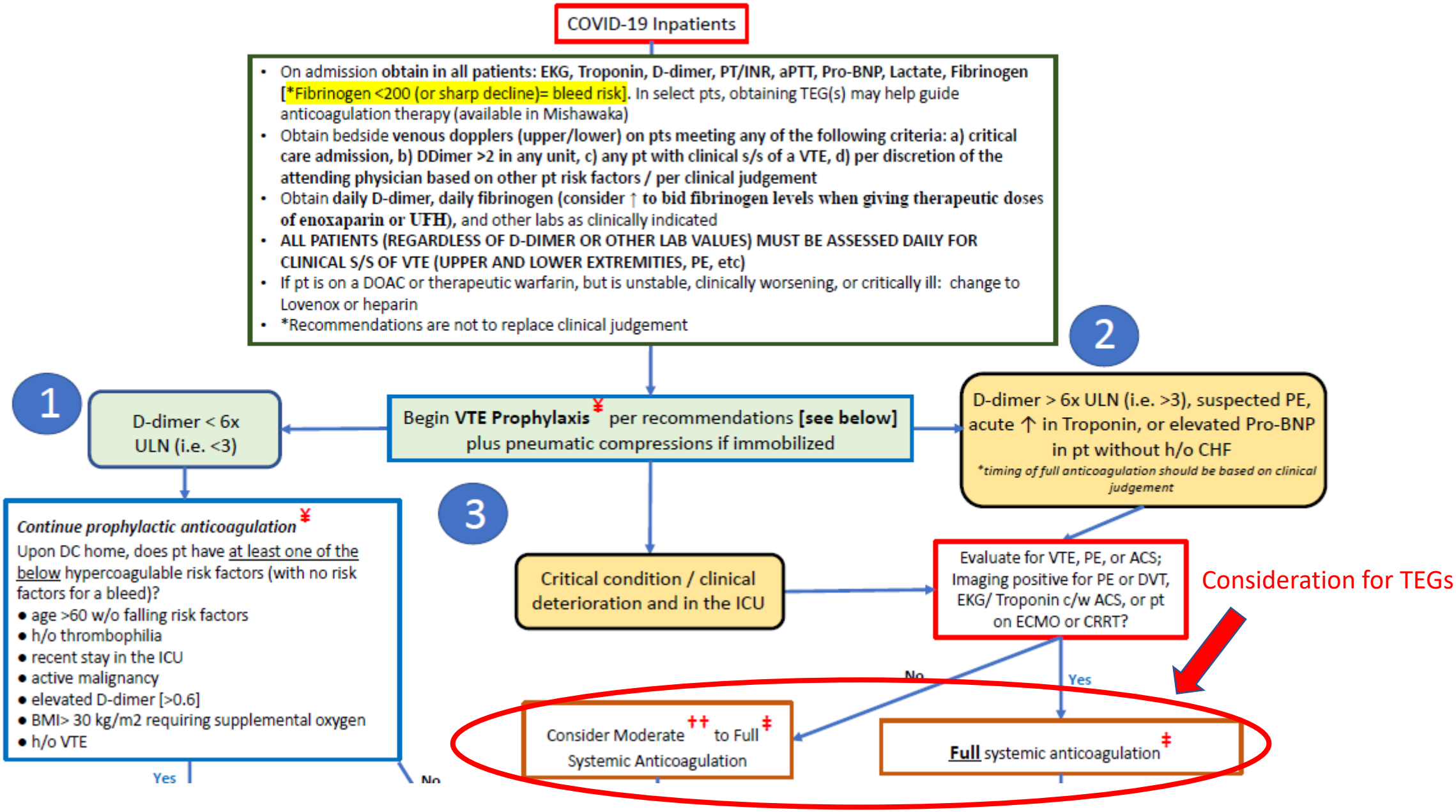
-67 total thrombotic events

- 22 PEs
- 56 DVTs (68% upper/32% lower)

When to Obtain Dopplers (UE/LE):

Only obtain bilateral upper and lower extremity dopplers on those meeting the following criteria:

1. Critical care or PCU/ intermediate care admission
2. DDimer >2 in any unit
3. Any patient with clinical s/s of a VTE,
4. Per discretion of the attending physician based on other patient risk factors / per clinical judgement


COVID-19 Inpatients
On admission obtain in all patients: EKG, Troponin, D-dimer, PT/INR, aPTT, Pro-BNP, Lactate, Fibrinogen [*Fibrinogen <200 (or sharp decline)= bleed risk]. In select pts, obtaining TEG(s) may help guide anticoagulation therapy (available in Mishawaka)
Obtain bedside venous dopplers (upper/lower) on pts meeting any of the following criteria: a) critical care admission, b) DDimer >2 in any unit, c) any pt with clinical s/s of a VTE, d) per discretion of the attending physician based on other pt risk factors / per clinical judgement
Obtain daily D-dimer, daily fibrinogen (consider ↑ to bid fibrinogen levels when giving therapeutic doses of enoxaparin or UFH), and other labs as clinically indicated
ALL PATIENTS (REGARDLESS OF D-DIMER OR OTHER LAB VALUES) MUST BE ASSESSED DAILY FOR CLINICAL S/S OF VTE (UPPER AND LOWER EXTREMITIES, PE, etc)
If pt is on a DOAC or therapeutic warfarin, but is unstable, clinically worsening, or critically ill: change to Lovenox or heparin
*Recommendations are not to replace clinical judgement
1
D-dimer < 6x ULN (i.e. <3)
Begin VTE Prophylaxis¥ per recommendations [see below] plus pneumatic compressions if immobilized
2
D-dimer > 6x ULN (i.e. >3), suspected PE, acute ↑ in Troponin, or elevated Pro-BNP in pt without h/o CHF
*timing of full anticoagulation should be based on clinical judgement
3
Continue prophylactic anticoagulation¥
Upon DC home, does pt have at least one of the below hypercoagulable risk factors (with no risk factors for a bleed)?
age >60 w/o falling risk factors
h/o thrombophilia
recent stay in the ICU
active malignancy
elevated D-dimer [>0.6]
BMI> 30 kg/m2 requiring supplemental oxygen
h/o VTE
Yes
No
Critical condition / clinical deterioration and in the ICU
Evaluate for VTE, PE, or ACS; Imaging positive for PE or DVT, EKG/ Troponin c/w ACS, or pt on ECMO or CRRT?
No
Yes
Consider Moderate ++ to Full ‡ Systemic Anticoagulation
Full systemic anticoagulation ‡
Consideration for TEGs

For ALL patients, consider consulting hematology if patient has an active bleed, thrombocytopenia, or fibrinogen <200 (or sharp fibrinogen decline)
~Anticoagulation dosage recommendations based upon hypercoagulable state associated with COVID-19~

VTE Prophylaxis Recommendations ¥

If CrCl > 30 mL/min:
BMI up to 39: Enoxaparin 30 mg SC q12h
BMI >39-50: Enoxaparin 40 mg SC q12h
BMI >50: Enoxaparin 60 mg SC q12h

If AKI or CKD (CrCl <30 mL/min) or dialysis:
All BMIs: Unfractionated Heparin 5,000 units SC q8h *(must monitor at least once daily aPTTs while on)*

If pt is on a DOAC or therapeutic warfarin, but is unstable, clinically worsening, or critically ill: consider change to Lovenox or heparin

Full systemic anticoagulation ‡

Enoxaparin 1 mg/kg SC q12h or *COVID-specific Heparin gtt*
or
If AKI / CKD (CrCl <30ml/min) / Dialysis: *COVID-specific Heparin gtt*
or
If HIT: Argatroban gtt
or
If ECMO, CRRT, or antithrombin III deficiency: Bivalirudin gtt

Moderate systemic anticoagulation ††

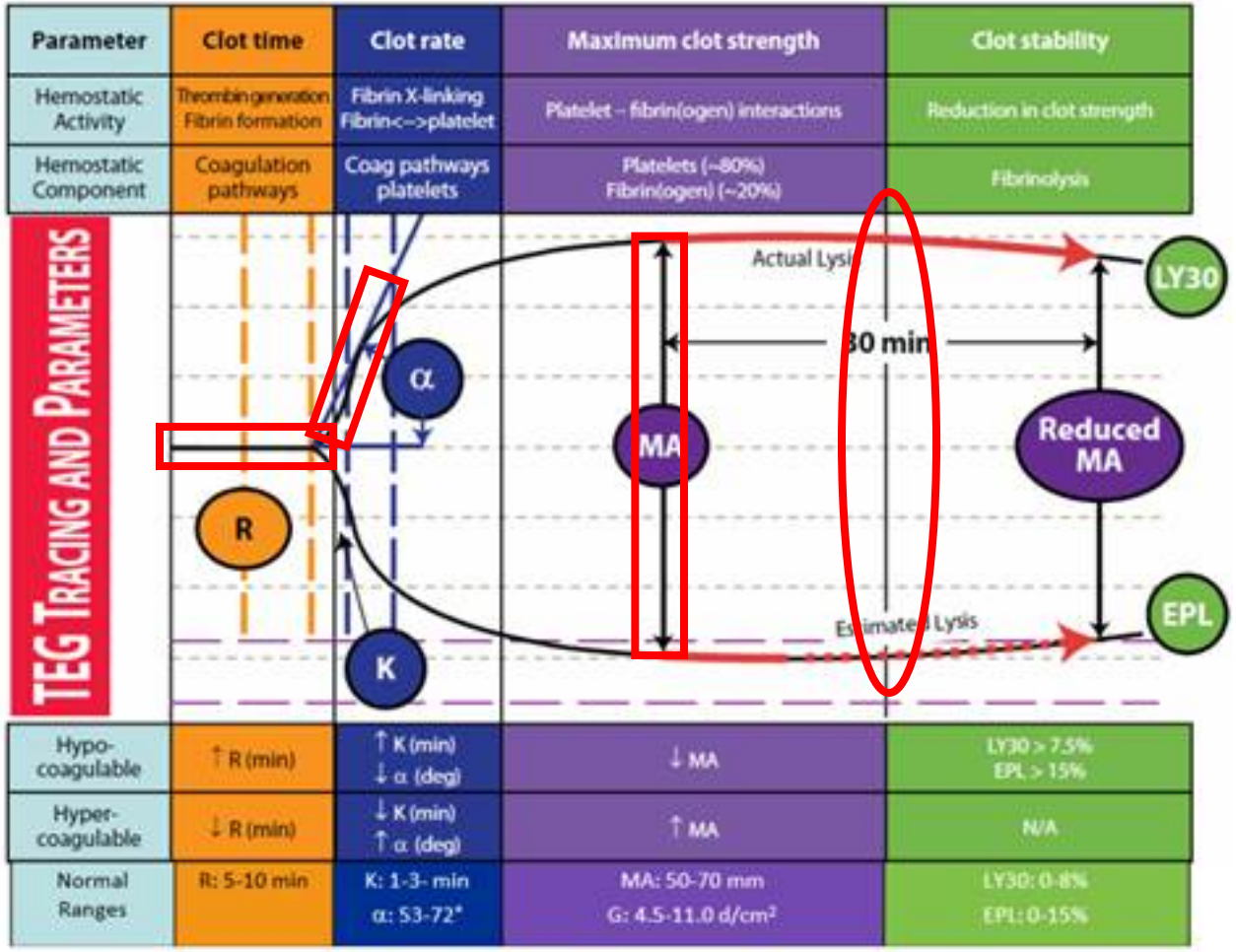
Enoxaparin 0.6 mg/kg SC q12h or *COVID-specific Heparin gtt*
or
For AKI / CKD, HIT, ECMO, CRRT, or AT III deficiency: See "Full systemic anticoagulation" guidance above

Thromboelastography (TEG)

Thromboelastography (TEG) = whole blood test / coagulopathy "big picture:“

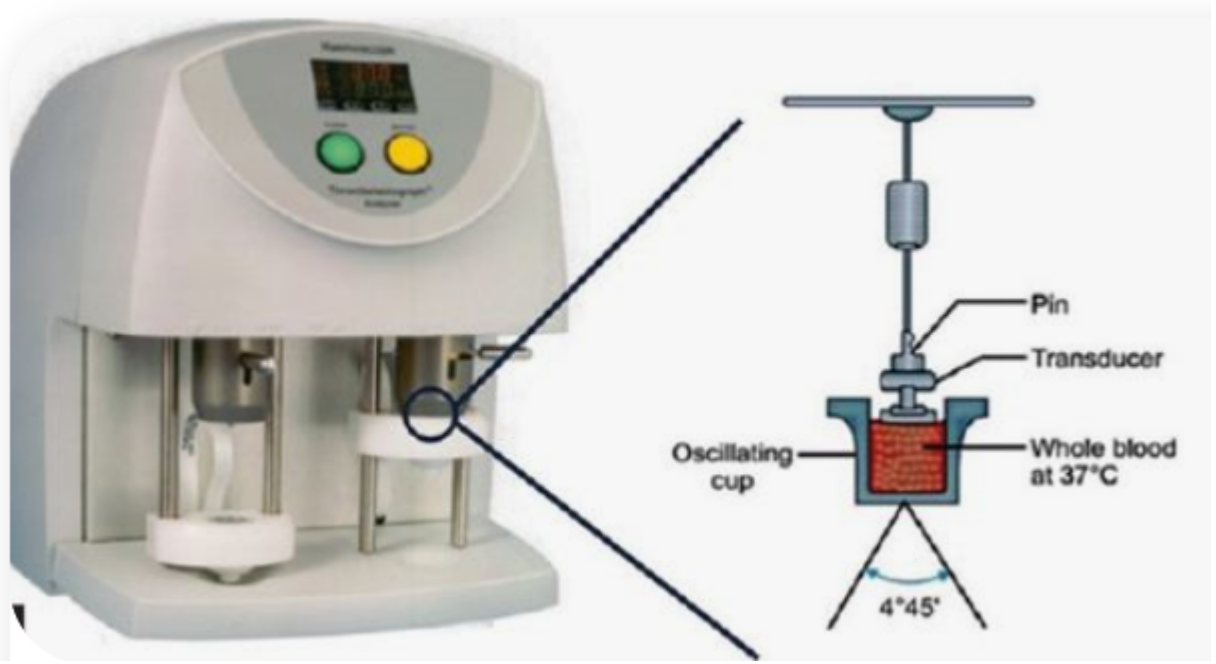
- patient's ability/time to clot (R value)
- rate of increase in the clot (alpha angle)
- strength of the clot (MA)
- ability to break down the formed clot (LY30)

*better “overall picture” / representation than: aPTT, fibrinogen, platelets, coagulation factor levels

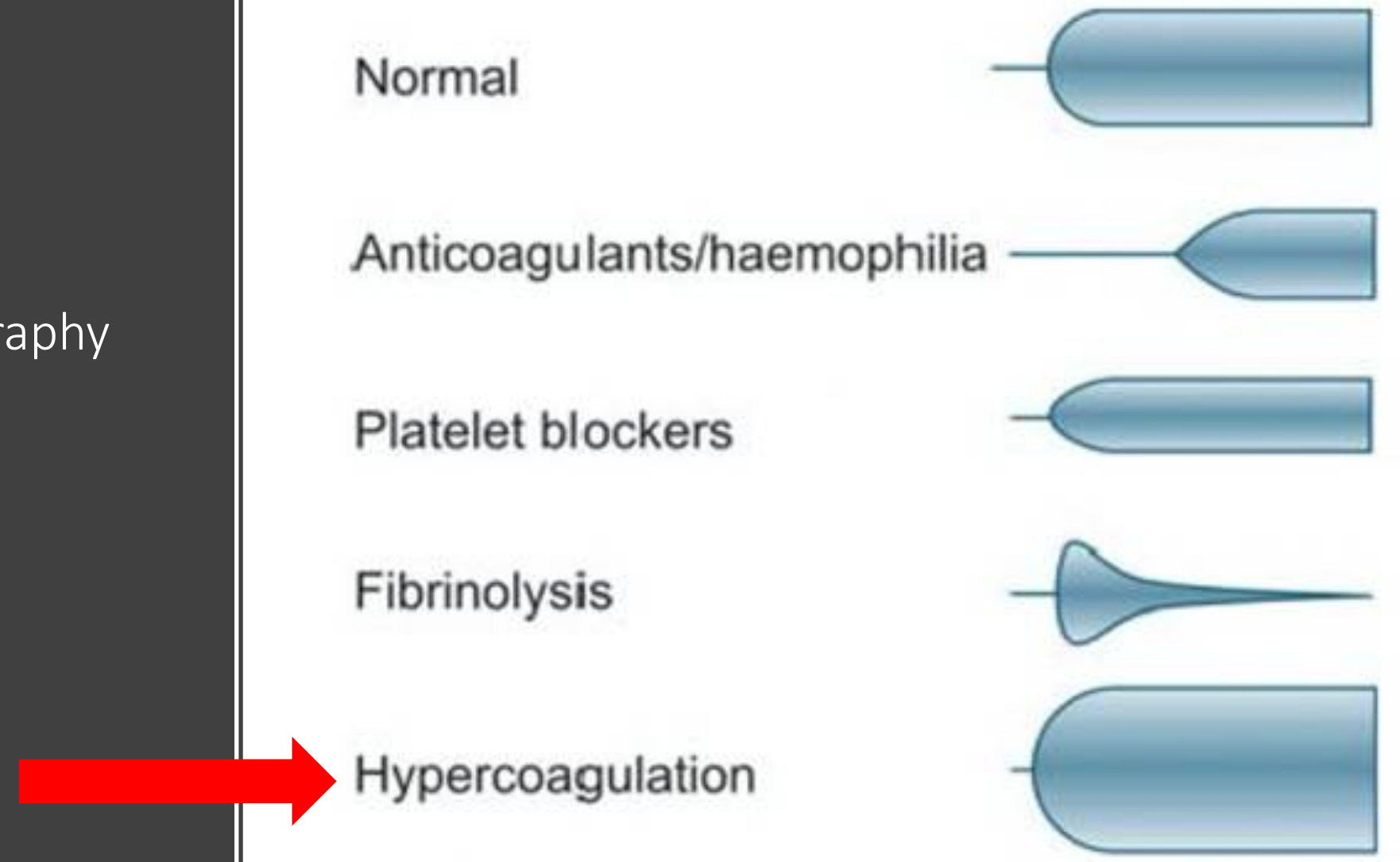


Thromboelastography (TEG)

Testing Procedure: small amount of blood is placed in a cup with a pin that is suspended from a torsion wire that is continuously oscillating. This mimics the patient's in vivo thrombus formation, and transfers the information into a graph.



Thromboelastography (TEG)



TEG / COVID

COVID-19: disease state that is at times

- **Hyper**coagulable (usually coincides with the cytokine storm, need for anti-inflammatory and anti-viral properties)
- **Hypo**coagulable (usually after the cytokine storm is over and clinical improvement, but can be intermittent throughout the storm)

KEY LABS:

*D-dimer-coagulation activation marker

*Fibrinogen-prothrombotic (500+)-*triggered by inflammation and/or tissue damage*

TEG / COVID

COVID-19:

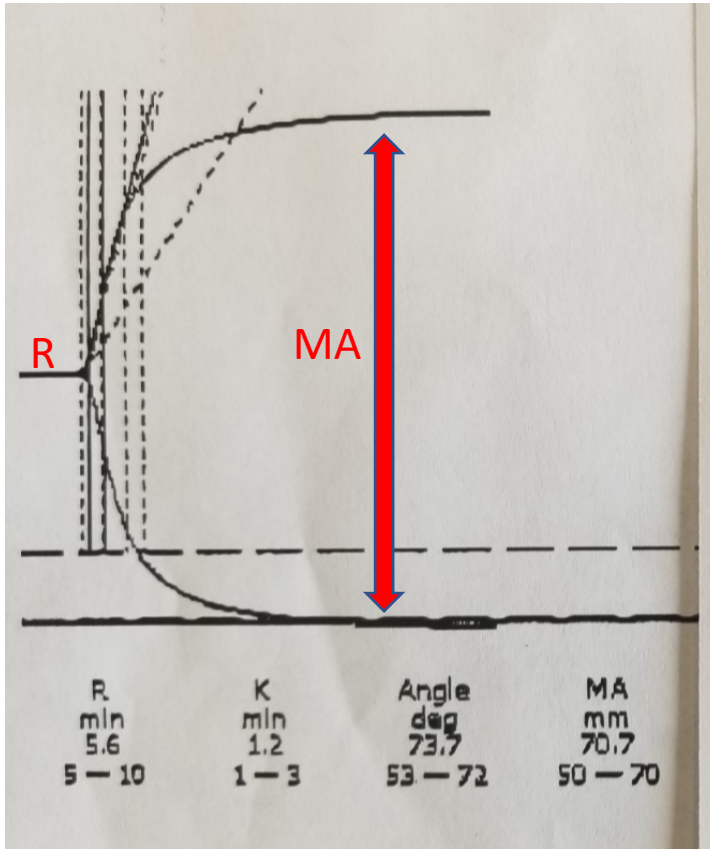
- TEGs gather real-time evaluation of patient's anticoagulation needs
- Prevent patients from bleeding
- Prevent patients from throwing clots
  - DVTs / PEs
  - widespread microthrombi into key organ systems (*researchers find in COVID patient autopsy reports)

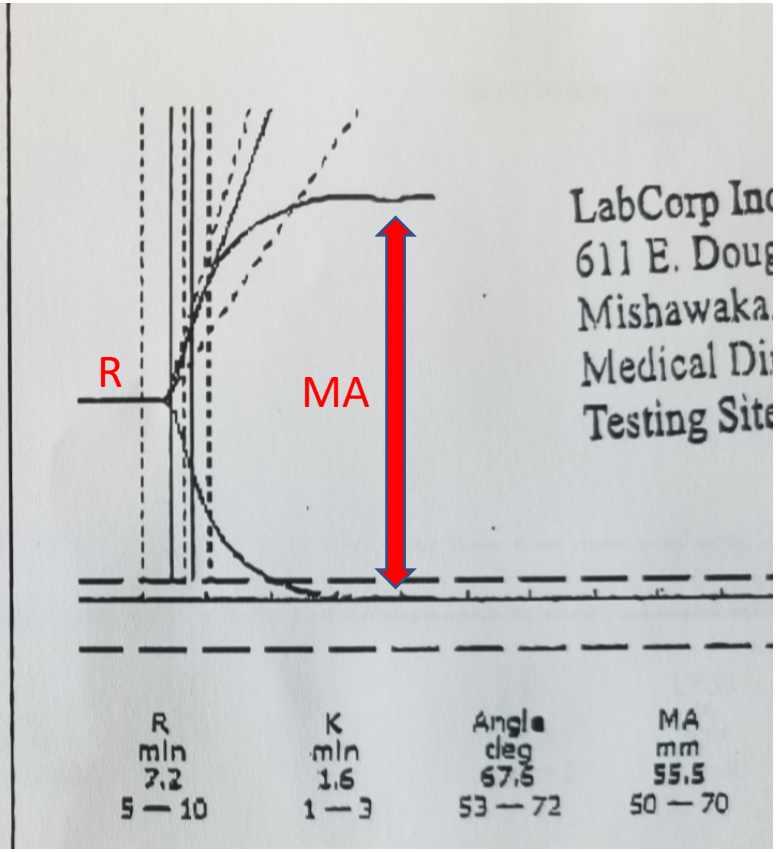
TEG Example: Before and After The Storm

GM admit to med floor on 7/18 on R.A. Respiratory status quickly deteriorated, transfer to ICU 7/22 on bipap. Left TEG below (7/23) shows hypercoagulable state. Lovenox escalated from 30mg BID to 1mg/kg q12h. Clinically improved and tx to med floor 7/30, on R.A. (Right TEG below).

*"Heparinase" samples

7/23: on bipap
R 5.6, MA 70.7





7/30: Room Air
R 7.2, MA 55.5

Critical time to deescalate AC

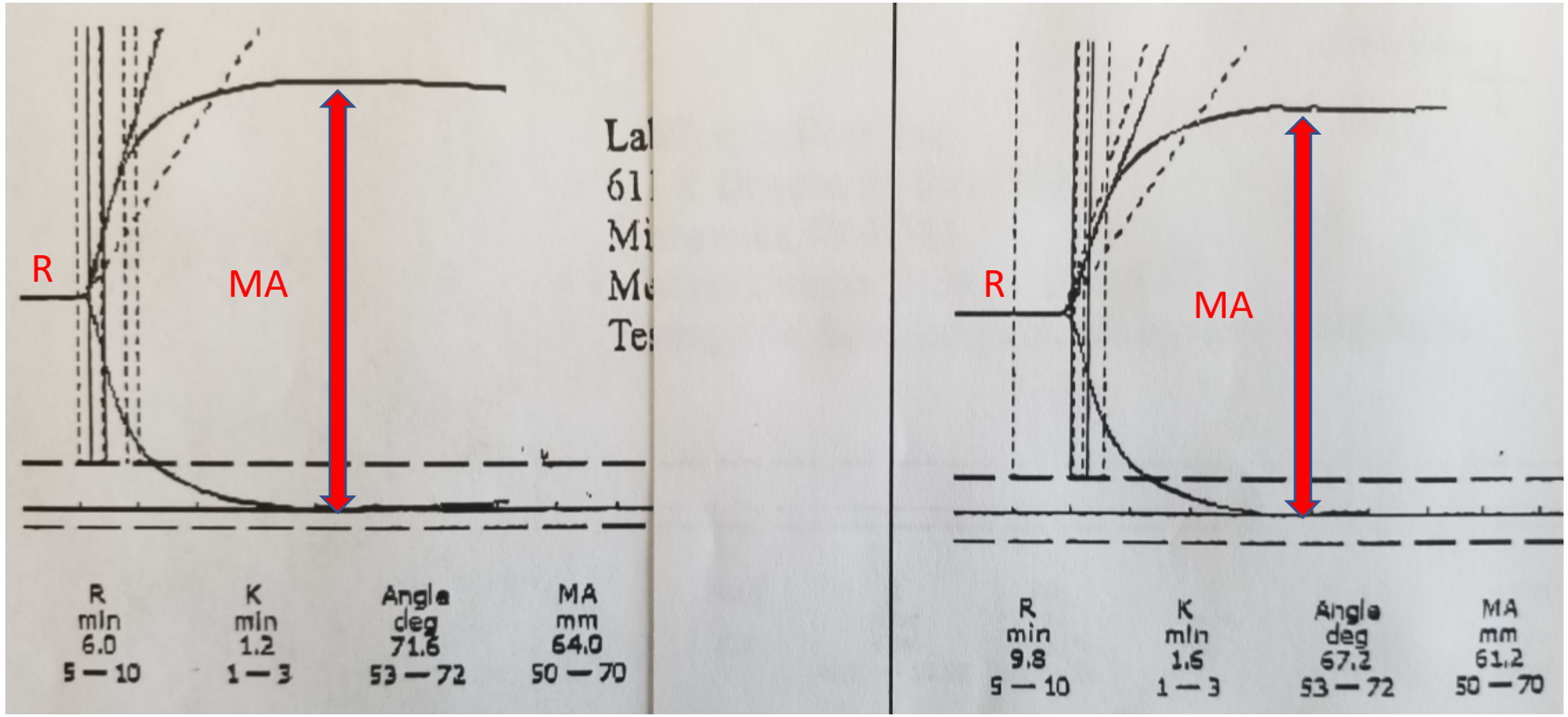
TEG Example: Heparinase vs Kaolin

- **Kaolin** (activator to trigger the coagulation pathway)
- Kaolin with **Heparinase** (lyses the heparin to deactivate it; gives visualization of the body's coagulation w/o heparin on board)

Pt GM on Lovenox 1mg/kg q12h

Heparinase Sample (body's natural coagulopathy)

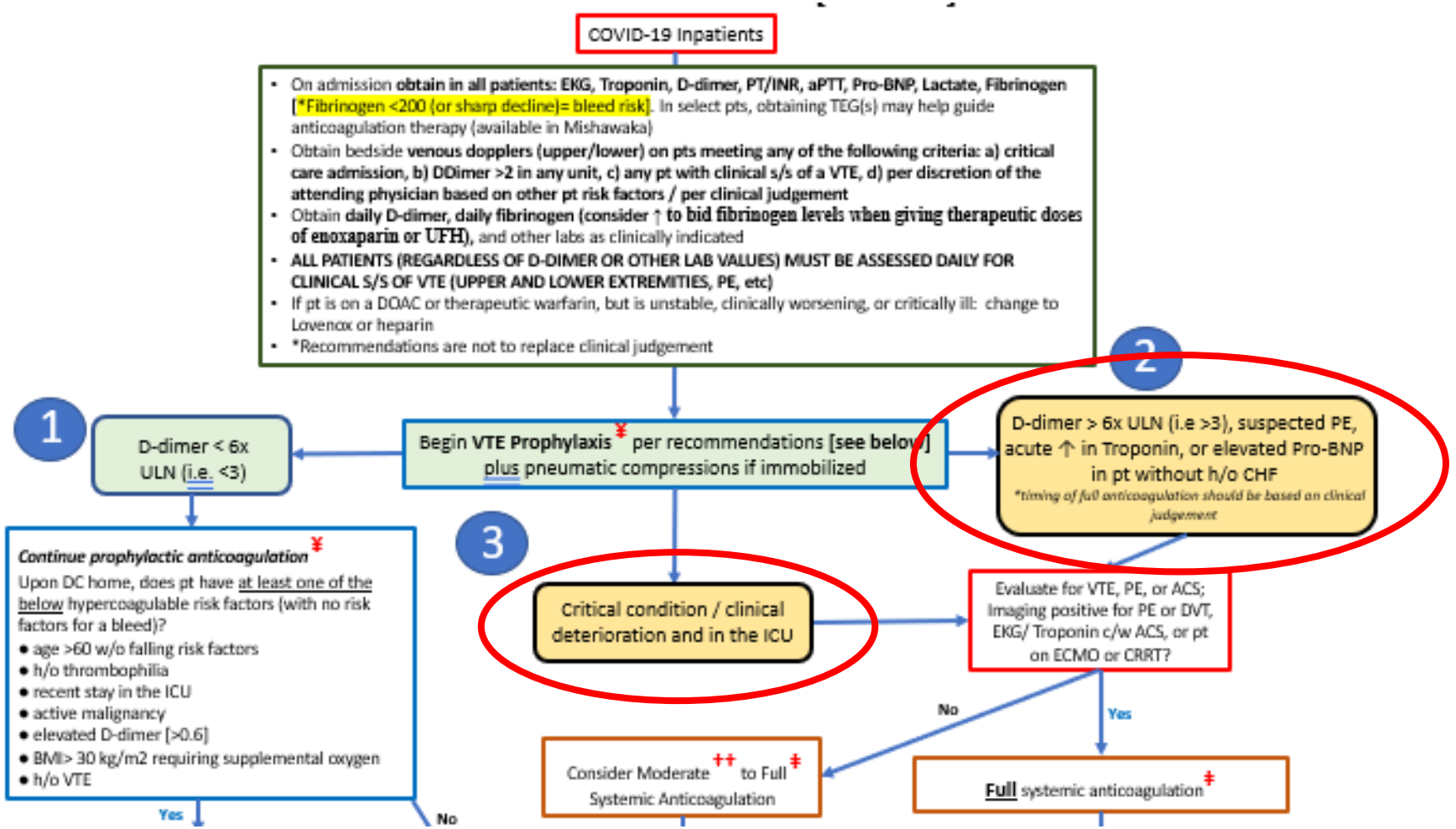
R 6, MA 64



Kaolin Sample (Lovenox anticoagulation effects)

R 9.8, MA 61.4

WHEN IS IT TIME TO ESCALATE?



When to Involve the Coagulation Team:

Example AC Escalation:

Pt TRW [redacted]; Admit 10/2pm to Med Floor

10/3-6: oxygen supplementation needs: 35-45L high flow, 70-90% FiO2

CRP: 160->193
Ferritin: 498->672
Fibrinogen: 798
Ddimer: 0.57->0.99->1.14->1.38→7.97

Pt on Lovenox 30mg bid

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10/7 Doppler US: R complete basilic vein DVT from elbow to mid upper arm

Consideration for AC Escalation:

- High oxygen supplementation needs (or needs ↑ing)
- DDimer trending ↑
- Fibrinogen trending ↑
- Inflammatory labs trending ↑ (or just not improving)
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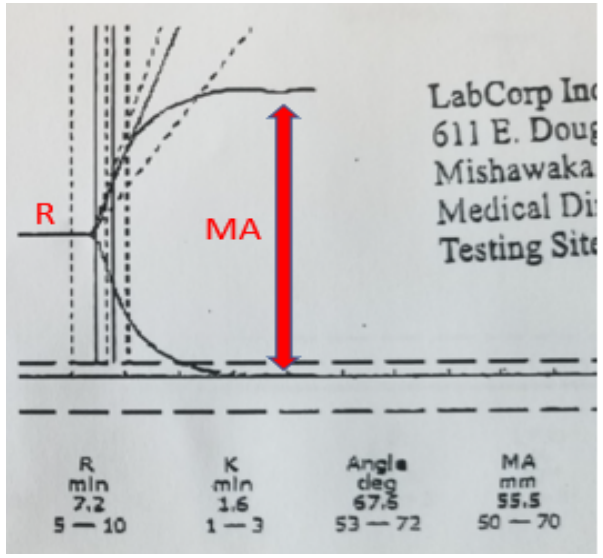
Deescalation in **Hypo**coagulation
COVID **HYPO**COAGULABILITY

COVID-19: disease state that is at times

- **Hypo**coagulable (usually after the cytokine storm is over and clinical improvement, but can be intermittent throughout the storm)



7/30: Room Air
R 7.2, MA 55.5

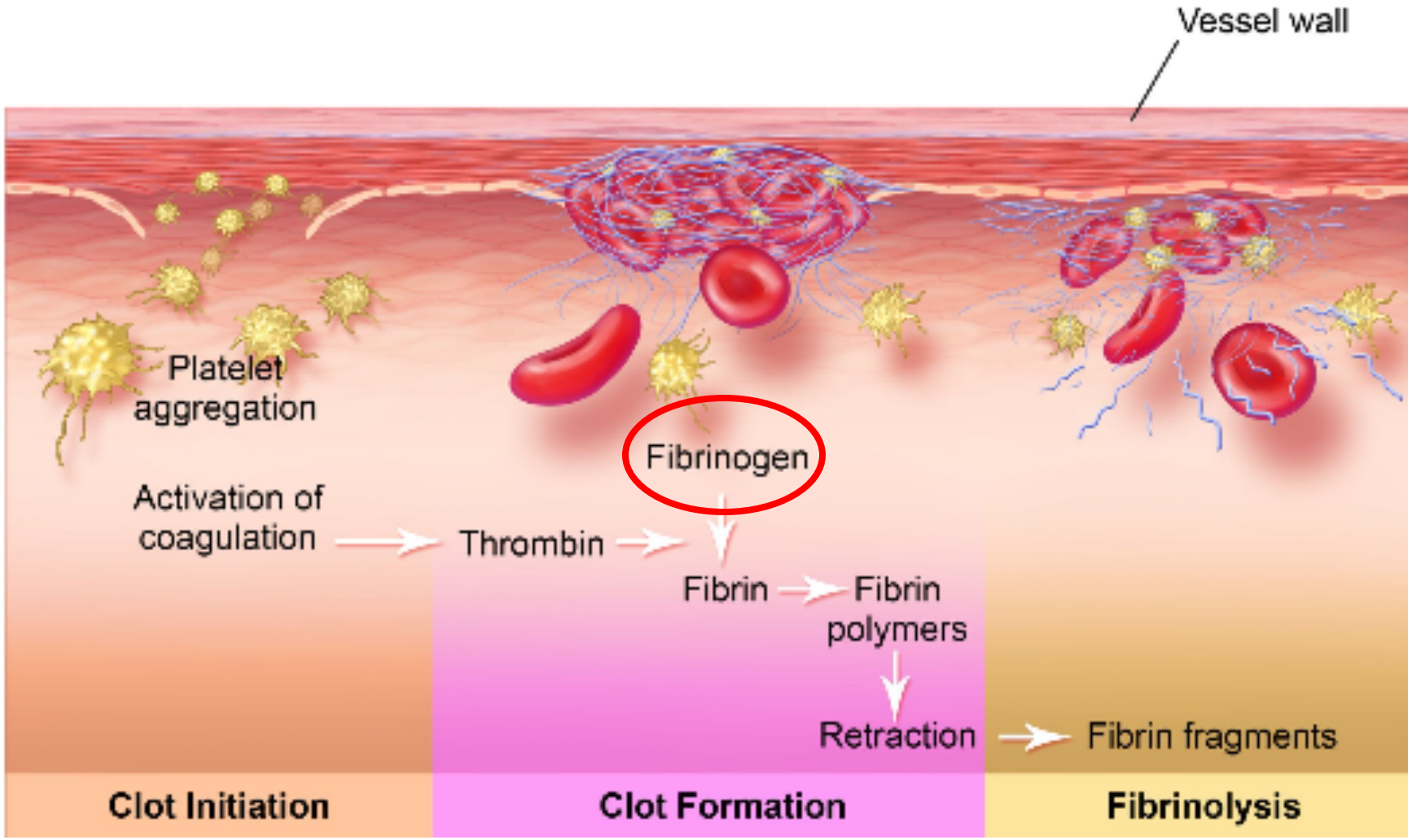
Critical time to deescalate AC

KEY LABS:

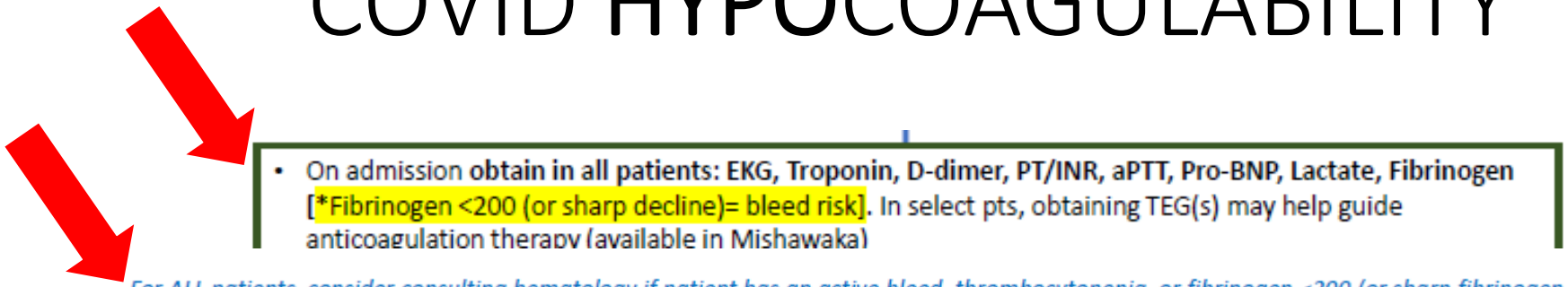
*D-dimer-coagulation activation marker

*Fibrinogen-prothrombotic (500+)-*triggered by inflammation and/or tissue damage*

Fibrinogen and the clotting cascade



COVID **HYPO**COAGULABILITY



➔Rec to obtain **daily fibrinogen** (consider ↑ to bid fibrinogen levels when giving therapeutic doses of enoxaparin/UFH, when levels in the 200s)

Fibrinogen plus ddimer plus Hgb/plts (and aPTTs if on UFH) are critical

-**replete with cryoprecipitate** for fibrinogen <200 if on moderate to therapeutic AC doses, <150 if on prophylactic doses or when on a DOAC (especially if not obtaining TEGs)

**This plus ddimer (and aPTTs if on UFH) are especially critical if TEG monitoring is not an option

HEPARIN (UFH) IN COVID

Heparin in COVID-19

- Extreme hypersensitivity to UFH (not Lovenox)
  - TEG examples
  - aPTT monitoring
    - SQ doses may result in therapeutic levels, or upwards of >100
    - Lower aPTT range gives therapeutic results

Fig. 1 (5/29: hep 5K units SQ q8h)

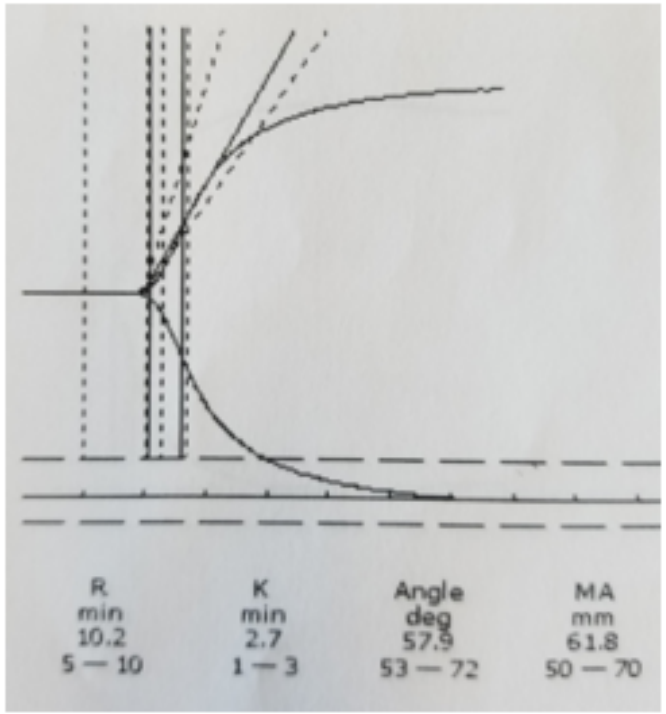
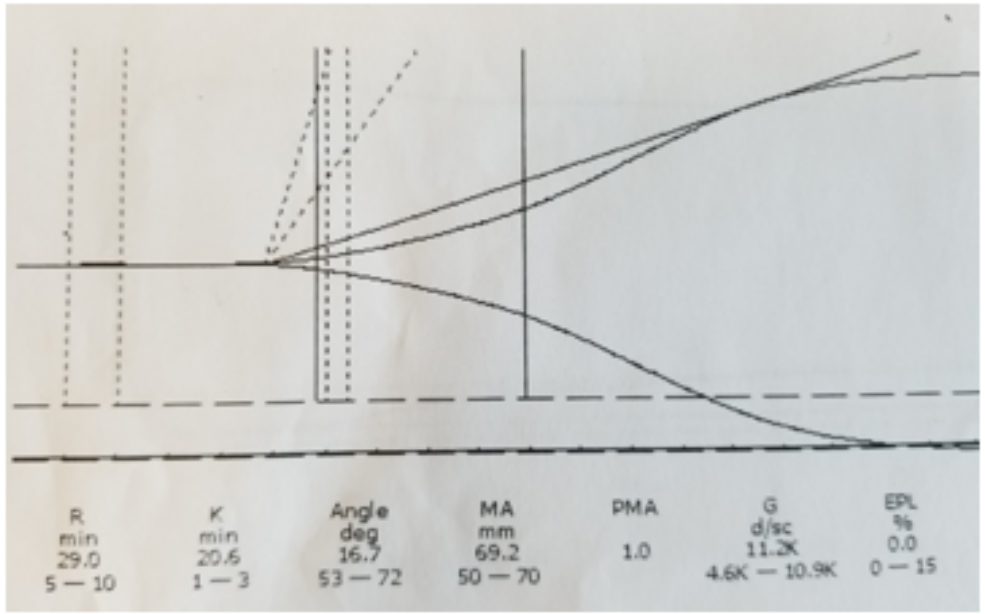


Fig. 2 (6/2: hep 5K units SQ q8h)



Heparin Drip Dosing Policy

All COVID patients: NO BOLUSES

HS: + PE=> 70unit/kg bolus, then 16units/kg/hr. Baseline **aPTT 29.6→115.7** at 6hrs

- H/H dropped significantly; unknown source of bleed
- Diagnosis one month PTA

SD: + PE, segmental branch to RUL=> 70units/kg bolus, 16units/kg/hr. Baseline **aPTT 2[illegible]→135.7** at 6hrs

- Immediate bleeding from chest tube
- 5 days feeling ill

MM: + R brachial DVT=> 70unit/kg bolus, 16units/kg/hr. Baseline **aPTT 31.9→145.2** at 6hrs

- Immediate L upper anteri[illegible]bdominal wall intramuscular hematoma
- Diagnosis <1 week PTA

ES: + PE=> 70unit/kg bo[illegible] 16units/kg/hr x 34min, shut off x 46min (IR); restart at 12units/kg/hr x 2hr
Baseline **aPTT <21→139.1** at 2hrs

- One week into illness

Heparin Drip Dosing Policy

- All COVID patients: NO BOLUSES

- **INTERMEDIATE AC**:
  - Drip rate of 8 units/kg/hr
  - Goal aPTT: 37-45 (1.5x baseline)

- **FULL AC**:
  - Drip rate 14 units/kg/hr
  - Goal aPTT: 50-59

Anticoagulation Dosing Policy

I. COVID / NO VTE

COVID-19 Heparin Dosing
(Dose based on Actual Body Weight)

COVID-19 **NO VTE** No Bolus Doses (includes initially and throughout the duration of the heparin drip)
INITIAL INFUSION: **8 units/kg/hr (*see COVID sliding scale algorithm below)**

I. Heparin Sliding Scale for all COVID-19 patients and **NO VTE**
(Dose based on Actual Body Weight)

aPTT (Seconds)	Bolus (Units/kg)	Rate Change Program Sigma Pump in units/hr
<30	NO BOLUS	Increase by 1 unit/kg/hr Repeat aPTT in 4-6 hours
30-36.9	NO BOLUS	Increase by 0.5 units/kg/hr *Repeat aPTT in 4-6 hours*
37-45 (1.5x baseline) **GOAL**	NO BOLUS	***No Change*** *aPTT monitoring may be reduced from q6h to q12h per discretion of the physician after 3 (THREE) consecutive aPTTs in therapeutic range*
45.1-50	NO BOLUS	Decrease infusion by 1 unit/kg/hr Repeat aPTT in 4-6 hours
50.1-80	NO BOLUS	**HOLD 1 HOUR** Decrease infusion by 2 units/kg/hr Repeat aPTT in 4-6 hours
>80	NO BOLUS	**HOLD 1 HOUR THEN RECHECK STAT APTT:** a) Restart gtt only if **level <70**, at a gtt rate of 3 units/kg/hr less than previous rate, and **recheck aPTT in 3 hours** b) If repeat **level is 70.1-90**, restart gtt after a total hold time of 2 hours, at a rate of 3 units/kg/hr less than previous rate; **recheck aPTT in 4 hours** c) If repeat **level >90**, continue to hold gtt and **recheck another level at 2 hours** s/p the most recent level.

Anticoagulation Dosing Policy

II. COVID / POSITIVE VTE

COVID-19 Heparin Dosing (Dose based on Actual Body Weight)
COVID-19 NO VTE: No Bolus Doses (includes initially and throughout the duration of the heparin drip) INITIAL INFUSION: **8 units/kg/hr (*see COVID sliding scale algorithm below)**
COVID-19 POSITIVE VTE: No Bolus Doses (includes initially and throughout the duration of the heparin drip) INITIAL INFUSION: 14 **units/kg/hr (*see COVID sliding scale algorithm below)**

II. Heparin Sliding Scale for all COVID-19 patients and **POSITIVE VTE** (Dose based on Actual Body Weight)		
aPTT (Seconds)	**Bolus** (Units/kg)	**Rate Change** Program Sigma Pump in units/hr
<45	NO BOLUS	Increase by 1 unit/kg/hr Repeat aPTT in 4-6 hours
45-49.9	NO BOLUS	Increase by 0.5 units/kg/hr *Repeat aPTT in 4-6 hours*
50-59 **GOAL**	NO BOLUS	***No Change*** *aPTT monitoring may be reduced from q6h to q12h per discretion of the physician after 3 (THREE) consecutive aPTTs in therapeutic range*
59.1-69.9	NO BOLUS	Decrease infusion by 1 unit/kg/hr Repeat aPTT in 4-6 hours
70-80	NO BOLUS	**HOLD 1 HOUR** Decrease infusion by 2 units/kg/hr Repeat aPTT in 4-6 hours
>80	NO BOLUS	**HOLD 1 HOUR THEN RECHECK STAT APTT:** a) Restart gtt only if **level <70**, at a gtt rate of 3 units/kg/hr less than previous rate, and **recheck aPTT in 3 hours** b) If repeat **level is 70.1-90**, restart gtt after a total hold time of 2 hours, at a rate of 3 units/kg/hr less than previous rate; **recheck aPTT in 4 hours** c) If repeat **level >90**, continue to hold gtt and **recheck another level at 2 hours** s/p the most recent level.

OUTCOMES DATA

Outcomes Data—Heparin /TEG Algorithm Work

- Prior to Sept 16, 2020: 12 out of 33 patients studied had a bleeding event
- Sept 16-Dec 1, 2020: one out of 71 patients had a bleeding event

- Pre-print. Thromboelastography-Guided Management of Anticoagulated COVID-19 Patients to Prevent Hemorrhage. Semin Thromb Hemost 2021. In Press.
- Pre-print. Thromboelastography-Guided Anticoagulant Therapy for the Double Hazard of Thrombohemorrhagic Events in COVID-19: A Report of Three Cases. Am J Case Rep. 2021. In Press.

Outcomes Data—Overall Health System Success

St Joseph Health System COVID 19 Outcome Analysis			
Total Number of Patients Resulted as of 12/07/2020	47,918		Indiana Statewide Comparison
Total Number of Patients Returning Positive Results	4,501	9%	8.0%
Number of Unique Patients With Inpatient Hospitalization Stay	921	20%	
Number of Inpatient episodes of Care for Covid Positive Patients (Includes Readmissions)	976		
Number of Positive Inpatients Requiring Mechanical Ventilation	38	4%	*Comparable Data Not available*
Number of Positive Patients Expired from all causes	95		*Comparable Data Not available*
Number of Hospitalized Patients Expired (Thru Sept 2020)	12	4.8%	Midas Comparative Database of 214 Hospitals Nationwide Covid Mortality 15.13% (Thru Sept)
Average Daily Percentage of Positive patients Requiring Mechanical Ventilation	4.4%		12.4%
Today's Census - Average Age of Hospitalized Covid Patients	66		

Outcomes Data—Overall Health System Success

Comparison Of SJRMC Covid Mortality Vs. National Group								
	Q1 / Q2		Q3		Q4		CY 2020	
	Mort	N	Mort	N	Mort	N	Mort	N
SJHS Indiana	5	108	11	182	84	809	100	1099
National Compare	1485	7723	526	4298	1484	11937	3495	23958
SJHS Mortality Rate	4.63%		6.04%		10.38%		9.10%	
National Mortality Rate	19.23%		12.24%		12.43%		14.59%	
Expected Deaths	20.8		22.3		100.6		160.3	
Actual SJHS Deaths	5		11		84		100	
O/E	0.24		0.49		0.84		0.62	
P - Val	0.0000		0.0007		0.0659		0.0000	
Lives Difference	16		11		17		60	

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QUESTIONS?