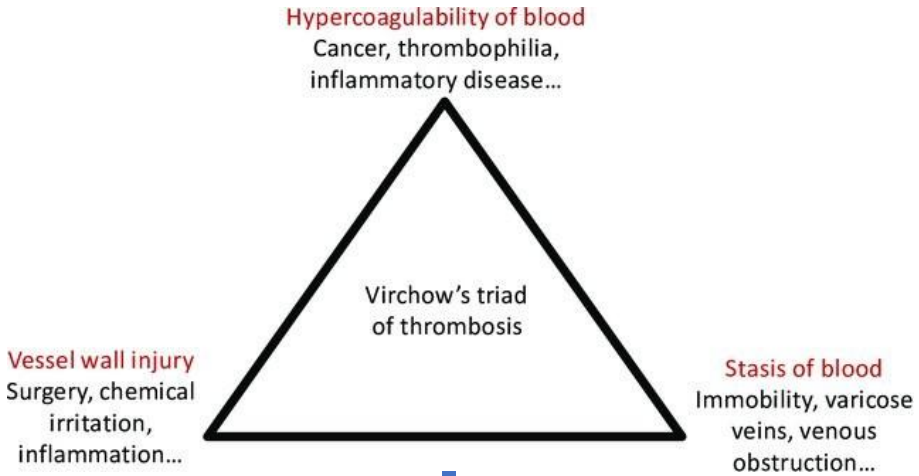
Modificari ale hemostazei la pacientul cu infectie Covid-19

- patogenie si abordare terapeutica -

Dr. Mihaela Andreescu

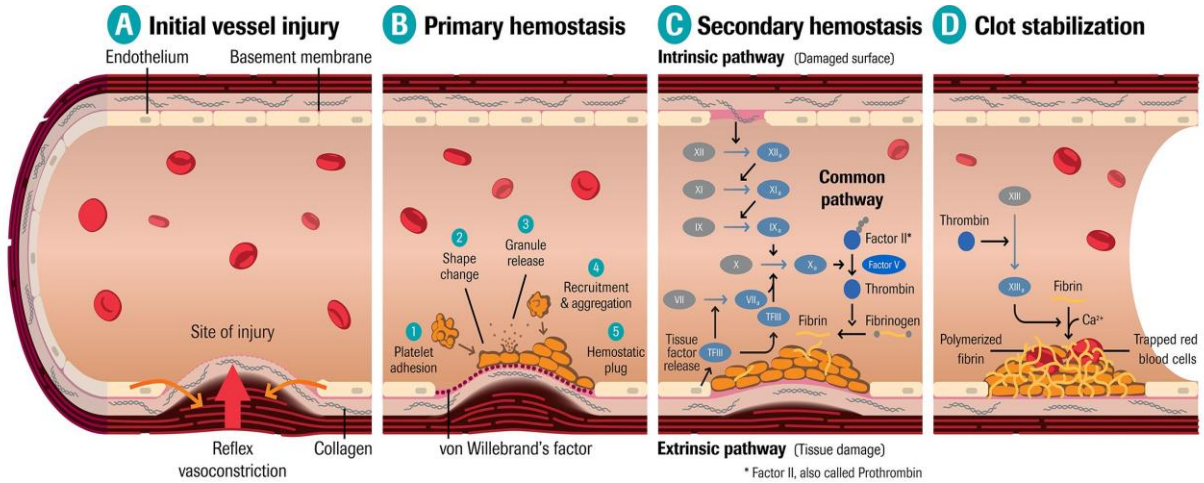
Coagulation
Virchow's triad



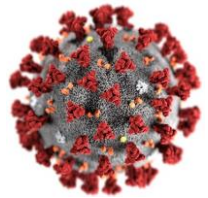
Deep vein thrombosis

Embolisation

Pulmonary embolism



Immunothrombosis

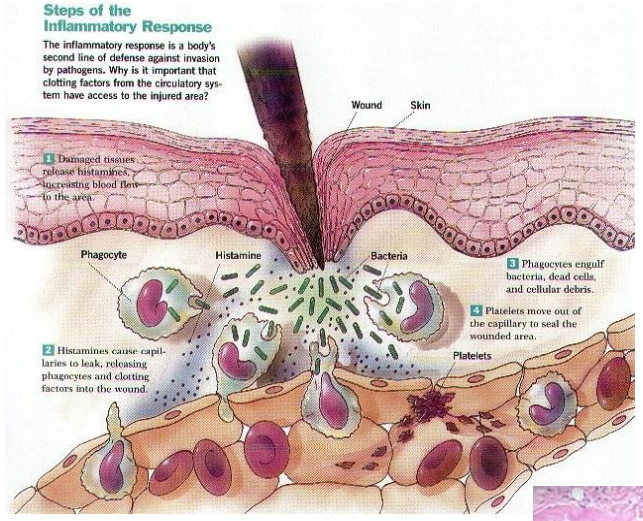


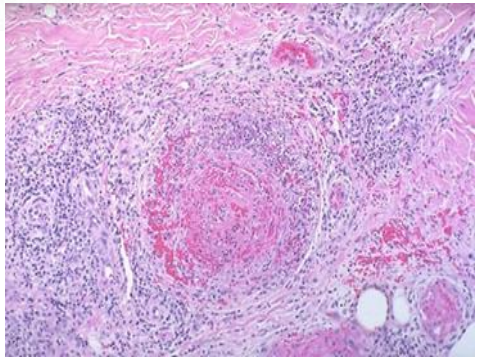
COVID-19 pneumonia

Local inflammation in pulmonary vasculature

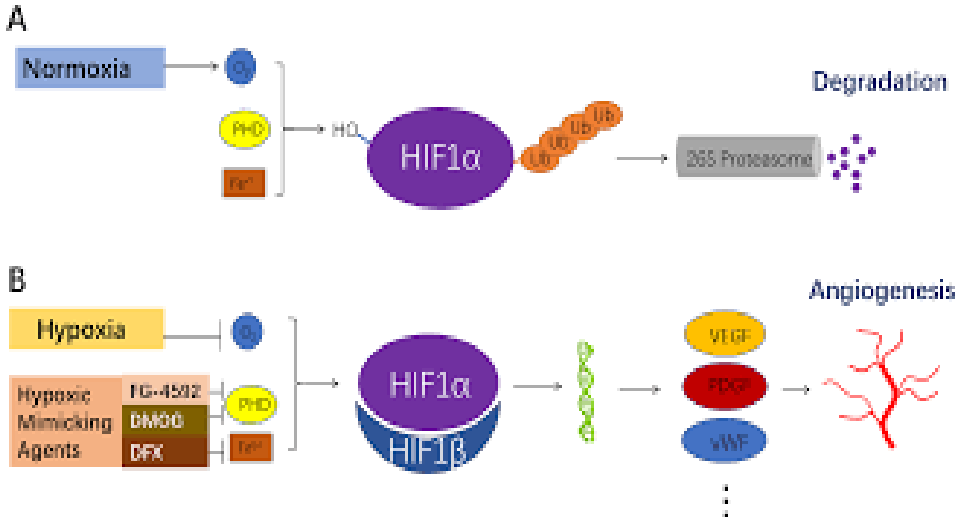
Pulmonary thrombosis

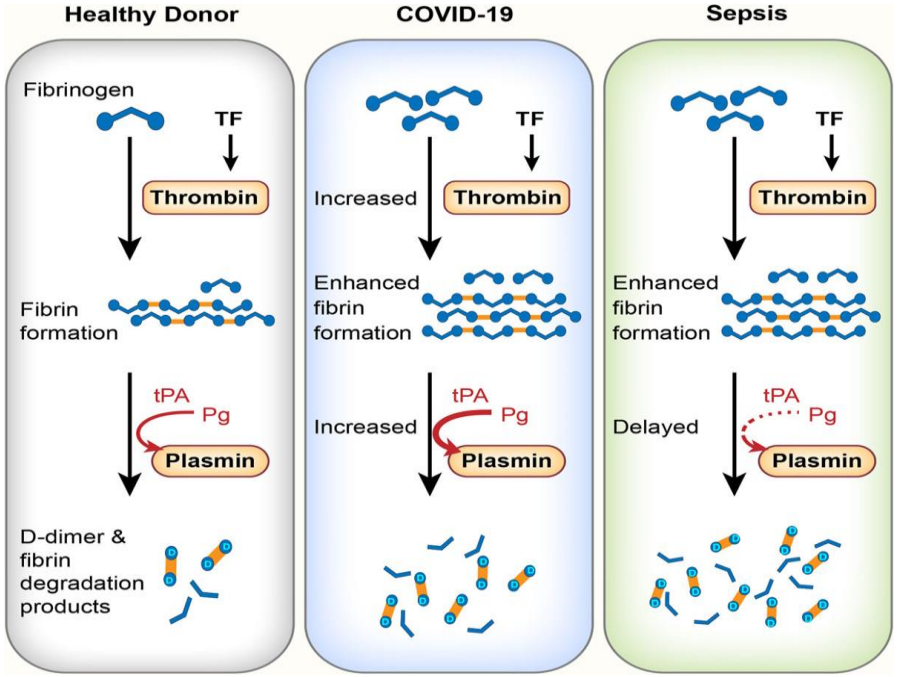
A reminder of concepts around haemostasis in sepsis, inflammation & hypoxia



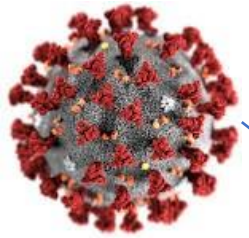


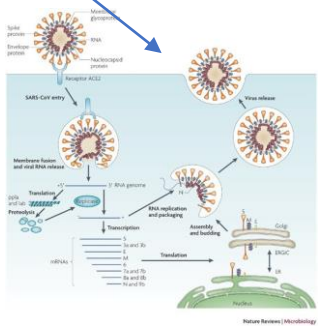
- The coagulation system evolved as an **effector pathway of the immune response**, laying down fibrin around bacteria to physically entrap them & prevent their dissemination. Thus the end point of inflammation is thrombosis…and anticoagulants do not improve outcome in these states. Instead we treat the inflammatory process.
- Hypoxia → **hypoxia- inducible transcription factors** which leads to a prothrombotic state (affect tissue factor & PAI-1 genes)





COVID-19 pathogenesis

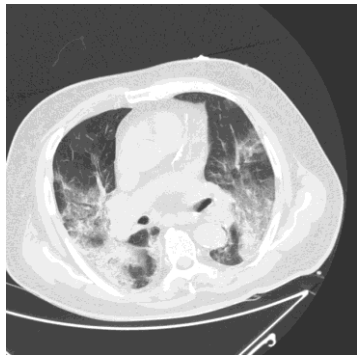




ACE2 receptor on
Pulmonary epithelium
& endothelium

Asymptomatic
Minor infection
7-10 days fever &/or flu-likesymptoms
anosmia

In a minority
COVID-19 pneumonia
Massive inflammatory response
Cytokine storm/macrophage activation



Moderate
(needs O2)

Severe
(needs mechanical
Ventilation)

Prothrombotic state due to effects of IL1, IL-6

Does a pre-existing inflammatory state make COVID-19 pneumonia more likely? e.g atherosclerosis, diabetes, obesity?

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

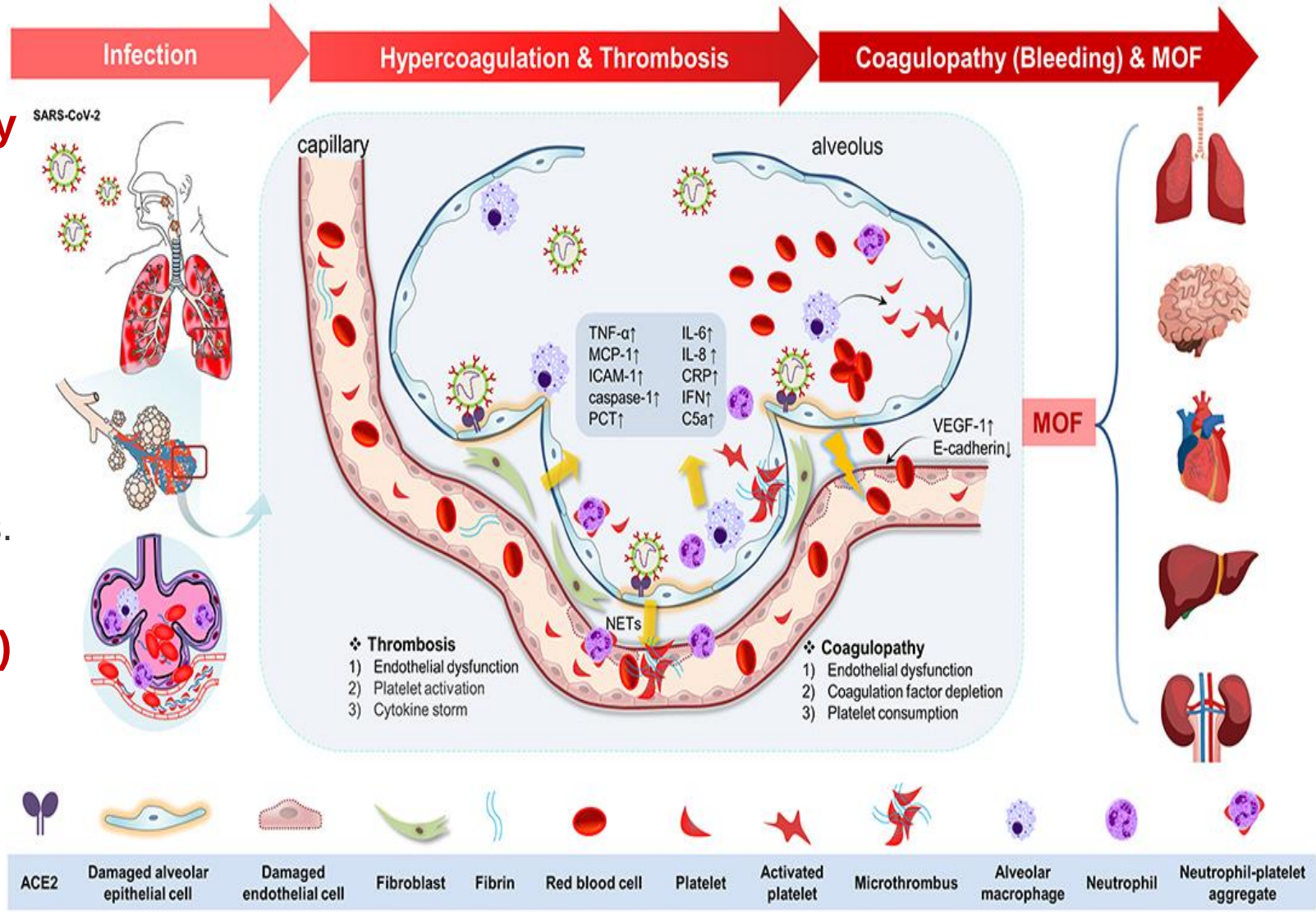
Mechanisms of immunothrombosis and VTE in COVID-19

COVID-19-associated coagulopathy (CAC):

- pathology,
- endothelial dysfunction and haemostasis,
- the immune system and thrombosis,
- genetic associations and
- additional thrombotic mechanisms.

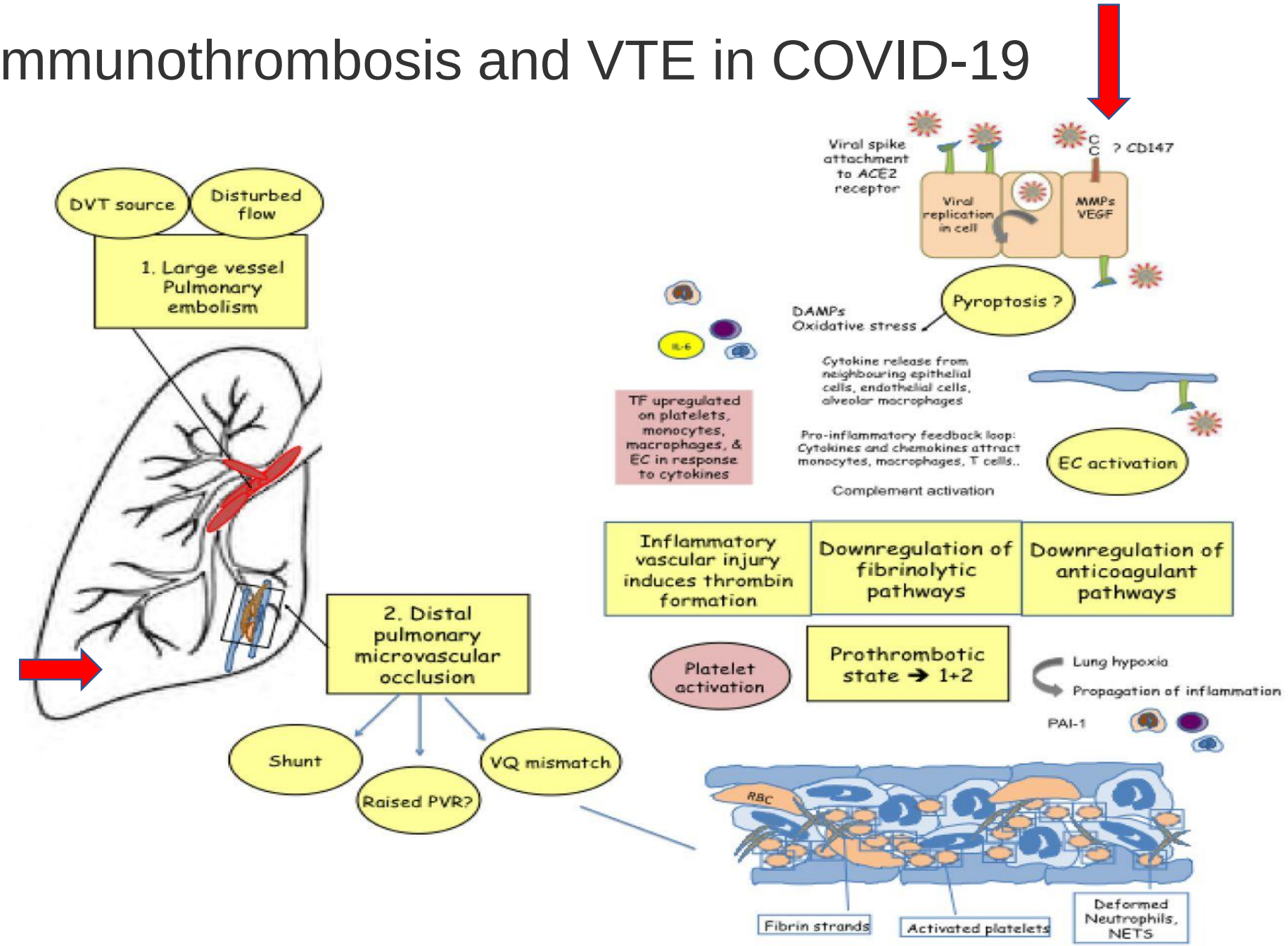
Sepsis-induced coagulopathy (SIC)

Disseminated intravascular coagulation (DIC)



Mechanisms of immunothrombosis and VTE in COVID-19

- SARS-CoV2 binds to ACE2 receptors on type II pneumocytes and possibly on vascular endothelial cells and causes **lysis of the cells** (pyroptosis - *pro-inflammatory apoptosis*) leading to
- **direct activation of the endothelium** causing **procoagulant activity** and activates **accumulation of fibrin deposits** in pulmonary microcapillary venous vessels.
- The fibrin deposits cause a compensatory mechanism of **increased plasminogen at the beginning** but as the disease progresses fail to break down the fibrin deposits reflected in increased d-dimer levels.



Mechanisms of immunothrombosis and VTE in COVID-19

Pathological changes in COVID-19:

- diffuse alveolar damage,
- activation of type II pneumocytes,
- hyaline membrane formation and
- fibrin deposition;

} changes consistent with ARDS

Distinctive pulmonary microvascular abnormalities:

- intravascular fibrin deposition,
- perivascular monocyte infiltration,
- angiogenesis and
- microthrombi formation.

The microvascular changes in COVID-19 are more pronounced than in H1N1-infected lungs, suggesting disease-specific effects rather than epiphenomenon of ARDS or viral pneumonia.

The ACE2 receptor is widely expressed by different cells and SARS-CoV-2 has been detected in the kidneys, liver, heart and brain, which may account for extrapulmonary thrombotic complications along with the ubiquitous presence of endothelium in different organs.

Endothelial dysfunction in COVID-19.

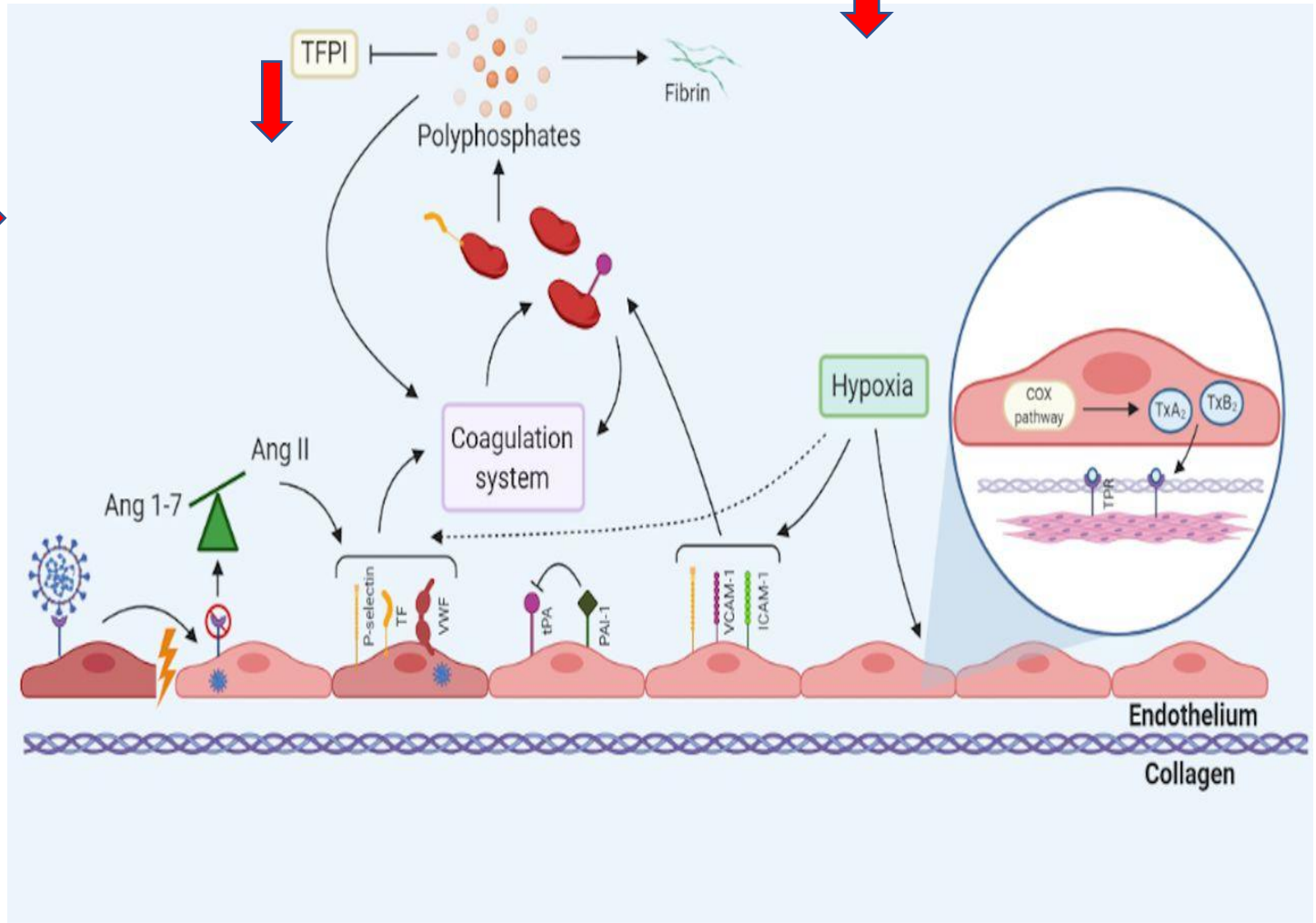
Internalisation of the ACE2 receptor causes accumulation of AngII that promotes the endothelial expression of

- P-selectin,
- tissue factor (TF) and
- von Willebrand factor (VWF).

Expression of these **prothrombotic proteins** activates the extrinsic coagulation cascade. **Recruitment of platelets** contributes to hypercoagulability. **Polyphosphates** are secreted by activated platelets and promote the activation of coagulation factors.

- inhibit tissue factor pathway inhibitor (TFPI) and
- encourage fibrin polymerisation.

Local hypoxia exacerbates the prothrombotic phenotype. **Hypoxia-induced activation of the cyclooxygenase (COX) pathway** releases thromboxanes A_2 and B_2 (TxA_2 and TxB_2, respectively). TxA_2 and TxB_2 bind to thromboxane prostanoid receptors (TPRs) present on smooth muscle cells, resulting in vasoconstriction.



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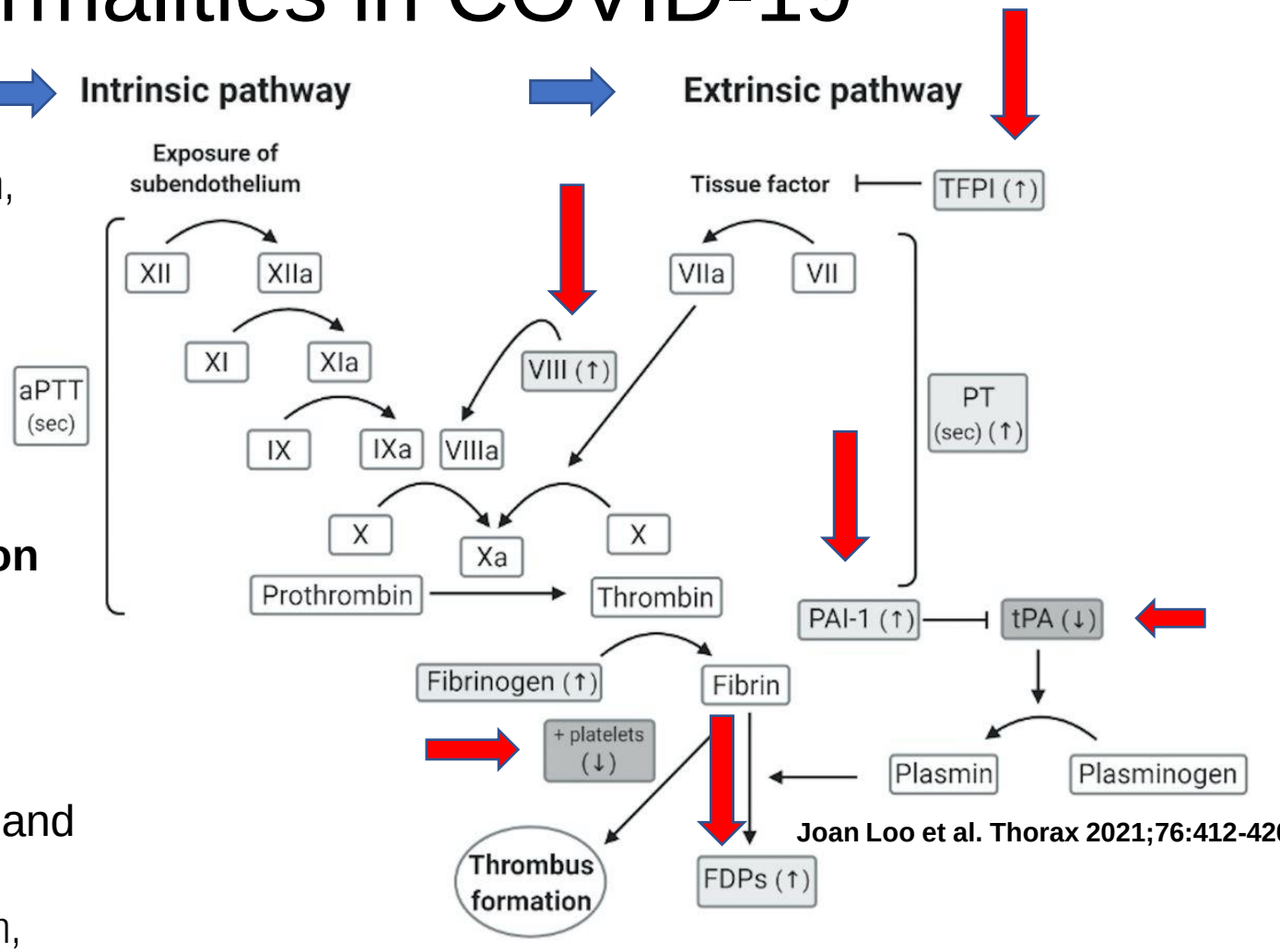
Clotting cascade abnormalities in COVID-19

- Tissue factor, usually hidden on the subendothelium, is upregulated on platelets, leucocytes and EC during inflammation, leading to activation of both the extrinsic and intrinsic coagulation pathways to make thrombin and conversion of fibrinogen to fibrin which, together with platelet aggregates, forms blood clots.
- In COVID-19, **tissue factor pathway inhibitor (TFPI), factor VIII, fibrinogen, plasminogen-activator inhibitor-1 (PAI-1) and fibrin degradation products (FDPs)** have been shown to be elevated.
- Mild **prolongation of PT** in CAC (particularly in severe disease) could signify activation of the TF (extrinsic) pathway.
- Studies have shown **reduced platelet numbers** and **levels of tPA** in COVID-19.
- Endogenous anticoagulant levels (α2-antiplasmin, protein C/S, antithrombin) are normal in COVID-19, which is further evidence that CAC is distinct from DIC.

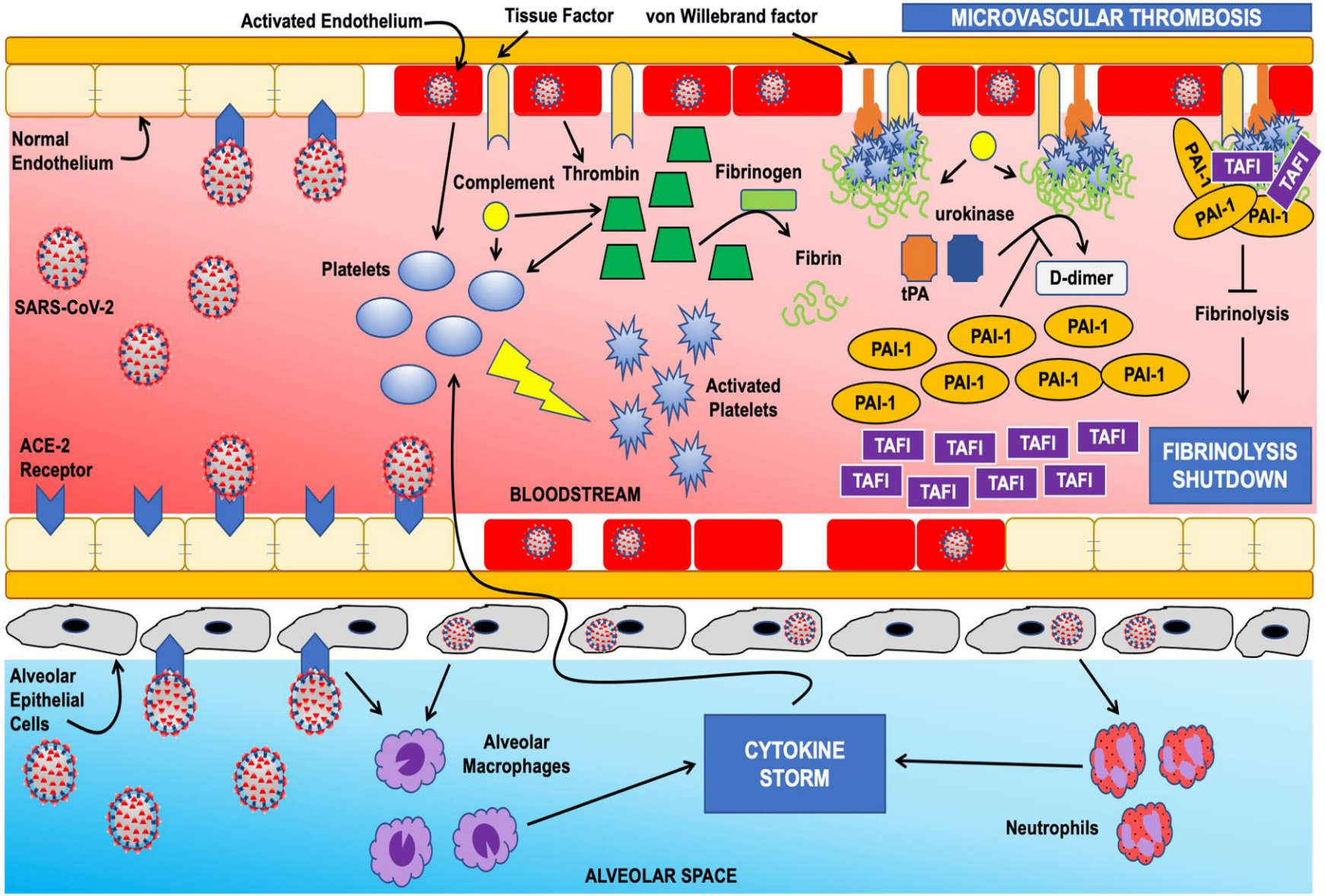


Joan Loo et al. Thorax 2021;76:412-420

Components of the clotting cascade that are abnormal or putatively associated with COVID-19, particularly severe disease, are shown in shaded symbols. Elevated parameters are indicated with a ↑ symbol, decreased parameters with a ↓ symbol.

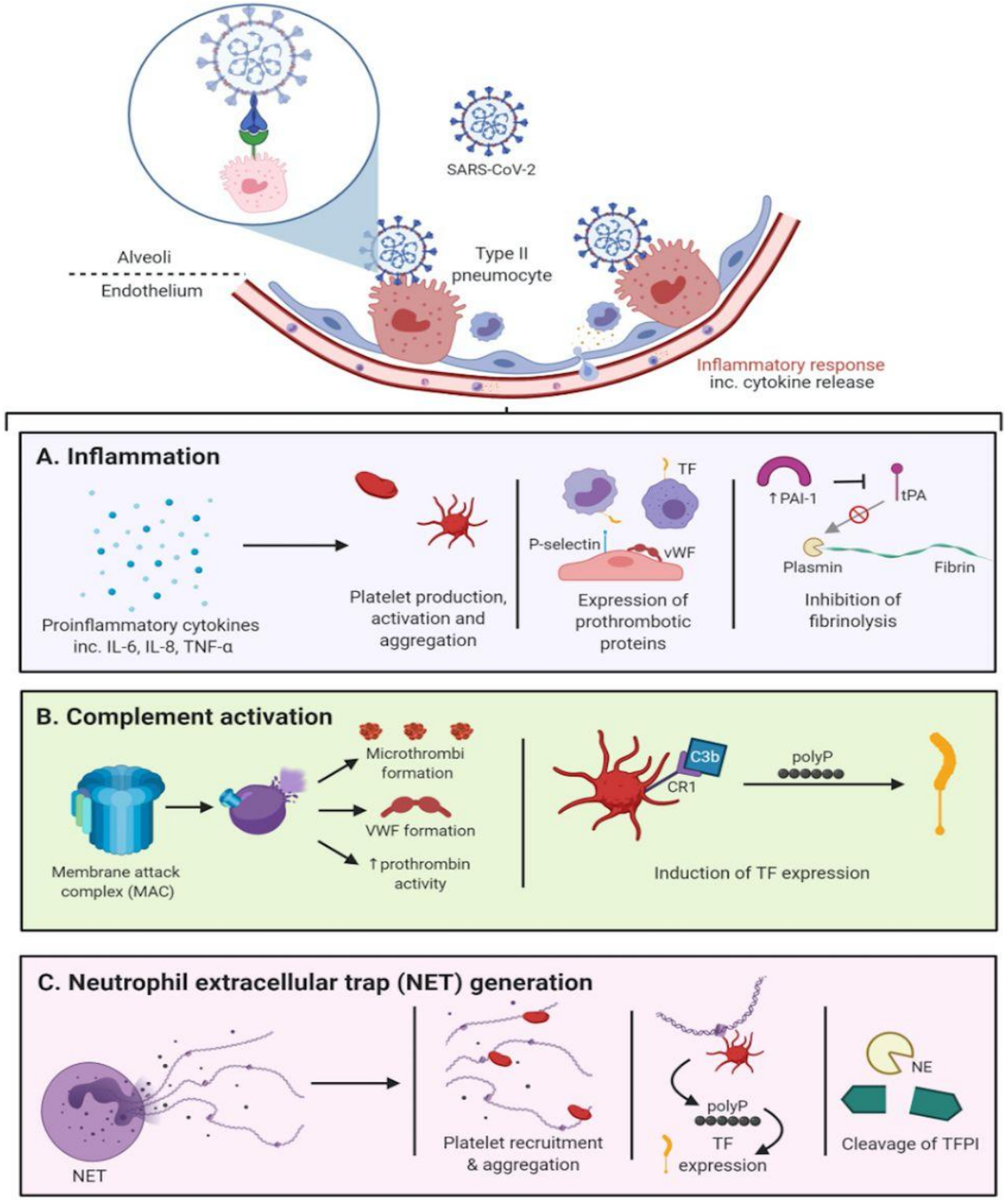
Fibrinolysis in COVID-19

- The **fibrinolytic inhibitor plasminogen activator inhibitor 1 (PAI-1) is increased** in COVID-19, SARS-CoV-1 infection suggesting a role in disease pathobiology and progression that is not only related to ARDS.
- **Complement is also activated**.
- **Inflammation promotes PAI-1 release from endothelial cells**, which **suppresses urokinase-plasminogen activator and tissue-type plasminogen activator (tPA)** from converting plasminogen to plasmin, which ultimately leads to **reduced fibrin degradation**.



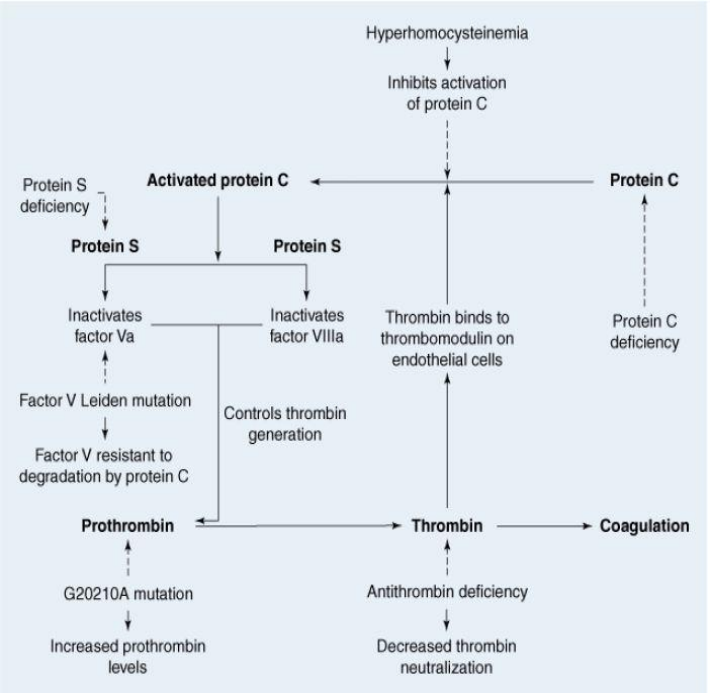
The immune system and thrombosis in COVID-19

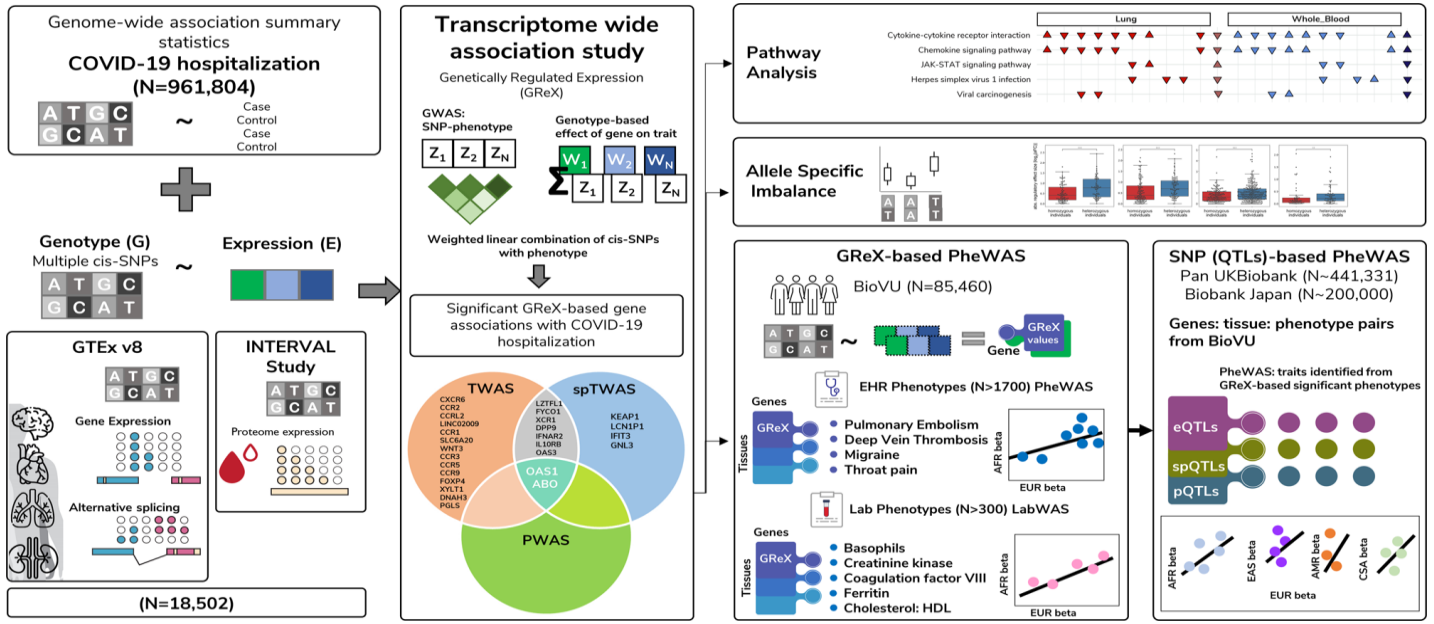
- **Proinflammatory cytokine release** induce the *release of platelets* and their activation and aggregation (IL-6), TNF-α and IL-6 *upregulate tissue factor (TF) expression* by a number of different cell types, TNF-α triggers a *rise in plasminogen-activator inhibitor-1* (PAI-1),
- **Complement activation** is an important inducer of coagulation; MACs initiate the cell lysis of the target cell, which contributes to coagulopathy by initiating *microthrombi and von Willebrand factor (VWF) formation*, as well as *increasing prothrombin activity*.
- The generation of **neutrophil extracellular traps (NETs)**, as a defence mechanism by neutrophils, also promotes coagulation. Histones, a major component of NETs, *attract and bind platelets* resulting in their aggregation. Activation of platelets, as a result of their binding to histones, induces TF expression.



COVID-19 and VTE genetic associations

- VTE is a polygenic disease associated with common and rare genetic variants including **heritable thrombophilias** (factor V Leiden, prothrombin mutations and antithrombin, protein C/S deficiencies).
- A genome-wide association study (GWAS) of patients with severe COVID-19 identified genetic associations in the **ABO gene and in a chromosome 3 locus (3p21.31)** spanning several genes (SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6 and XCR1).
- **Genetic variation in ACE2 / TMPRSS2** may influence COVID-19 susceptibility but this requires validation.
- **Genetic variation in HLA** could affect immune response by varying the affinity for SARS-CoV-2 binding.
- Furthermore, rare variants in **genes related to type I IFN immunity** are enriched in severe COVID-19.

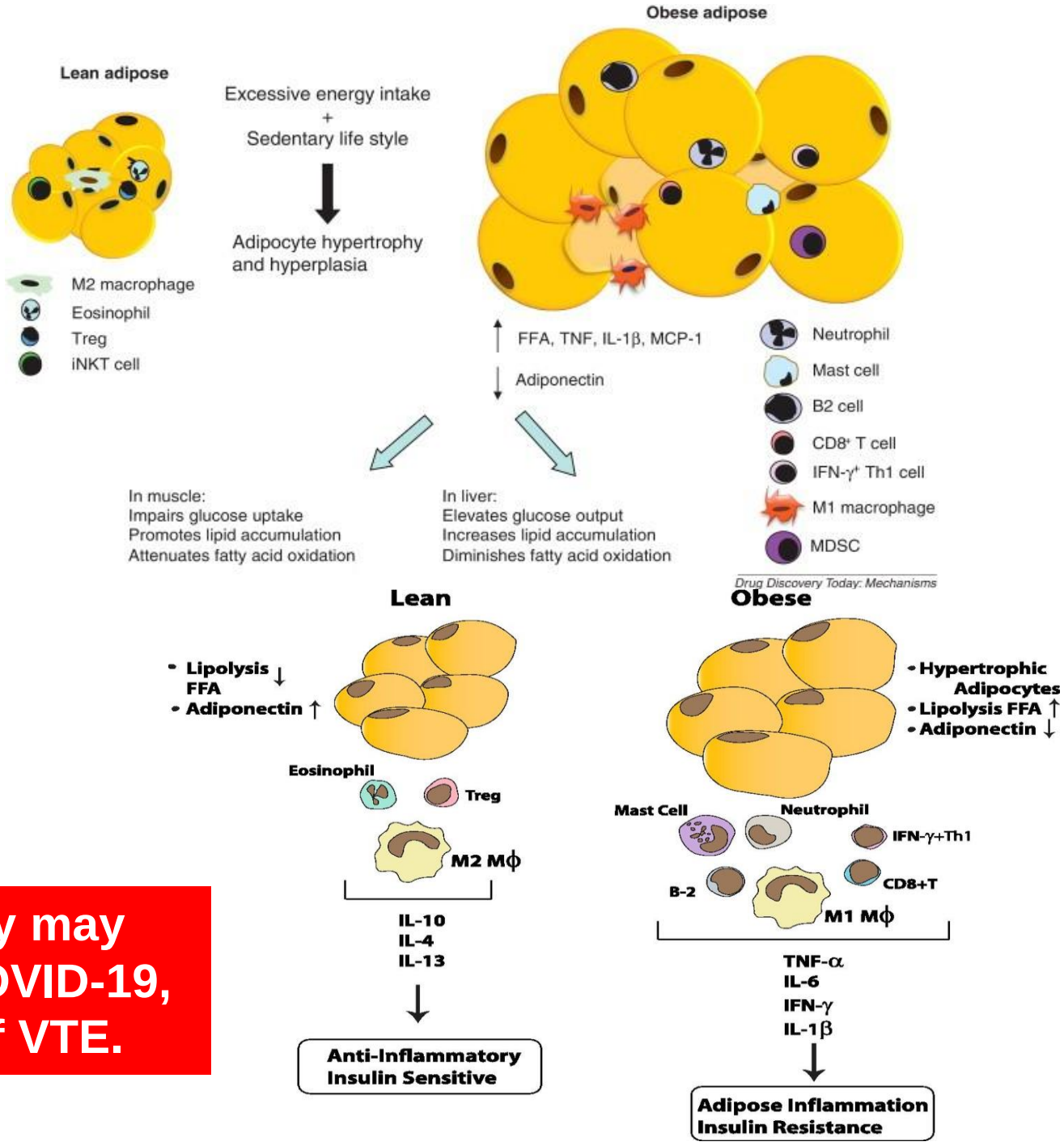




Additional thrombotic mechanisms

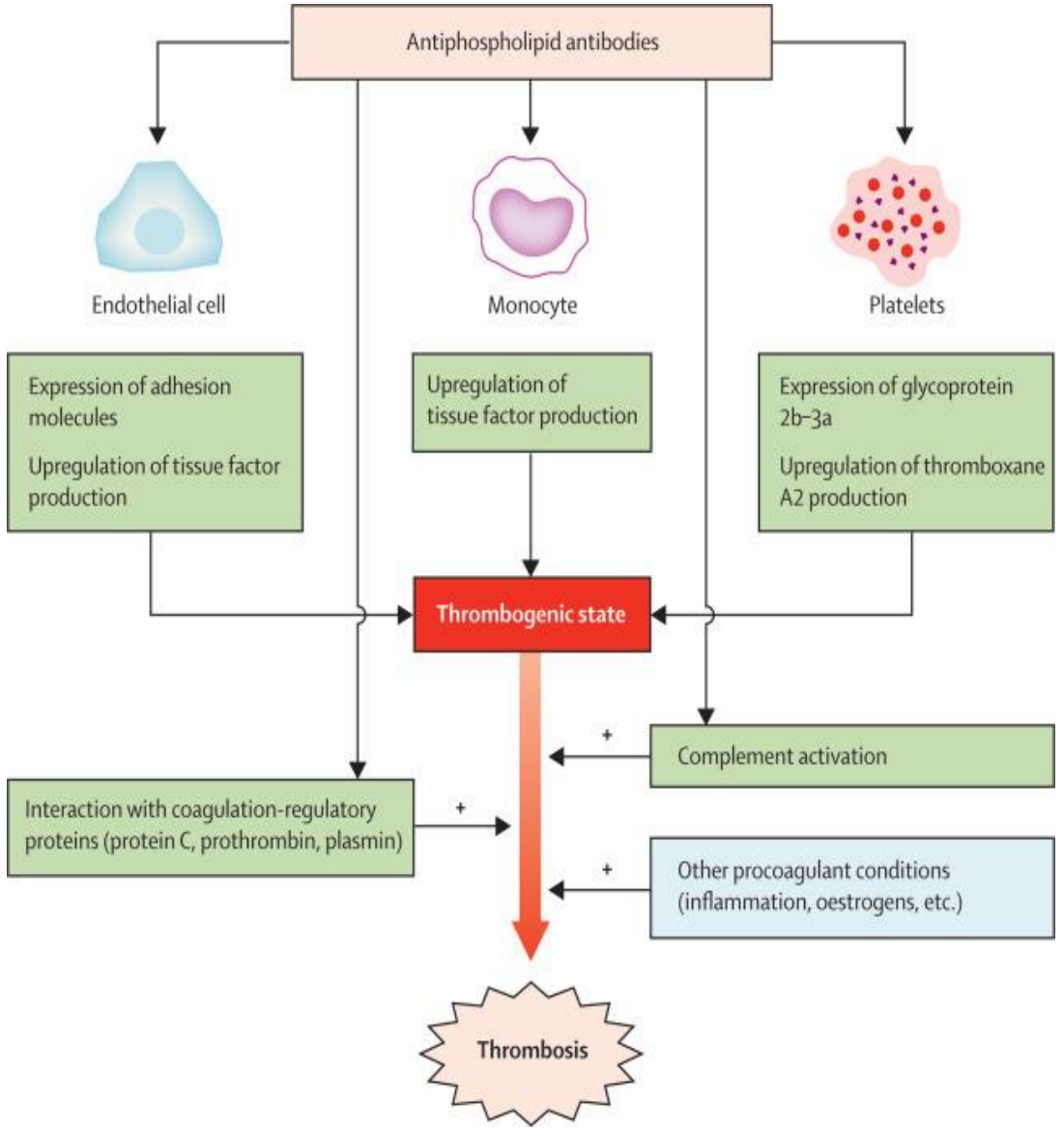
- Hypertrophic adipocytes induce an inflammatory state.
- The associated dysfunction in adipose metabolism causes the release of **IL-6, PAI-1 and TF**, which activate the coagulation system.
- **Platelet aggregation** is also promoted with the decreased release of adiponectin and increased release of leptin.
- **Insulin resistance**, associated with obesity, also reduces the modulatory effect that insulin appears to have on platelet activity.

The inflammatory state in obesity may account for its association with COVID-19, and result in an increased risk of VTE.



Additional thrombotic mechanisms

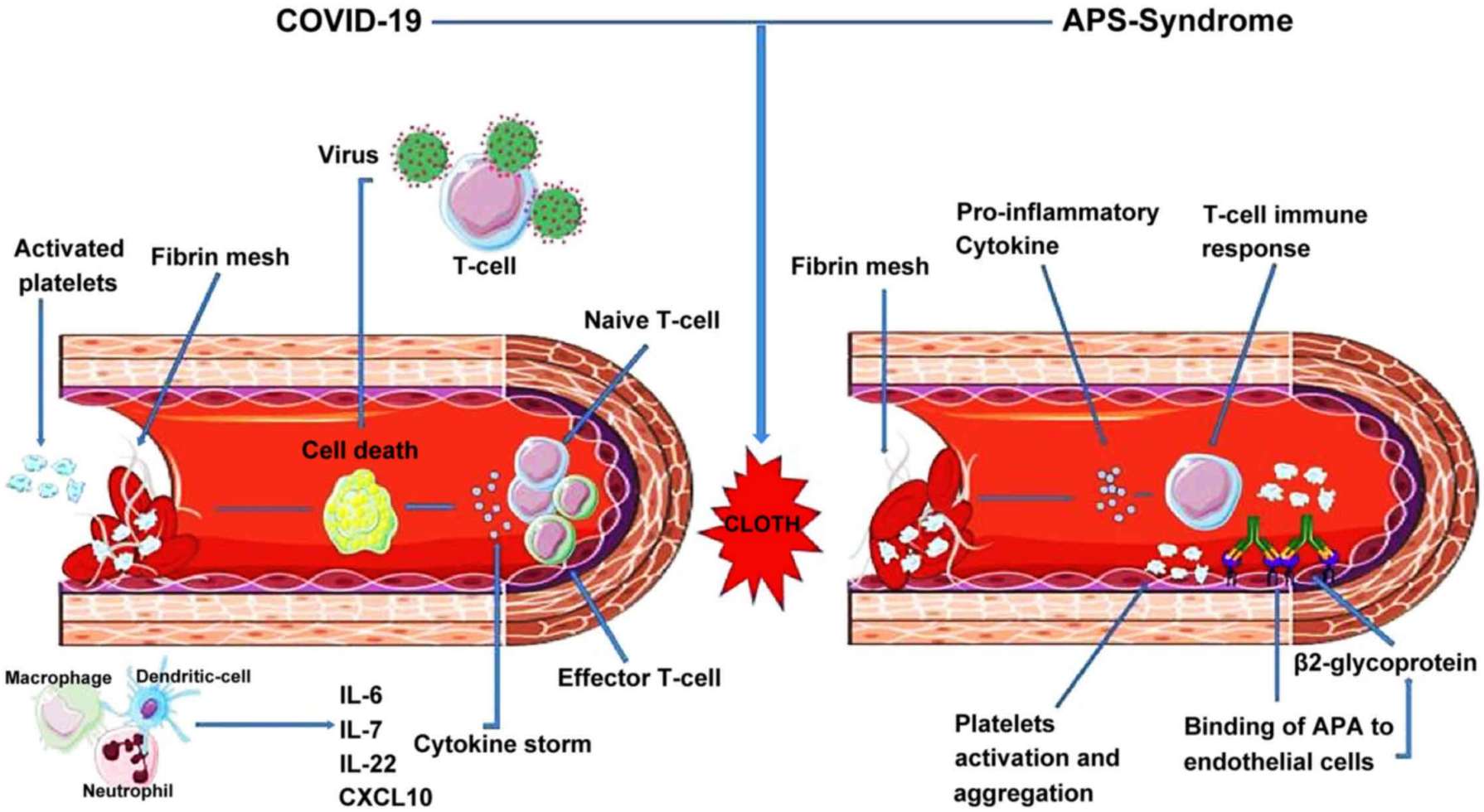
- **Increased levels of ferritin** in COVID-19 are likely to reflect cellular damage and could contribute to inflammation. High levels of ferritin may have detrimental effects on mitochondria, leading to the release of reactive oxygen species, which cause cell death. *Mitochondrial dysfunction in platelets may contribute to inflammation and a prothrombotic state.*
- **Elevated antiphospholipid antibody (APA)** titres have been described in COVID-19. APAs can interact with the endothelium, leucocytes and platelets, triggering the release of prothrombotic factors and can also interact with the complement system. *APAs can be raised in acute infection, and a diagnosis of antiphospholipid syndrome requires APAs to be measured on two separate occasions 12 weeks apart, which needs confirmation before being implicated in COVID-19 pathophysiology.*



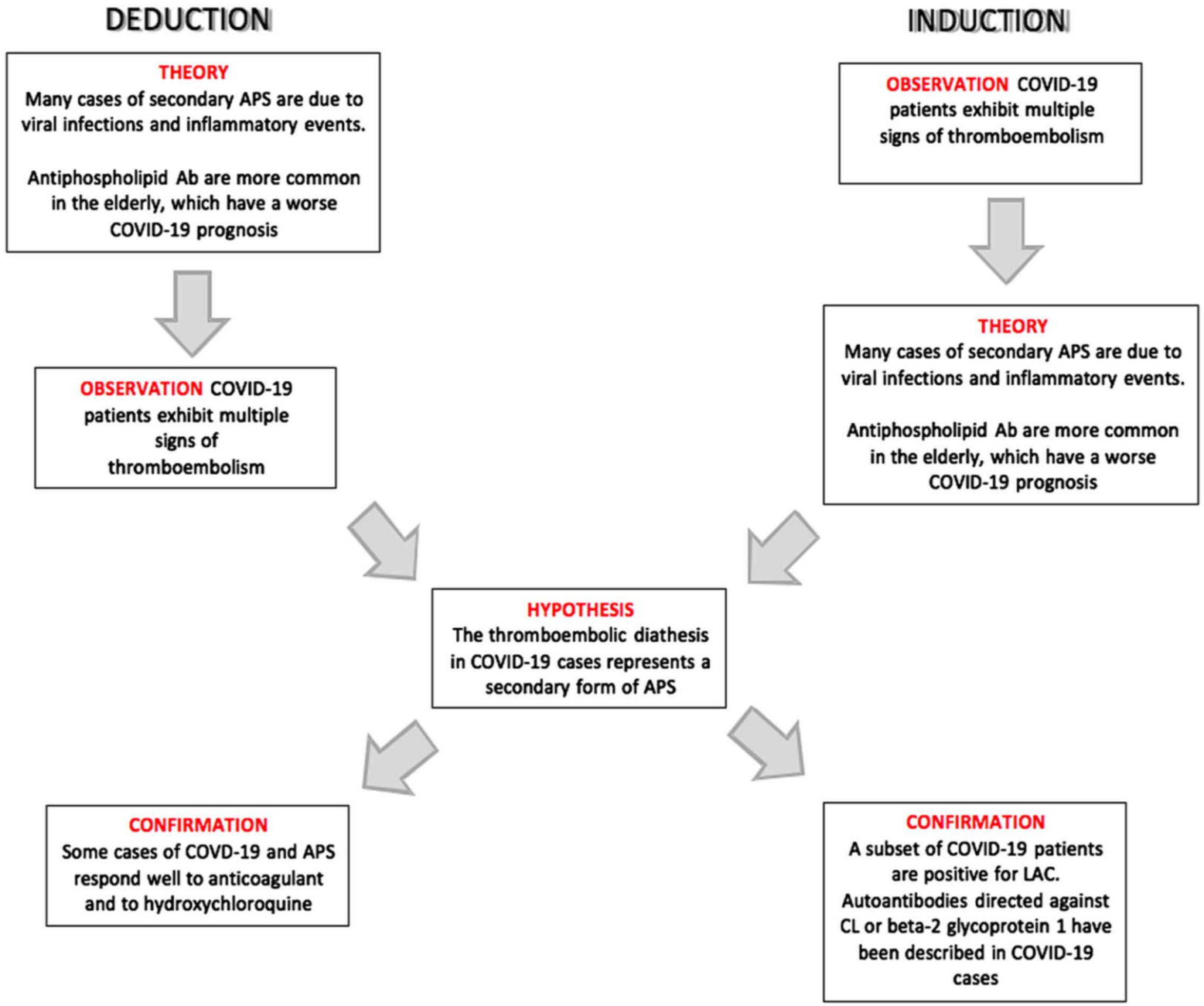
Can immunothrombosis during COVID-19 and APS be the same face of two different coins?

The 3 main culprits responsible for activating immunoinflammatory responses and thrombosis appear to be the same in both diseases, namely:

- **upregulated cytokine secretion** from cells of the innate immune system and activated macrophages,
- **thrombus formation** and
- **complement activation**.



Understanding if and to what extent COVID-19 infection **induces different production of aPL Abs** in population is of great relevance as the ***temporary or persistent presence*** of these autoantibodies may **increase further the thrombotic risk** and would require particular therapeutic attention for **thromboprophylaxis.**



Areas for future COVID-19 research

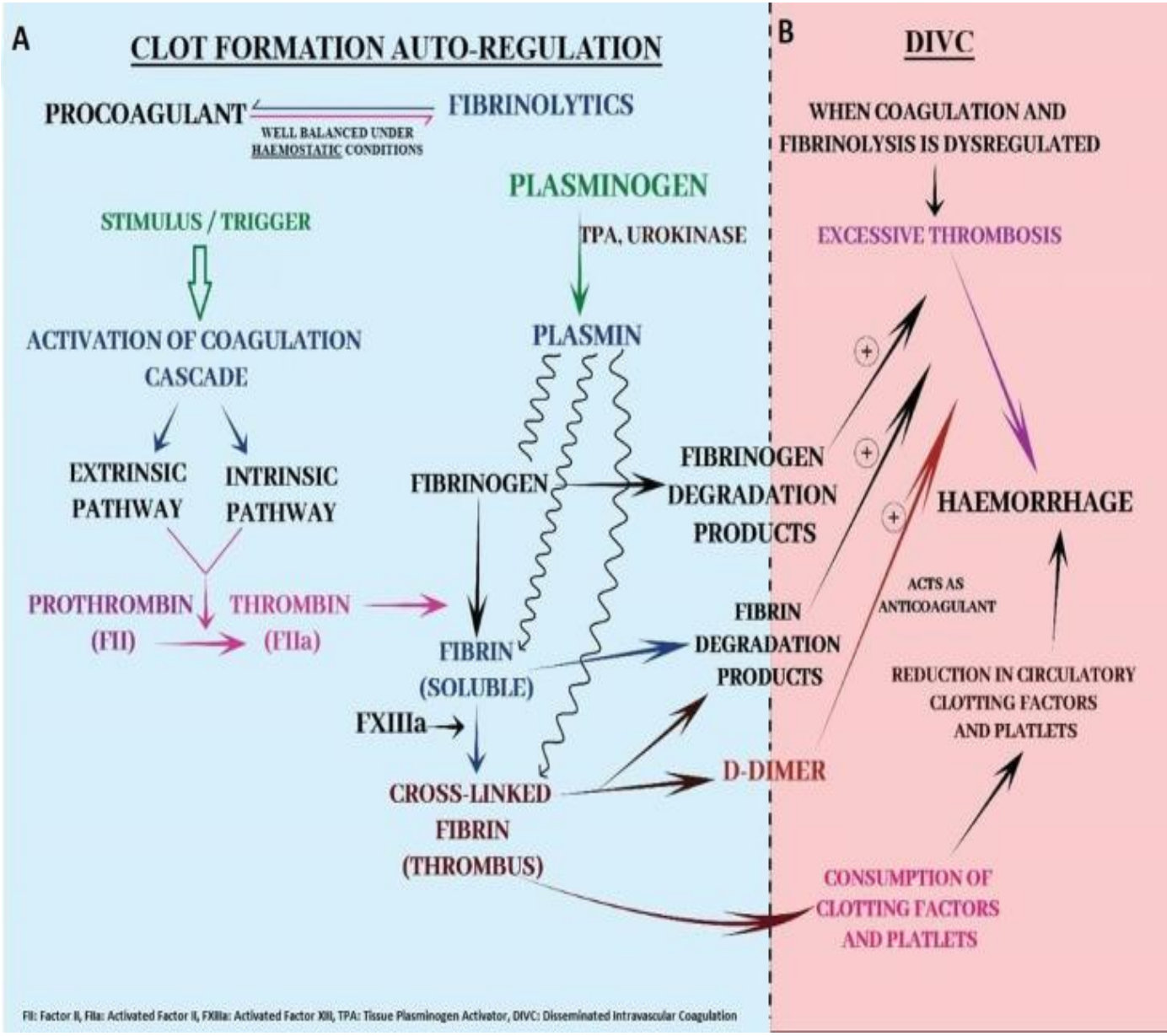
- small pulmonary thromboses represent VTE, immunothrombosis or a combination?
- can diagnostic strategies (eg, radiological, biochemical) accurately diagnose and differentiate between VTE and immunothrombosis?
- can the risk of immunothrombosis be accurately predicted?
- can immunothrombosis be prevented with prophylactic anticoagulation, or treated with anticoagulation?
- developing novel immunothrombosis targeted interventions and defining how other COVID-19 treatments (eg, dexamethasone) affect immunothrombosis/VTE in COVID-19.

Disseminated intravascular coagulation (DIC)

- advanced stage of immuno-thrombosis, where the immune system is no longer able to restrict intrinsic associated molecular patterns and immuno-thrombosis becomes overwhelming.
- thrombosis is detrimental because it can cause multiple organ failure.

When compared to DIC of other etiologies such as malignancies or sepsis, **low platelet count and prolonged PT** are rarely seen in COVID related coagulopathy. *In sepsis-associated DIC a more severe thrombocytopenia is observed, much lower levels of clotting factors and marked decreased plasma concentrations of coagulation inhibitors, such as antithrombin and protein C.*

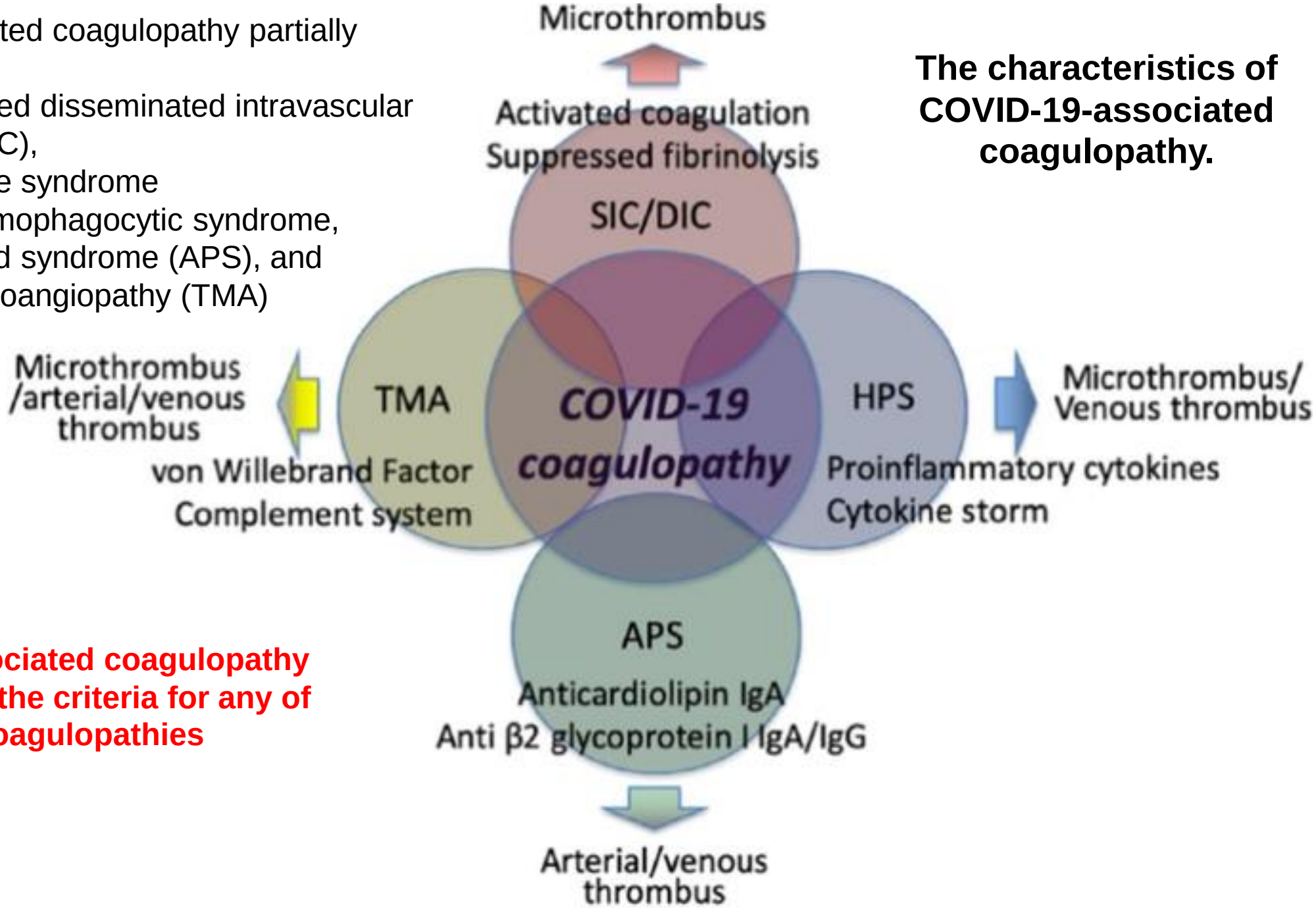
Martin-Rojas et al demonstrated a very **low percentage (5.3%) of patients with COVID-19 that met the ISTH criteria for DIC.**



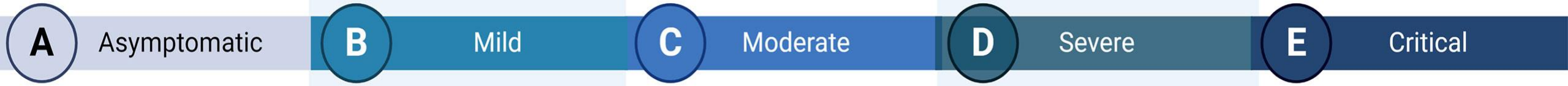
COVID-19-associated coagulopathy partially overlaps with:

- infection-induced disseminated intravascular coagulation (DIC),
- cytokine release syndrome (CRS/HPS)/hemophagocytic syndrome,
- antiphospholipid syndrome (APS), and
- thrombotic microangiopathy (TMA)

The characteristics of COVID-19-associated coagulopathy.



COVID-19-associated coagulopathy does not meet the criteria for any of these coagulopathies



Clinical Manifestations

Absence of clinical manifestations

Fever, dry cough, sore throat, runny nose, sneezing, fatigue, myalgia, tiredness, muscle pain, headache, and smell loss.

Atypical clinical manifestations: nausea, vomiting, diarrhea, abdominal pain.

Symptoms of mild to moderate pneumonia: fever (usually persistent, >37.8°C), dry cough, dyspnea, fast breathing, SpO_2 ≥90% on room air.

Dyspnea, hypoxia, >50% lung involvement, diarrhea, vomiting, nausea, and one of the following manifestations: respiratory rate >30 breaths/min; severe respiratory distress; or SpO2 <90% on room air. Patients show clinical worsening.

Severe shortness of breath, chest pain, movement impairments, loss of speech. Patients show clinical worsening.

Complications: Acute respiratory distress syndrome or respiratory failure, myocardial injury, arrhythmia, heart failure, acute kidney injury, acute liver injury, encephalopathy, disseminated intravascular coagulation, rhabdomyolysis, septic shock, multiple organ dysfunctions.

Frequency

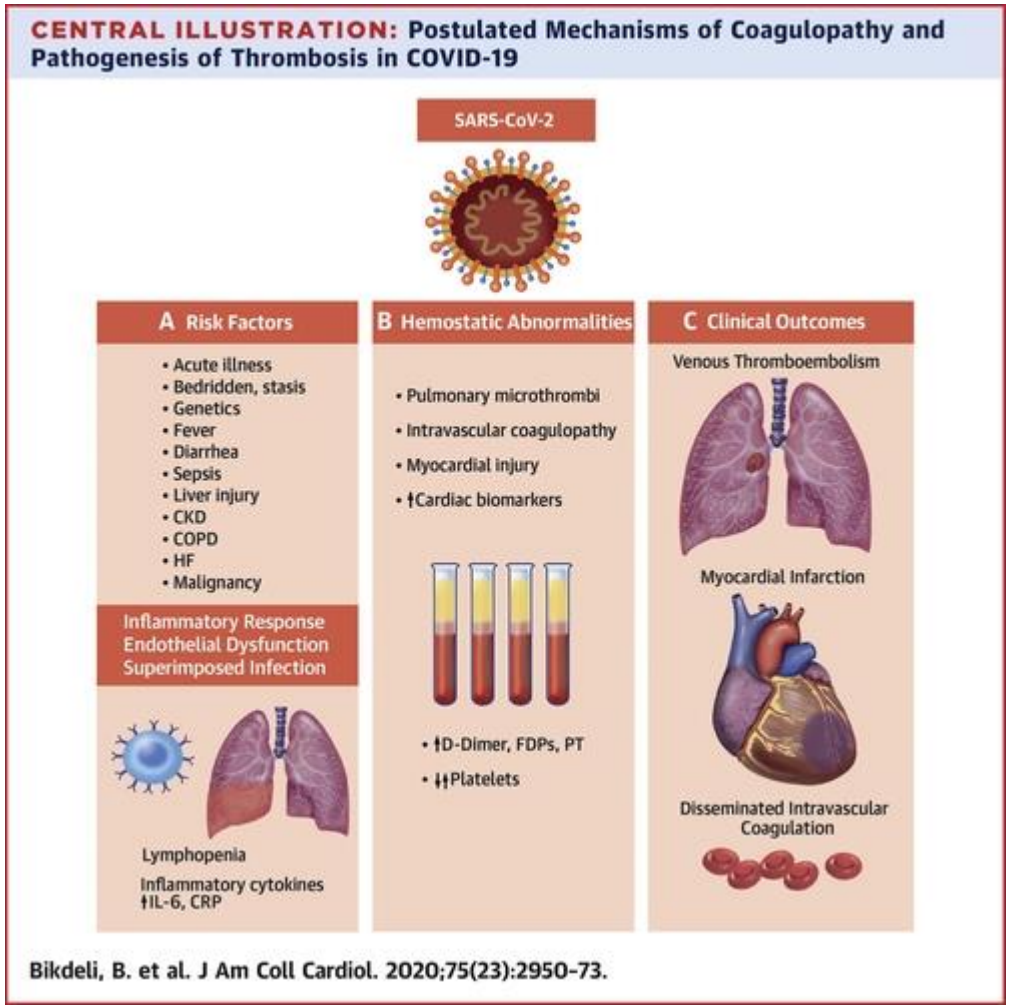
Table 1 Blood markers of coagulation, fibrinolysis and inflammation in COVID-19

Blood test	Direction of change	Comparator (case vs control)	Reference(s)
D-dimer	↑	Severe versus non-severe	17
Fibrinogen	↑	ICU versus ref range	16
Platelets	→ / ↓	Severe versus non-severe	17 101
aPTT	→	Severe versus non-severe	17 90
PT	→ / ↑	Severe versus non-severe	17 102
Antithrombin	→ / ↑	COVID-19 versus healthy control	103
PAI-1	↑	Autopsy versus ref range	43
Leucocytes	↑	Severe versus non-severe	17
Lymphocytes	↓	Severe versus non-severe	17
Neutrophils	↑	Severe versus non-severe	17
Factor VIII	↑	ICU versus non-ICU	39
VWF	↑	ICU versus non-ICU	39
Soluble P-selectin	↑	ICU versus non-ICU	39
CRP	↑	Severe versus non-severe	17
Procalcitonin	↑	Severe versus non-severe	17 90
Ferritin	↑	Severe versus non-severe	90
Complement	↑	Autopsy versus ref range	64

Arrows indicate the direction of change (↑=increase, ↓=decrease, →=no change) in COVID-19 with respect to a control group or reference range defined in the comparator column. The magnitude of change (ie, marked increase vs mild increase) is not indicated in this table.

Overview

- Standard thromboprophylaxis for medical inpatients (pre-COVID era)
  - VTE risk and standard LMWH dosing
  - Weight adjusted LMWH dosing
  - Role of mechanical thromboprophylaxis
- The concern with COVID – is this enough?
  - Rate of VTE in patients with COVID
- Interim guidelines
  - Risk stratification

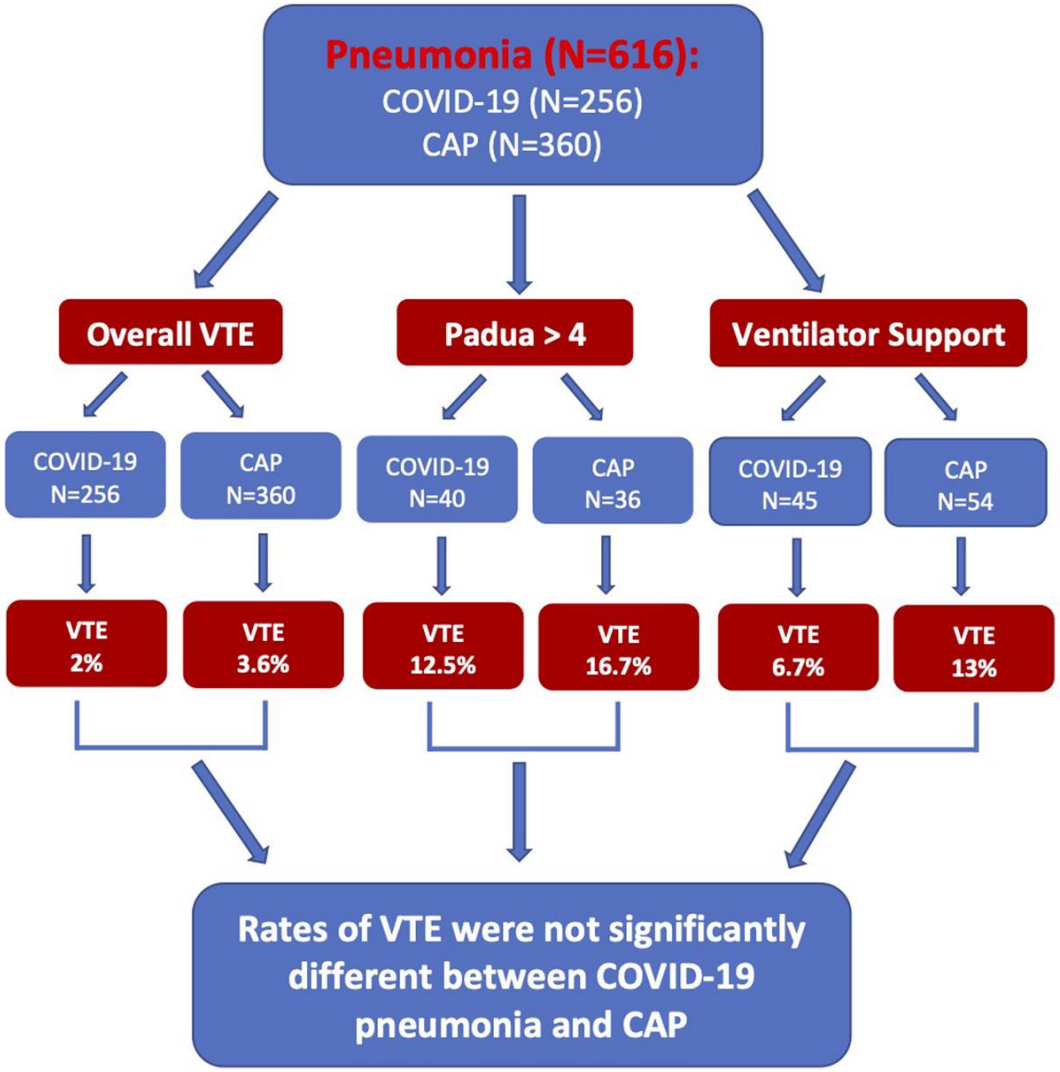


SCORING SYSTEM	POPULATION AT RISK	# OF INPUTS/ VARIABLES	OUTPUTS AND RISK CATEGORIES	LOWEST RISK CATEGORY	HIGHEST RISK CATEGORY	COMMENTS
CAPRINI (2005)	Surgical Patients	>30	Risk of VTE at 3 months	Lowest risk <0.7% (0 points)	Highest risk 10.7% (≥ 9 points)	No formal validation with original study. External validation studies in surgical subpopulations [115-119]. Meta analysis: approximately 14-fold variation in VTE risk across 11 studies [118].
Padua Prediction Score	Medical Inpatients	11	Risk of VTE at 3 months	Lowest Risk 1.1% (<4 points)	Highest risk 3.5% (≥ 4 points)	Internal validation showing 32-fold variation in VTE (without prophylaxis) [125]. An external validation in patients with sepsis did not find correlation with VTE risk [126].
IMPROVE Score	Medical Inpatients	7	Risk of VTE at 3 months	Lowest Risk 0.4% (0 points)	Highest risk 5.7% (≥ 4 points)	Validation includes 1 retrospective, 1 case control, and 1 prospective multicentre study* [120,128,129]
Khorana Score	Ambulatory Cancer patients	5	Risk of VTE at 2.5 months	Lowest risk 0.8% (0 points)	Highest risk 7.1% (≥3 points)	Internal development and validation cohort included in original study† [165]. Multiple prospective and retrospective validation studies [166,167].

* AUC 0.69-0.77 for predicting VTE

† Negative predictive value 98.5%, Positive predictive value 6.7%, C-statistic = 0.7

Incidence of VTE in the patient with Covid-19 pneumonia



Cohort studies in COVID-19 - ICU alone

Study	Key points	Thrombosis rate (VTE+arterial)
Klok et al Netherlands	**184 patients**	31% @ 7 days
April 2020 Throm Res	100% received TP: at least standard dose, dose increased over time Median f/u 14 days	**41% @14 days** **35% PE** **2% other VTE** **4% arterial**
	35% still hospitalised	
Helms et al France	**150 patients**	**42.6%**
April 2020 Intensive Care Medicine	100% received TP: 70% prophylactic, 30% therapeutic Median f/u not stated 67% still intubated	**PE 16.7%** **DVT 2%** 2.7% arterial 18.7% RRT filter clotting 2.7% major bleed
		Comparison to historical non-covid ARDS: more PEs 11.7 v 2.1%

Cohort studies in COVID-19: ICU and non-ICU

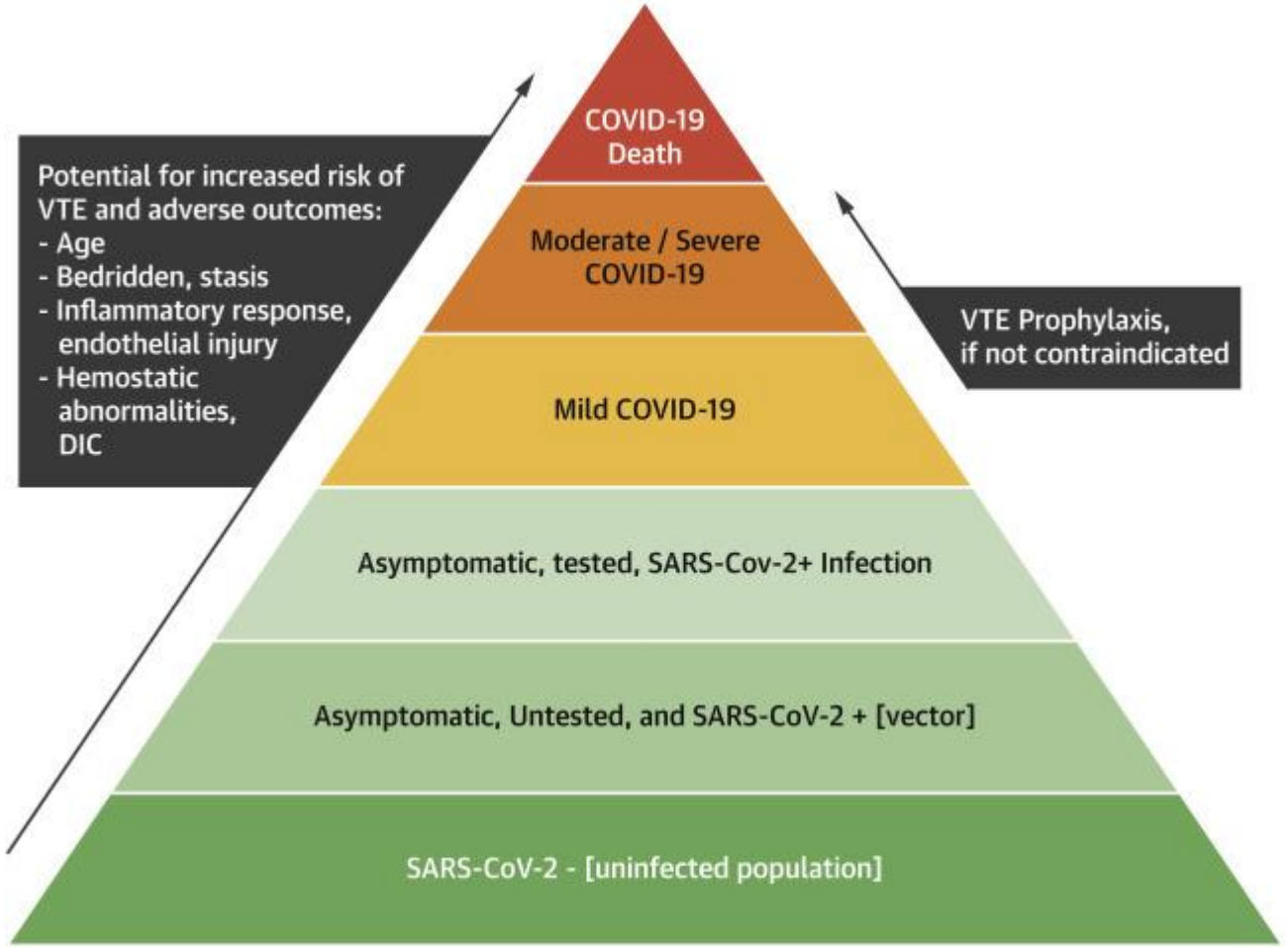
Study	Key points	Thrombosis rate
Middledorp et al	**ICU/non-ICU**	All VTE 20%
Netherlands	**75/123**	Symptomatic VTE 13%
May 2020 JTH		
Standard dose TP doubled for ICU during study, not associated with reduced risk of VTE 	USS screening in 25% 95% received TP Median f/u 7 days (ICU 15; ward 4 days) 8% still hospitalised	**PE 6.6%** **DVT 13%** ICU v ward HR 3.9 VTE was associated with death HR 2.3 Bleeding data not described
Lodigiani et al	**ICU/non-ICU**	In closed cases,
Italy	**61/327**	**ICU: VTE 8.3%**
Thromb Res May 2020	TP:100% ICU, 75% ward	**Ward: VTE 3.8%**
	(standard, intermediate,	**Half of VTE diagnosed**
	therapeutic)	**within 24 hours of**
	Median f/u 10 days	**admission**
	7% patients still hospitalised	

Incidence of VTE in the patient with Covid-19 pneumonia

References	The incidence of VTE	Significant laboratory parameter
Middeldorp et al. (14)	ICU patients (26% and 59% at 7 and 21 days) Regular ward patients (5.8% and 9.2% at 7 and 21 days)	D-dimer
Helms et al. (15)	COVID-19-ARDS patients 16.7% Non-COVID-19-ARDS patients 1.3%	D-dimer Fibrinogen
Cui et al. (17)	Severe COVID-19 patients 25%	D-dimer
Lodigiani et al. (24)	ICU patients 27.6% Regular ward patients 7.7%	Not stated
Trimaille et al. (25)	Regular ward patients 17.0% Transfer to ICU (VTE vs. non-VTE, 43.8% vs. 21.33%)	Not stated
Nopp et al. (26)	ICU patients 22.7% Non-ICU patients 7.9%	Not stated
Klok et al. (27)	ICU patients 37%	Not stated
Hippensteel et al. (18)	All the hospitalization patients 26.1%	Not stated
Llitjos et al. (28)	Severe COVID-19 patients 69% Prophylactic Anticoagulation vs. Therapeutic Anticoagulation (100% vs. 56%)	Not stated
Poissy et al. (29)	ICU patients 20.6%	Not stated
Thomas et al. (30)	ICU patients 27%	Not stated

If we ***increase intensity*** / ***duration*** / ***lower threshold*** for thromboprophylaxis, will we:

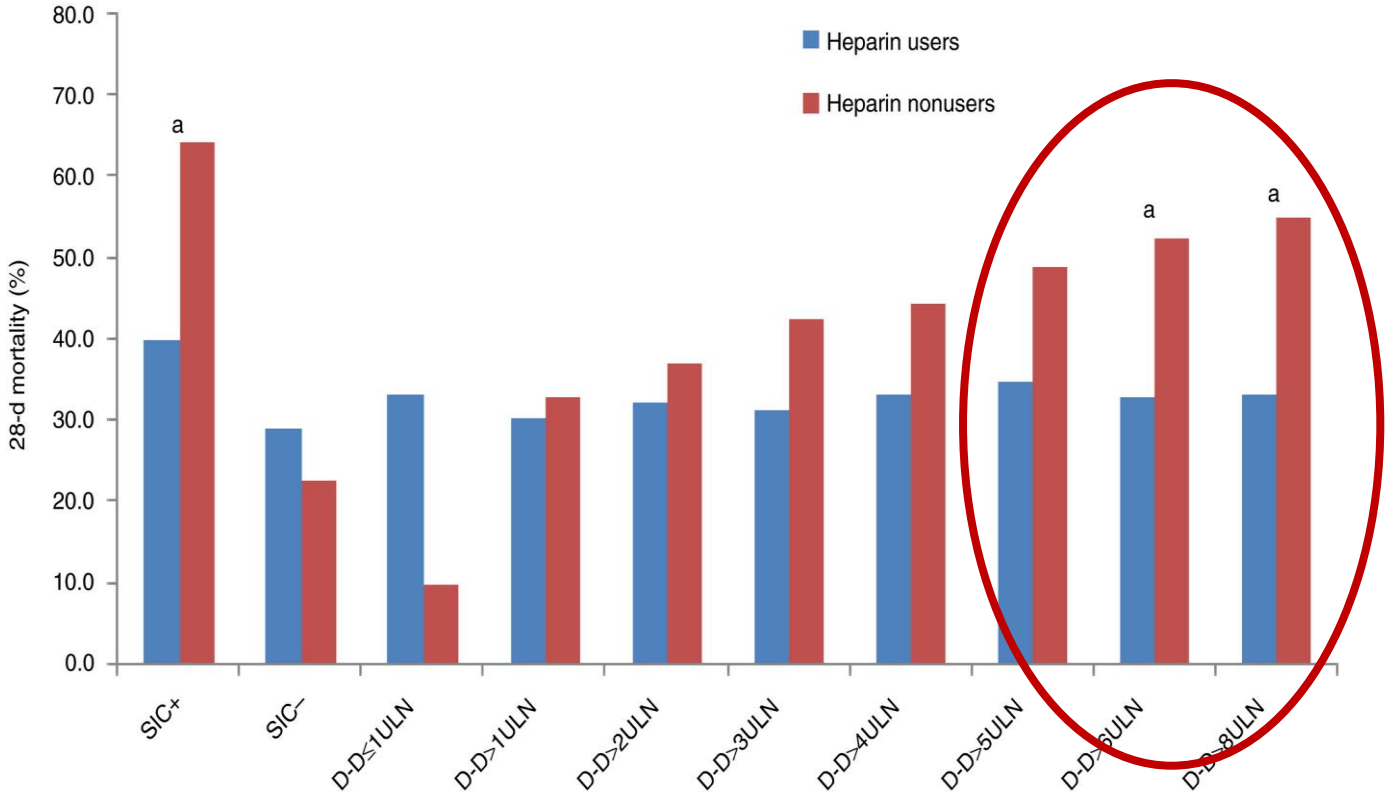
- reduce risk of VTE?
- reduce risk of death?
- and what is risk/benefit with likely increased bleeding risk?



Prophylactic LMWH associated with reduced mortality

- Retrospective observational analysis
  - 449 patients
- 22% of patients received thromboprophylaxis
  - (95% 40-60mg enoxaparin; 5% therapeutic)
- 28 day mortality 30%
  - Overall no difference in mortality between patients given heparin and not
- In patients with ***DDimers > 6x ULN or SIC (sepsis induced coagulopathy) score ≥4***, heparin was associated with reduced mortality
  - mortality 64.2% to 40% (40% RRR)

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

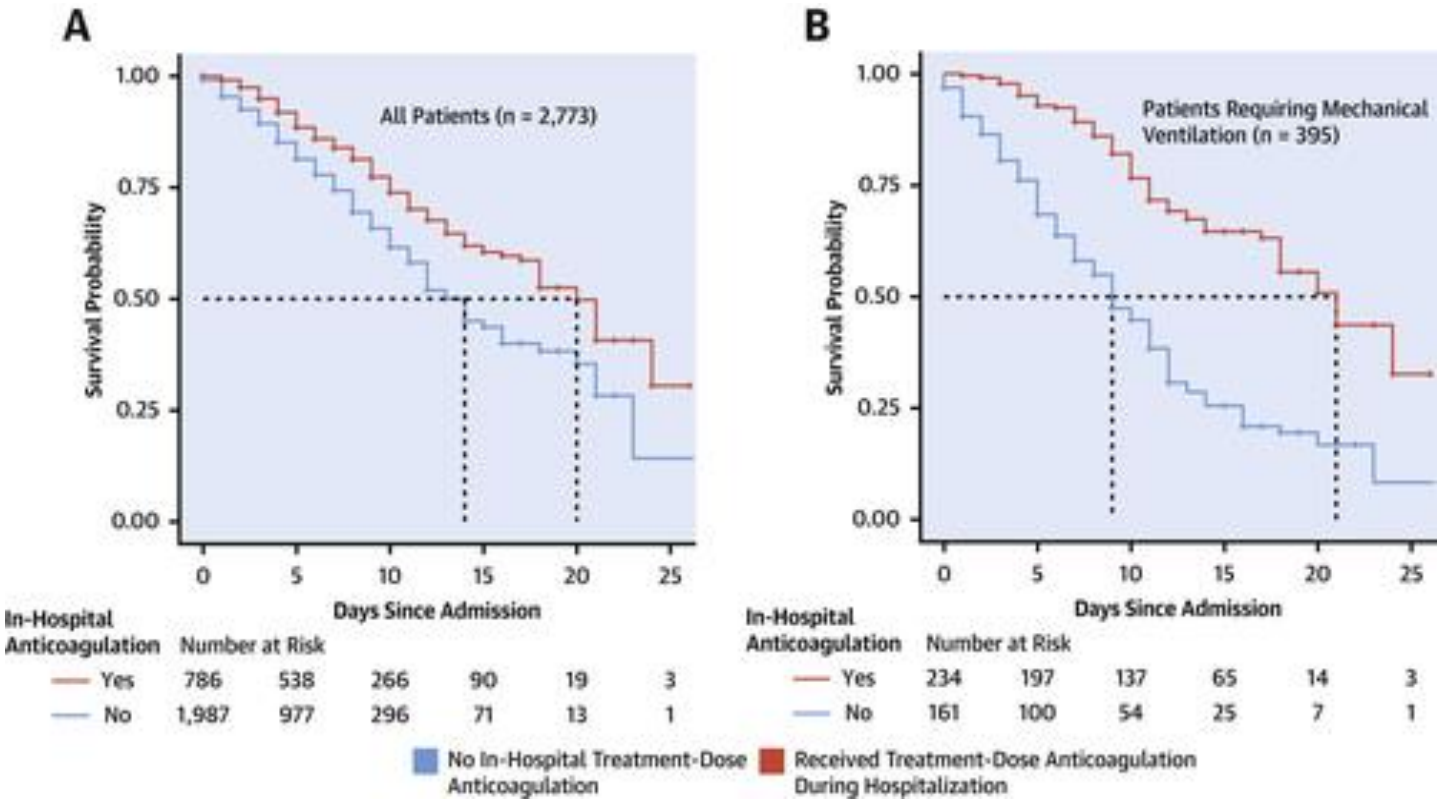


Journal of Thrombosis and Haemostasis, Volume: 18, Issue: 5, Pages: 1094-1099, First published: 27 March 2020, DOI: (10.1111/jth.14817)

Tang et al JTH 2020

Therapeutic anticoagulation associated with reduced mortality?

- 2,773 hospitalized patients with COVID-19 -28% received systemic treatment-dose AC. The median hospitalization duration was 5 days. In-hospital mortality for patients treated with AC was 22.5% with a median survival of 21 days, compared to 22.8% and median survival of 14 days in patients who did not receive treatment-dose AC (**Figure A**).



- In patients who required mechanical ventilation (n = 395), in-hospital mortality was 29.1% with a median survival of 21 days for those treated with AC as compared to 62.7% with a median survival of 9 days in patients who did not receive treatment-dose AC (**Figure B**).

- In a multivariate proportional hazards model, longer duration of AC treatment was associated with a reduced risk of mortality (adjusted HR of 0.86 per day; 95% confidence interval: 0.82 to 0.89; $p < 0.001$).

Ishan Paranjpe et al. *J Am Coll Cardiol* 2020; 76:122-124.

JACC JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Interim guidelines?

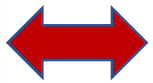
Possible thromboembolic risk stratification in Covid-19

	LOW-RISK COVID-19	HIGH-RISK COVID-19†
HIGH-RISK ACS OR VTE*	**For ACS:** • GDMT per ACS algorithm • Urgent/emergent angiography and intervention • Consider need and safety of hemodynamic support and monitoring **For VTE:** • Anticoagulant therapy • If recurrent symptoms or deterioration, consider systemic thrombolysis or potentially catheter-directed therapy as an alternative • Consider need and safety of hemodynamic support and monitoring‡	**For ACS:** • GDMT per ACS algorithm • Consider emergent TTE • Urgent/emergent angiography and intervention vs. systemic fibrinolysis • Consider need and safety of hemodynamic support and monitoring in select patients **For VTE:** • Anticoagulant therapy • Consider systemic fibrinolysis • Catheter-directed or surgical therapies in case not suitable for systemic fibrinolysis • Consider need and safety of hemodynamic support and monitoring
LOW/INTERMEDIATE RISK ACS OR VTE	**For ACS:** • GDMT per ACS algorithm • Angiography and intervention only if recurrent/persistent symptoms or decompensation **For VTE:** • Anticoagulant therapy • Catheter-directed or surgical therapies only if recurrent/persistent symptoms or decompensation	**For ACS:** • GDMT per ACS algorithm • Other therapies reserved for select cases such as those with significant recurrent/persistent symptoms or decompensation **For VTE:** • Anticoagulant therapy • Other therapies reserved for select cases such as those with significant recurrent/persistent symptoms or decompensation

Possible thromboembolic risk stratification in Covid-19

European data – thrombosis and mortality:

- Higher rates of thrombosis associated with ICU admission
- Higher rates of mortality associated with ICU admission, particularly ventilation.

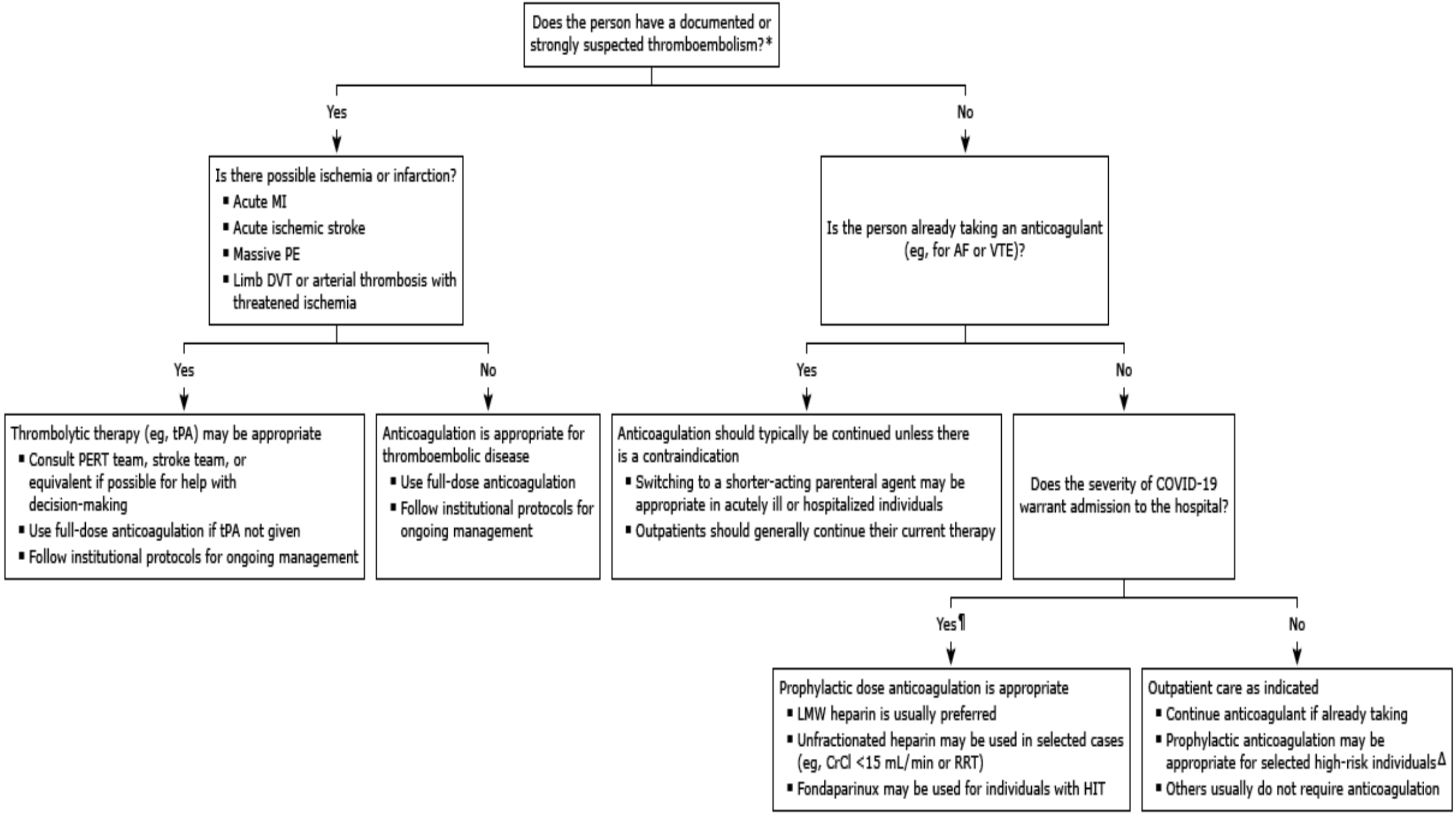


Traditional VTE risk factors

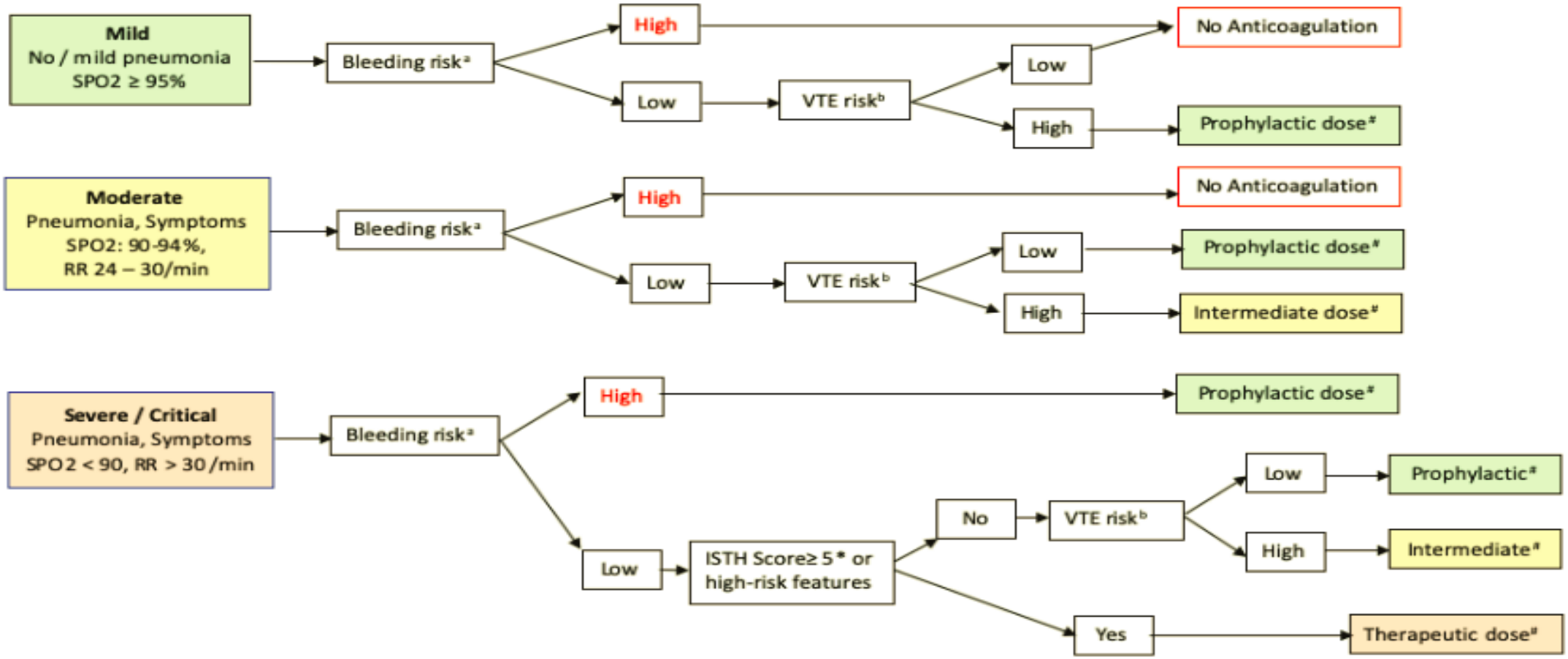
- Previous VTE but not on long-term anticoagulation
- Active cancer

Community

- Hospital assessed ambulatory patients
- Community


Does the person have a documented or strongly suspected thromboembolism?*
Yes
No
Is there possible ischemia or infarction?
Acute MI
Acute ischemic stroke
Massive PE
Limb DVT or arterial thrombosis with threatened ischemia
Is the person already taking an anticoagulant (eg, for AF or VTE)?
Yes
No
Yes
No
Thrombolytic therapy (eg, tPA) may be appropriate
Consult PERT team, stroke team, or equivalent if possible for help with decision-making
Use full-dose anticoagulation if tPA not given
Follow institutional protocols for ongoing management
Anticoagulation is appropriate for thromboembolic disease
Use full-dose anticoagulation
Follow institutional protocols for ongoing management
Anticoagulation should typically be continued unless there is a contraindication
Switching to a shorter-acting parenteral agent may be appropriate in acutely ill or hospitalized individuals
Outpatients should generally continue their current therapy
Does the severity of COVID-19 warrant admission to the hospital?
Yes¶
No
Prophylactic dose anticoagulation is appropriate
LMW heparin is usually preferred
Unfractionated heparin may be used in selected cases (eg, CrCl <15 mL/min or RRT)
Fondaparinux may be used for individuals with HIT
Outpatient care as indicated
Continue anticoagulant if already taking
Prophylactic anticoagulation may be appropriate for selected high-risk individuals Δ
Others usually do not require anticoagulation

FLOW CHART: ANTICOAGULATION THERAPY FOR COVID-19



[a] HAS-BLED Score
[b] Padua Score

*Look for high risk features If parameters needed for ISTH Score are not available [e.g. increasing ferritin, CRP, oxygen need, D-dimer]

[#] Withhold anticoagulation: Current or recent bleeding, Platelet count < 50000 / µliter

PROPHYLACTIC DOSE
Enoxaparin: 40 mg SC once a day
UFH: 5000 IU SC twice a day
Apixaban: 2.5 mg twice a day
Rivaroxaban: 10 mg once a day

INTERMEDIATE DOSE
Enoxaparin: 60 mg SC once a day [or]
40 mg SC twice a day
UFH: 5000 IU subcutaneous thrice a day
[or] IV infusion [target aPTT 50 -70 sec]

THERAPEUTIC DOSE
Enoxaparin: 60 mg SC twice a day
UFH: IV infusion [target aPTT 70-110 sec]
Apixaban: 5 mg twice a day
Rivaroxaban: 10 mg twice a day

Interim COVID-19 - thromboprophylaxis guidelines

- ***VTE risk/bleeding risk assess to everyone*** on admission
- Dose-adjusted standard LMWH whilst an inpatient

Remaining questions

- Increase dose LMWH?
- Extended thromboprophylaxis?
- Hospital-assessed ambulatory patients?
- High risk patients in the community?

Obligations

- RCTs
- Audit – thrombosis and bleeding risk, ideally prospectively
- Regularly review ‘interim’ guidance