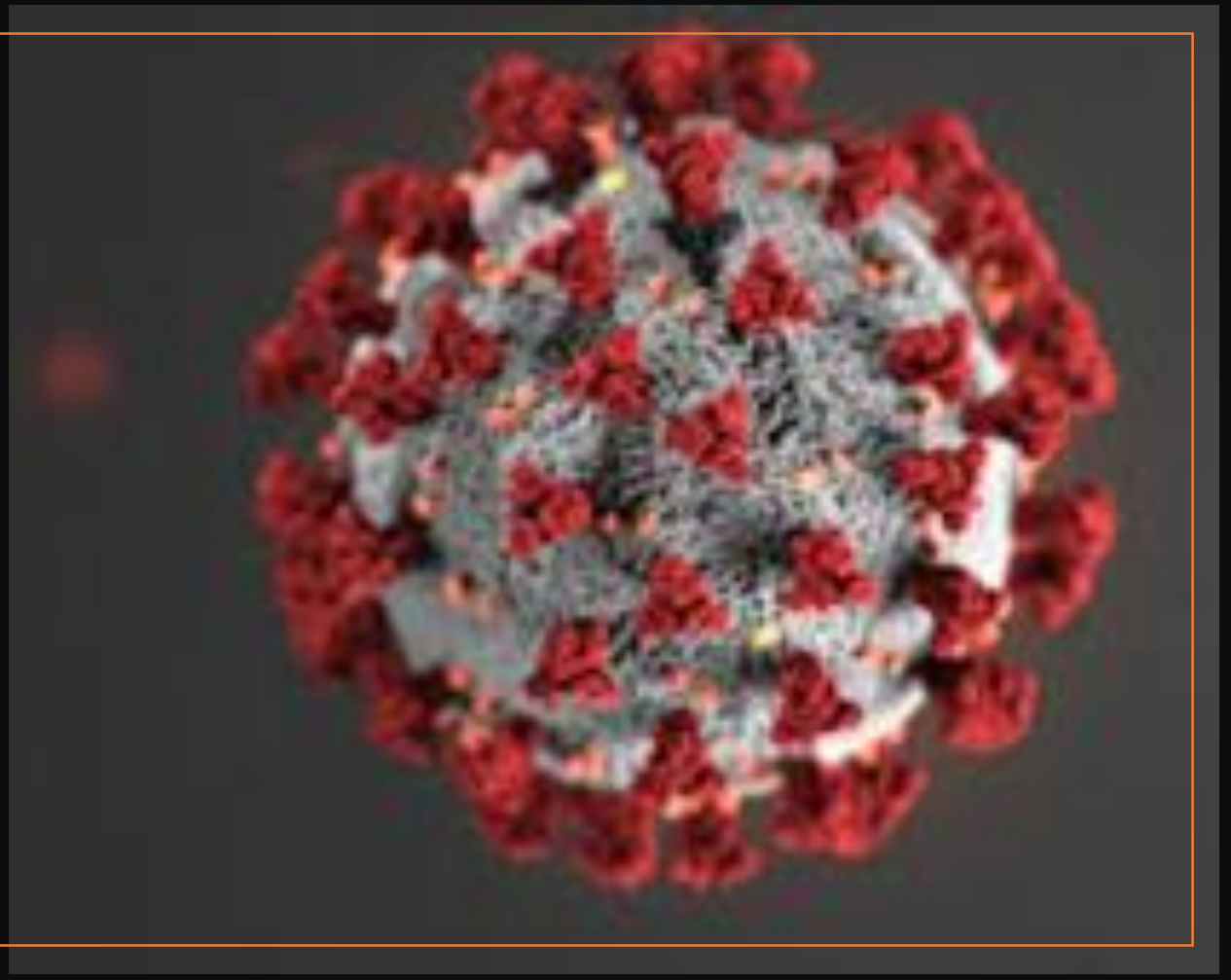
COVID-19: thrombosis & thromboprophylaxis

Prof Beverley Hunt OBE

Guys & St Thomas Trust/ Kings Healthcare partners , London, UK

Dedicated to my brother Philip who died of COVID-19 this week



COVID-19

- Originated in China in Dec 2019
- 101 days since WHO were notified
- Nearly every country of the world affected by April 2020 except for Antartica & Polynesian islands

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

COVID-19

- Originated in China in Dec 2019
- 101 days since WHO were notified
- Nearly every country of the world affected by April 2020 except for Antartica & Polynesian islands

- Aim of this talk
- To look at COVID-19 in the context of what we already know
- Not looking at haemostasis in isolation, for it reflects other organ dysfunction e.g liver disease

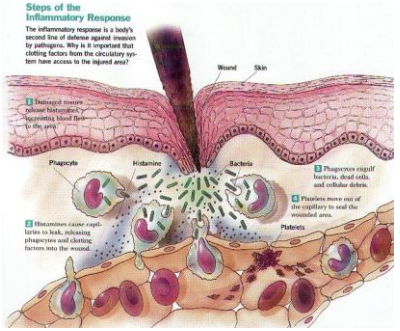
- Adhere to hard evidence rather than beliefs
- Recognise that many publications about COVID-19 are poor quality
- Recognition that doctors in their altruism want to help & may over diagnose & over treat in times of stress

WORLD THROMBOSIS DAY
13 OCTOBER

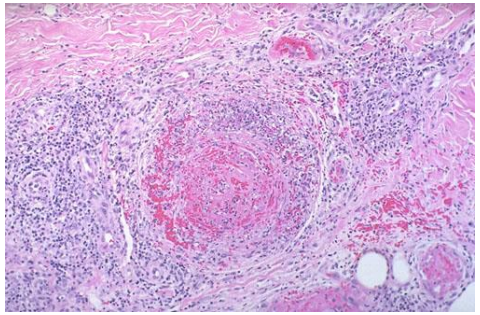
Thrombosis UK
Awareness • Research • Care

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

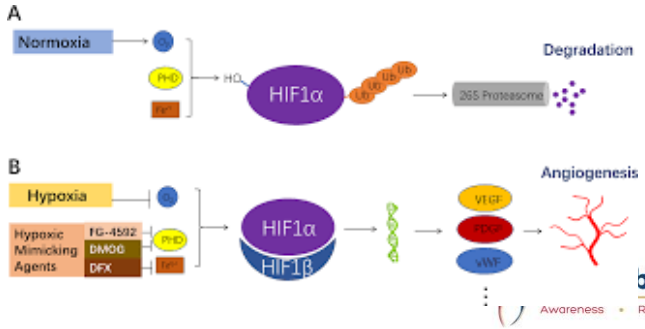
The coagulation system evolved as an effector pathway of the immune response:
laying down fibrin around bacteria to physically entrap them & prevent their dissemination



Thus the end point of inflammation is thrombosis
e.g Behcets disease, vasculitis
…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)

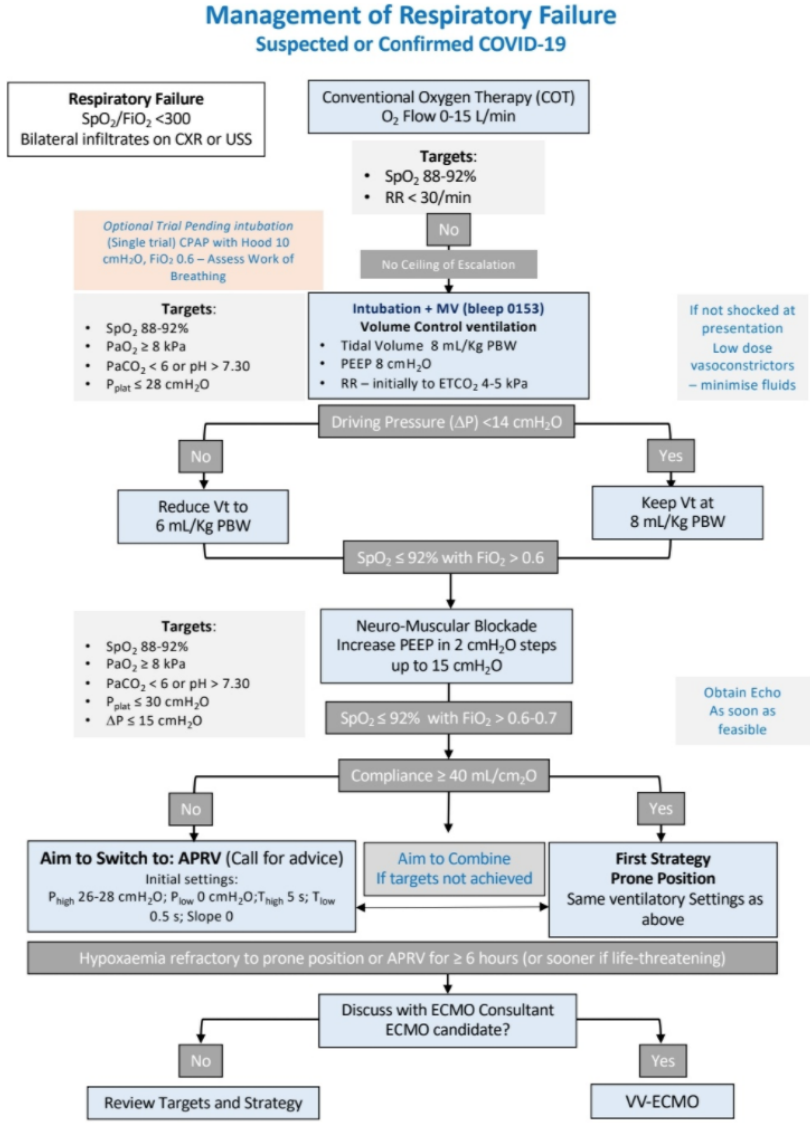


WORLD THROMBOSIS DAY
13 OCTOBER

Awareness • Research • Care

Admission for COVI-19 @GSTT

Category	Clinical criteria for oxygenation	Suggested action
Green	SaO_2 >94% on Room Air and RR≤20	Discharge for self-isolation as per PHE
Yellow	SaO_2 >94% on FiO_2 28-40%	Admit to medical ward
Amber	SaO_2 ≤ 94% on FiO_2 40% despite optimisation	Start 15L O2 via non-rebreathe mask CRT review in ED
Red	SaO_2 ≤94% on 15L O_2 via non-rebreathe mask	Urgent CRT review and prepare for intubation
Peri-arrest		Fast bleep CRT and MErIT



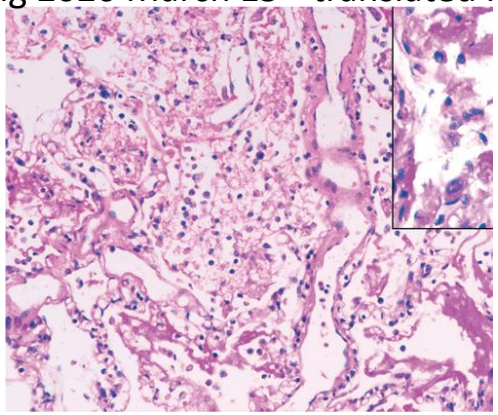
WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

What do we find in patients with COVID-19 pneumonia? Changes of acute lung injury

Hyaline membrane formation was observed in some alveoli. The infiltrated immune cells in alveoli were majorly macrophages and monocytes. Moderate multinucleated giant cells, minimal lymphocytes, eosinophils and neutrophils were also observed. Most of infiltrated lymphocytes were CD4-positive T cells. Significant proliferation of type II alveolar epithelia and focal desquamation of alveolar epithelia were also indicated. The blood vessels of alveolar septum were congested, edematous and widened, with modest infiltration of monocytes and lymphocytes. Focal hemorrhage in lung tissue, organization of exudates in some alveolar cavities, and pulmonary interstitial fibrosis were observed. Part of the bronchial epithelia were exfoliated. Coronavirus particles in bronchial mucosal epithelia and type II alveolar epithelia were observed under electron microscope. Immunohistochemical staining showed that part of the alveolar epithelia and macrophages were positive for 2019-nCoV antigen.

Yao et al Zhonhua Bing 2020 March 15th translated from Chinese

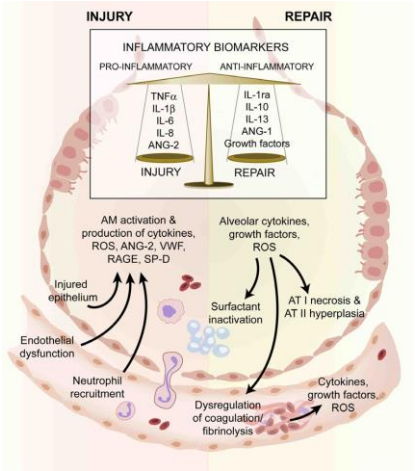


Acute lung injury leads to a profound inflammatory state due to a cytokine storm/macrophage/endothelial activation

⇧ IL-1, IL-6, IL-8, TNF-alpha

⇧

- ferritin
- CRP
- D-dimer
- Fibrinogen



WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

What do we find in patients with COVID-19 pneumonia? Changes of acute lung injury

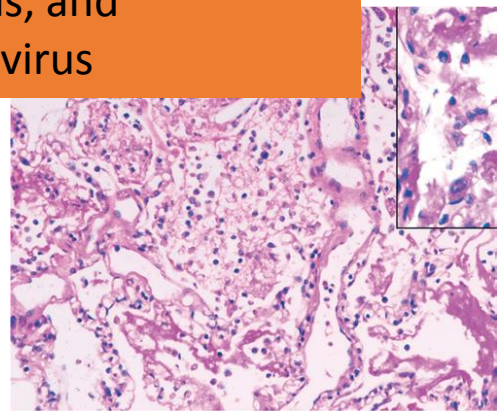
Hyaline membrane formation was observed in some alveoli. The infiltrated immune cells in alveoli were majorly macrophages and monocytes. Moderate multinucleated giant cells, minimal lymphocytes, eosinophils and neutrophils were also observed. Most of infiltrated lymphocytes were CD4-positive T cells. Significant proliferation of type II alveolar epithelia and focal desquamation of alveolar epithelia were also indicated. The exfoliated coronavirus particles in bronchial mucosal epithelia and type II alveolar epithelia were observed under electron microscope. Immunohistochemical staining showed that part of the alveolar epithelia and macrophages were positive for 2019-nCoV antigen.

Yao et al Zhonhua Bing 2020 March 15th translated from Chinese

Acute lung injury leads to a profound inflammatory state due to a cytokine storm/macrophage/endothelial activation

Also noted in only one of three separate studies that -hyaline thrombi were found in a minority of lung micro vessels. And that degeneration & necrosis of parenchymal cells, formation of hyaline thrombus in small vessels, and pathological changes of chronic diseases were observed in other organs …with no evidence of coronavirus

- ferritin
- CRP
- Procalicitonin
- Fibrinogen



WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

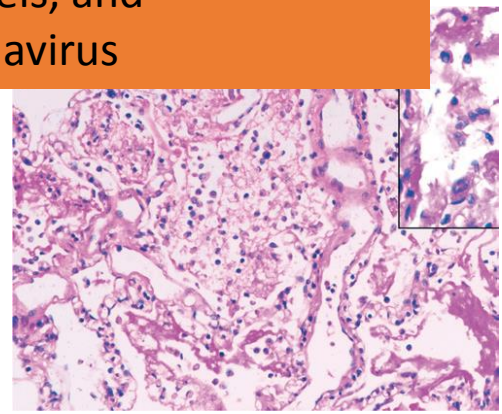
What do we find in patients with COVID-19 pneumonia? Changes of acute lung injury

Hyaline membrane formation was observed in some alveoli. The infiltrated immune cells in alveoli were majorly macrophages and monocytes. Moderate multinucleated giant cells, minimal lymphocytes, eosinophils and neutrophils were also observed. Most of infiltrated lymphocytes were CD4-positive T cells. Significant proliferation of type II alveolar epithelia and focal desquamation of alveolar epithelia were also indicated. The exfoliated. Coronavirus particles in bronchial mucosal epithelia and type II alveolar epithelia were observed under electron microscope. Immunohistochemical staining showed that part of the alveolar epithelia and macrophages were positive for 2019-nCoV antigen.

Yao et al Zhonhua Bing 2020

Acute lung injury leads to a profound inflammatory state due to a cytokine storm/macrophage/endothelial activation

Also noted in only one of three separate studies that -hyaline thrombi were found in a minority of lung micro vessels. And that degeneration & necrosis of parenchymal cells, formation of hyaline thrombus in small vessels, and pathological changes of chronic diseases were observed in other organs …with no evidence of coronavirus



- ferritin
- CRP
- Fibrinogen

Tentative conclusion: This is NOT primarily a thrombotic process but thrombosis is occurring secondary to inflammation & hypoxia

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

But

- **New England Journal today: Coagulation & Antiphospholipid Antibodies in Patients with COVID-19, a letter from Zhang et al**
- Who reviewed this?!!
- Anticardiolipin IgA not associated with thrombosis
- What were the titres of the antibodies? Need to be moderate or high..
- Transient antiphospholipid antibodies common in acutely ill
- …And if critically ill & an arteriopath you expect thrombotic events….
- KEY Q: Are arterial events greater with COVID-19 than other non-COVID illnesses on Critical Care?

WORLD THROMBOSIS DAY
13 OCTOBER

Table 1. Demographic and Clinical Characteristics and Laboratory Findings.*

Characteristic	Patient 1	Patient 2	Patient 3
Demographic characteristics			
Age — yr	69	65	70
Sex	Male	Female	Male
Initial findings			
Medical history	Hypertension, diabetes, stroke	Hypertension, diabetes, coronary artery disease, no history of thrombosis	Hypertension, emphysema, nasopharyngeal carcinoma, stroke
Symptoms at disease onset	Fever, cough, dyspnea, diarrhea, headache	Fever, cough, dyspnea	Fever, fatigue, dyspnea, headache
Imaging features	Ground-glass opacity, bilateral pulmonary infiltrates	Ground-glass opacity, bilateral pulmonary infiltrates	Bilateral pulmonary infiltrates
Treatment before admission to ICU	Oseltamivir, intravenous immune globulin	Antibiotics	Antibiotics, ribavirin, rosuvastatin
Days from disease onset to thrombotic event	18	33	10
Findings on admission to ICU			
Days since disease onset	24	21	24
Disease severity	Critical	Critical	Critical
Laboratory findings			
White-cell count (per mm^3)	17,790	6730	8710
Differential count (per mm^3)			
Total neutrophils	16,290	6230	7090
Total lymphocytes	430	290	790
Total monocytes	800	170	430
Platelet count (per mm^3)	78,000	79,000	180,000
Hemoglobin (g/liter)	111	99	92
Albumin (g/liter)	26.3	32.6	24.4
Alanine aminotransferase (U/liter)	15	11	8
Aspartate aminotransferase (U/liter)	23	20	20
Lactate dehydrogenase (U/liter)	632	233	417
Creatinine (μmol/liter)	80	58	86
Creatine kinase (U/liter)	63	335	16
EGFR (ml/min/1.73 m^2)	86.6	93.2	78.5
High-sensitivity cardiac troponin I (pg/ml)	3876.8	14.3	125.4
Prothrombin time (sec)	17.0	17.2	15.1
Activated partial-thromboplastin time (sec)	43.7	45.3	47.6
Fibrinogen (g/liter)	4.15	4.42	6.42
Fibrin degradation products (mg/liter)	85.5	8.1	7.3
D-dimer (mg/liter)	>21.00	2.84	3.23
Serum ferritin (μg/liter)	ND	2207.8	ND
Procalcitonin (ng/ml)	0.11	0.18	0.40
High-sensitivity C-reactive protein (mg/liter)	112.0	56.0	125.4
Antiphospholipid antibodies	Anticardiolipin IgA, anti-β_2-glycoprotein I IgA and IgG	Anticardiolipin IgA, anti-β_2-glycoprotein I IgA and IgG	Anticardiolipin IgA, anti-β_2-glycoprotein I IgA and IgG
Imaging features	Multiple cerebral infarctions in bilateral frontal parietal occipital lobe and bilateral basal ganglia, brain stem, and bilateral cerebellar hemispheres	Multiple cerebral infarctions in right frontal and bilateral parietal lobe	Multiple cerebral infarctions in frontal lobe, right frontal parietal temporal occipital lobe, and bilateral cerebellar hemispheres

* EGFR denotes estimated glomerular filtration rate, ICU intensive care unit, and ND not determined.

D-dimers are increased in inflammatory states, post operatively, pregnancy, going for a run and in ….**non COVID pneumonias**

Taken from Yin et al JTH 2020 on line 3 4 20

Table 1 Clinical and coagulation characteristics of COVID and non-COVID groups

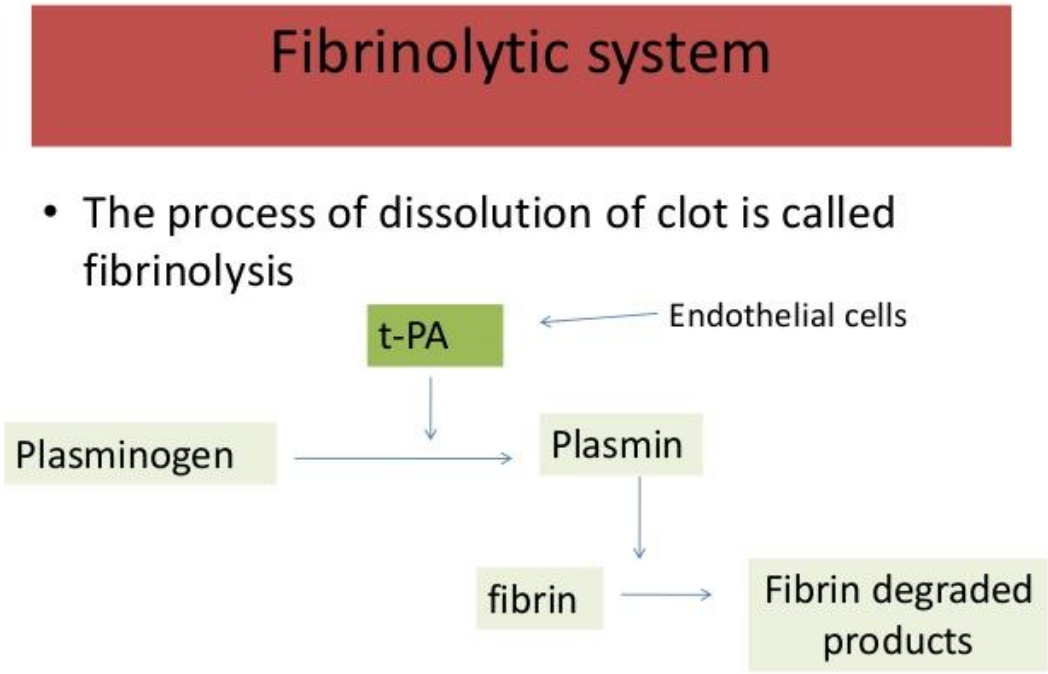
Parameters	Normal range	COVID (n = 449)	Non-COVID (n = 104)	*P* values
Age (years)		65.1 ± 12.0	58.4 ± 18.0	< 0.001
Sex ratio (male/female)		268/181	72/32	0.073
With underlying diseases		272 (60.6%)	64 (61.5%)	0.768
Receiving heparin		99 (22.0%)	22 (21.2%)	0.842
28-day mortality		134 (29.8%)	16 (15.4%)	0.003
Coagulation parameters				
PT (sec)	11.5–14.5	15.2 ± 5.0	16.2 ± 5.2	0.068
Platelet count (× 109/L)	125–350	215 ± 100	188 ± 98	0.015
D-dimer (μg/mL)	< 0.5	1.94 (0.90–9.44)	2.52 (1.40–5.81)	0.140

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

Why are D-Dimer levels↑ & prognostic in COVID-19?

- Assumptions made that fibrinolytic activation in COVID-19 is product of thrombin generation
- i.e due to secondary fibrinolysis i.e thrombin stimulates t-PA release from the endothelium



References

1*Wu et al., JAMA Intern Med*. doi:10.1001/jamainternmed.2020.0994. Published online March 13, 2020

Zhang et al, *Allergy.* 2020;00:1–12

Huang et al., *The Lancet* 2020; 395: 497–506

Zhou et al., *The Lancet* doi:10.1016/S0140-6736(20)30566-3. Published online March 9, 2020

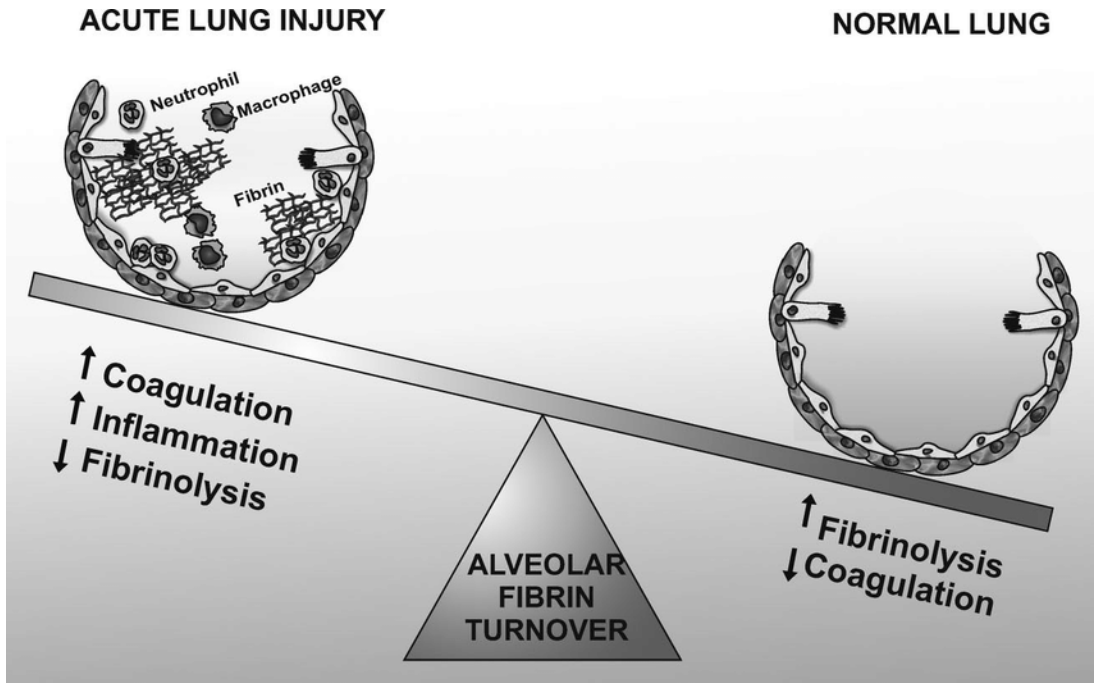
Tang et al., *J Thromb Haemost.* 2020;00:1–4.

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

Why are D-Dimer levels ↑& prognostic in COVID-19? Hypothesis 1: a result of acute lung injury

- The hallmark of acute lung injury is intra-alveolar fibrin deposition
- (& later remodeling of fibrin → lung fibrosis)
- Urokinase –type plasminogen activator (uPA) produced locally regulates extravascular proteolysis, inhibited by PAI-1
- In SARS -infected mice a dose-dependent ↑ in lung urokinase with dose of SARS injected but locally swamped by PAI-1
- Pathways not clearly understood



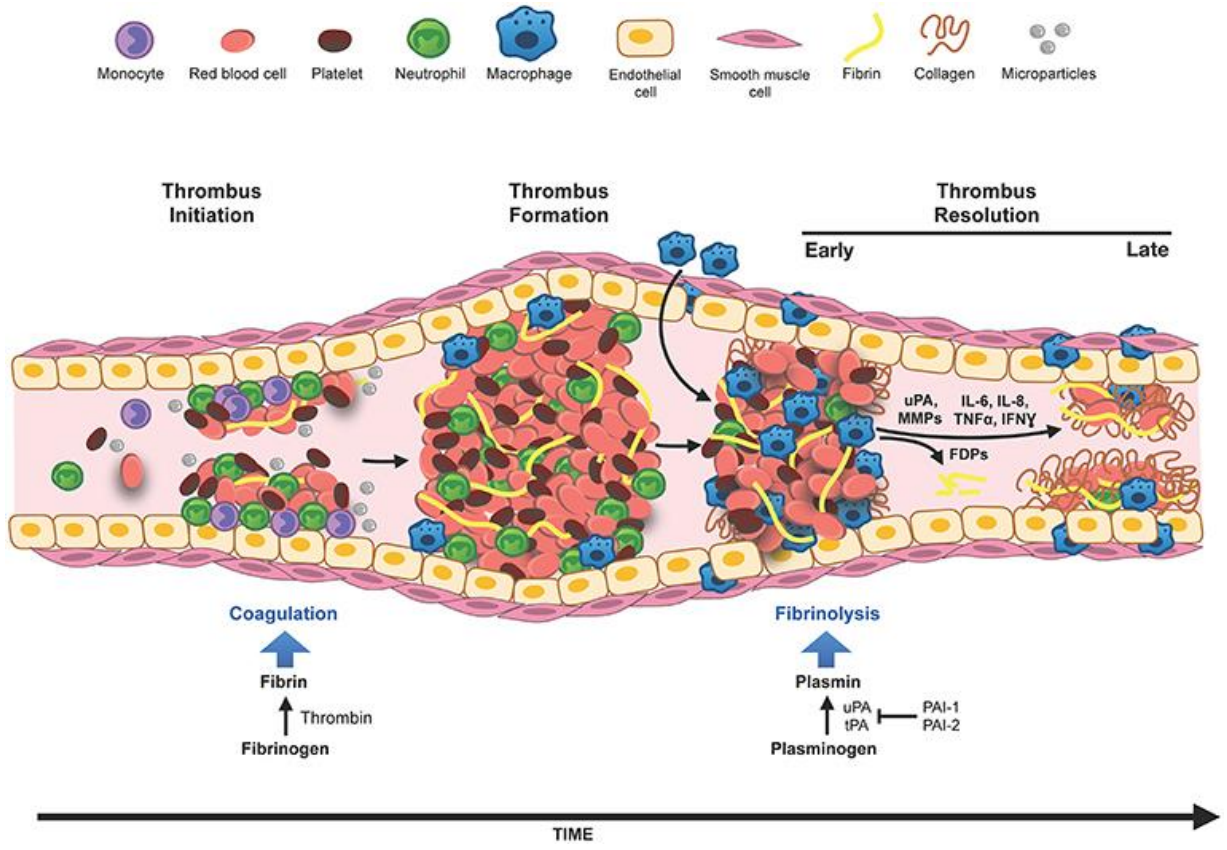
WORLD THROMBOSIS DAY
13 OCTOBER

Idell, Crit Care Med 2003:S213-20, Gralinski, mBIo 2013; 4:e00271-13

Thrombosis UK
Awareness • Research • Care

Why are D-Dimer levels ↑& prognostic in COVID-19? Hypothesis 2: produced by activated macrophages

- COVID-19 pneumonia lung histology characterized by many macrophages
- Macrophages generate plasmin & metalloproteinases (MMPs)
- Fibrin degradation also occurs by an alternative pathway- fibrin (ogen) binding to CD11b/CD18 I internalized into the lysosome where cathepsin D degrades it

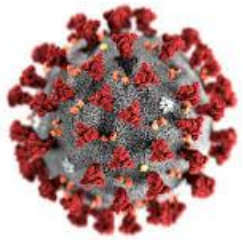


Loscalzo J. Semin Thromb Hemost 1996; 22:503-6

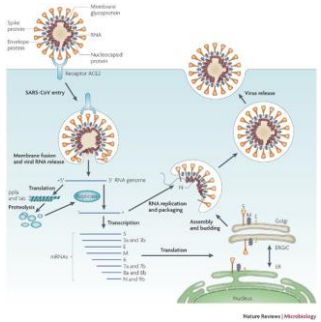
WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

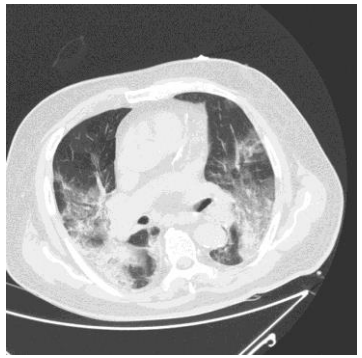
Severe COVID-19



ACE2 receptor on
Pulmonary epithelium
& endothelium



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

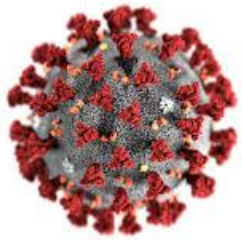


Prothrombotic state due to effects of IL1, IL-6

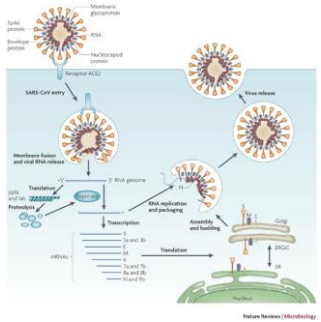
WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

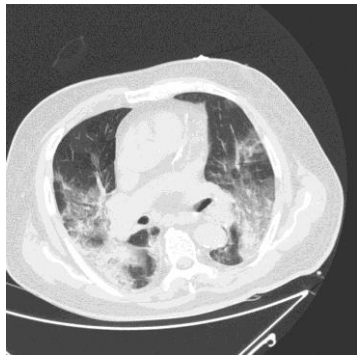
Severe COVID-19



ACE2 receptor on
Pulmonary epithelium
& endothelium



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



Prothrombotic state due to effects of IL1, IL-6

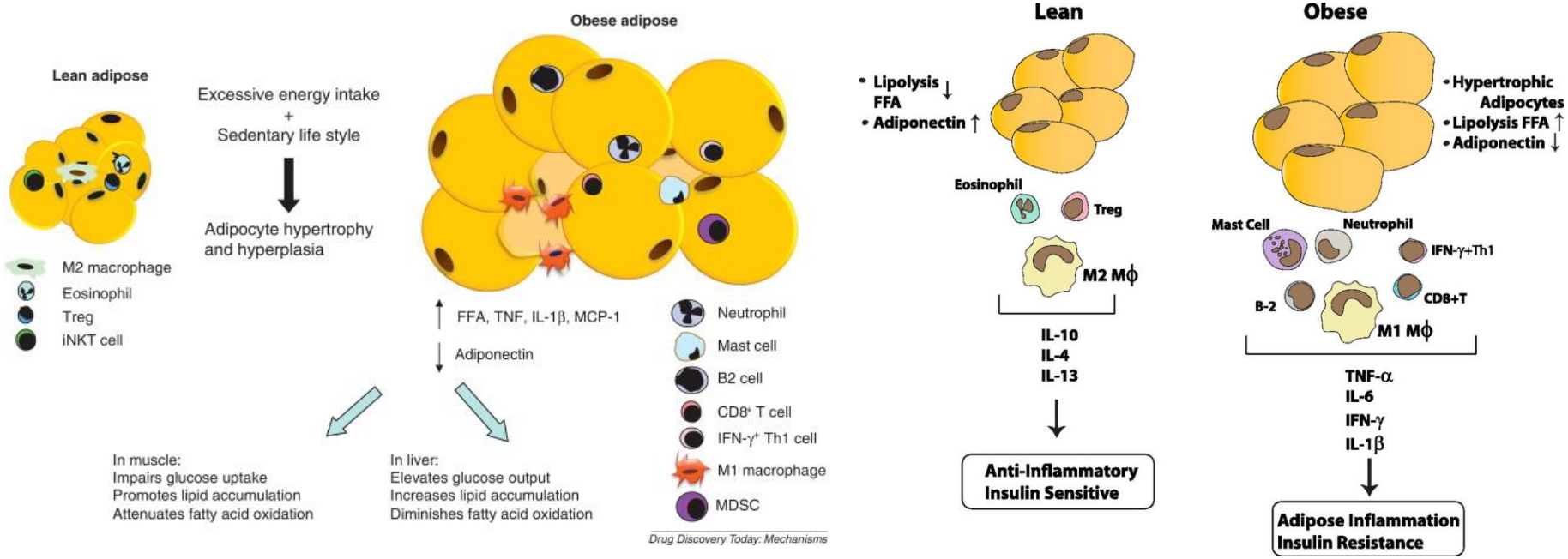
Does a pre-existing inflammatory state
make COVID-19 pneumonia more likely?
e.g atherosclerosis, diabetes, obesity

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

Obesity is common: BMI > 25 in 75% of UK patients with severe COVID-19 infection (Source @ICNARC)

Hypertrophic adipocytes (like atherosclerosis & diabetes) induce an inflammatory state



WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

High background risk of VTE in critically ill patients

- Hospital-associated VTE – VTE occurring in hospital & up to 90 days post discharge
- But lack of current data and variation in severity of illness to qualify for critical care beds across the world
- What is the current VTE risk in critical care?
- 1982 Cade 1982 119 patients DVT in 29% vs 13% UFH 5,000 BD by day 6
- 1999 MEDENOX 1102 pts placebo arm 15% had DVT/PE by day 14

Risk factors

- Increasing age
- Acute infective illness
- Use of venous lines
- Underlying patient risk factors
- Immobility
- Etc etc

Cade JF, Crit Care Med 1982; 10: 448-50, MEDENOX- Samama New Engl J Med 1999; 341: 793

Benefits of heparinoid thromboprophylaxis for 6-14 days over placebo in medical patients

Study	RRR	Thromboprophylaxis	Patients with VTE (%)
MEDENOX[1]	63%	Placebo	14.9*
P<0.001		Enoxaparin 40 mg	5.5
PREVENT[2]	45%	Placebo	5.0*
P=0.0015		Dalteparin	2.8
ARTEMIS[3]	47%	Placebo	10.5†
p=0.029		Fondaparinux	5.6

RRR = relative risk reduction

[1]Samama MM *et al. N Engl J Med* 1999;341:793–800
[2]Leizorovicz A *et al. J Circulation* 2004;110:874–9
[3]Cohen AT *et al. J Thromb Haemost* 2003;1 (Suppl 1):P2046

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

Thromboprophylaxis in Critical Care

Does LMWH/UFH reduce risk?

Alhazzani et al Crit Care Med 2013; 41: 2088

- Systematic review 7,226 pts in RCTs
- ↓sympt/asympt DVT RR 0.51 (95% CI 0.41-0.64); p <0.0001)
- ↓PE RR 0.52 (95% CI 0.28-0.92); p= 0.04)
- No difference in bleeding or mortality

Which is better?

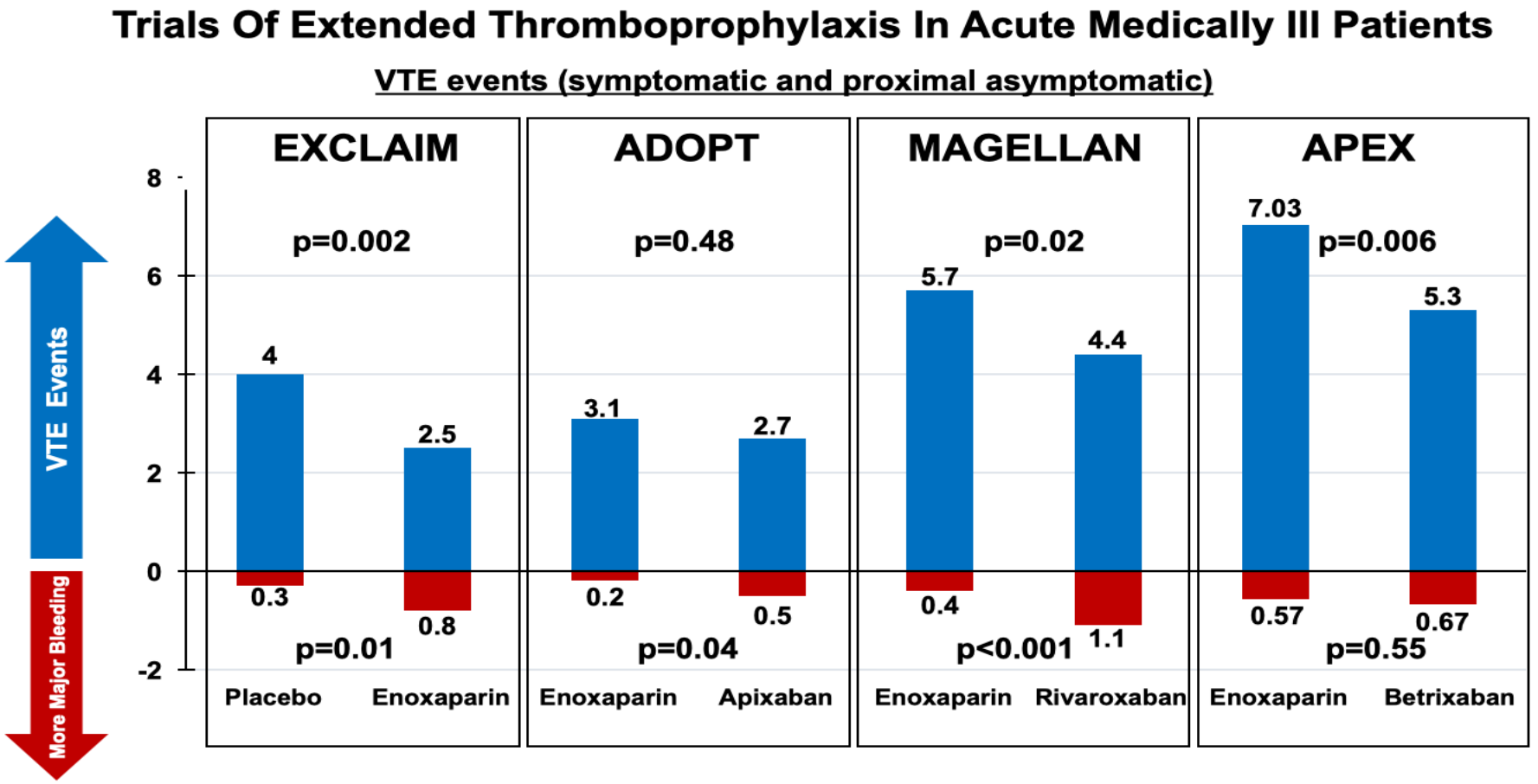
Lim et al Crit Care Med 212;40: 328

- Compared LMWH vs UFH in same group
- LMWH ↓ DVT & PE> UFH
- For PE RR 0.52: 95% CI 0.28,0.97) p=0.04)
- No difference in bleeding or mortality

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

Extended thromboprophylaxis in medical patients



MARINER trial (low dose rivaroxaban) excluded as only measured symptomatic & fatal VTE

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

Criteria for extending prophylaxis

- **Age ≥ 75 y or**
- **Past history of cancer or VTE or**
- **EXtra risk factors***
- *Known risk factors for VTE including: D-dimers ≥ 2 upper limit of normal range, Intensive Care Unit stay, or 2 other factors such as past history of superficial VT, obesity, varicose veins, chronic venous insufficiency, lower extremity paresis, hormone therapy, thrombophilia (congenital or acquired), concomitant use of erythropoiesis stimulating agents
- ** planned admission >2 days, but none of the admission criteria listed in the moderate risk group consider on a case by case basis

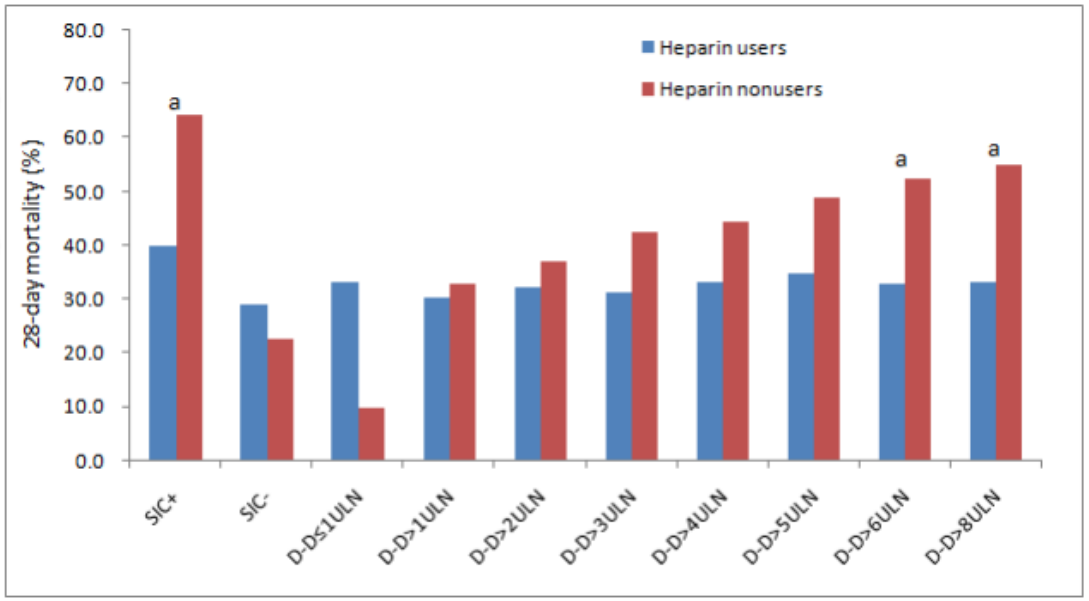
Criteria for extending prophylaxis

- **Age ≥ 75 y or**
- **Past history of cancer or VTE or**
- **EXtra risk factors***
- *Known risk factors for VTE including: D-dimers ≥ 2 upper limit of normal range, Intensive Care Unit stay, or 2 other factors such as past history of superficial VT, obesity, varicose veins, chronic venous insufficiency, lower extremity paresis, hormone therapy, thrombophilia (congenital or acquired), concomitant use of erythropoiesis stimulating agents
- ** planned admission >2 days, but none of the admission criteria listed in the moderate risk group consider on a case by case basis

Anticoagulant treatment is associated with decreased mortality in severe COVID-19 patients with coagulopathy

Tang et al, JTH 2020, preprint

- Retrospective study in Tongji Hospital, 449 patients with severe COVID-19 infection, 99 (22%) received heparin



jth_14817_f2.png

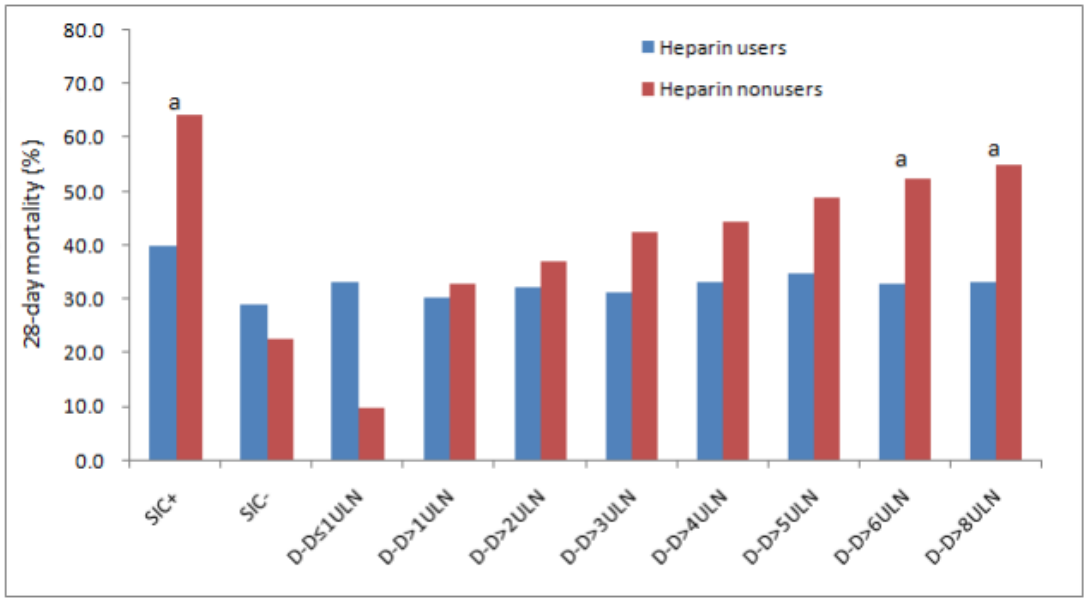
WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

Anticoagulant treatment is associated with decreased mortality in severe COVID-19 patients with coagulopathy

Tang et al, JTH 2020, preprint

- Retrospective study in Tongji Hospital, 449 patients with severe COVID-19 infection, 99 (22%) received heparin



jth_14817_f2.png

Why were only a few on heparin?
(routine VTE risk assessment & thromboprophylaxis is clearly not used, hence high rates of thromboembolism seen)
Which heparin?
What dose?

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

Unanswered Qs in thrombosis & thromboprophylaxis in COVID-19 infection

Rates of thromboembolism

- What are the current rates of VTE in critically ill patients?
- Are the rates of thrombosis higher than other patients on critical care especially can we compare with non-COVID-19 viral pneumonia?

Thromboprophylaxis

- Is weight adjusted thromboprophylaxis better than empirical dosing? (Many trial excluded high weight individual AND obesity rates have ⇧ since trials)
- Would a higher dose of thromboprophylaxis be beneficial without significantly increasing bleeding risk?
- Should we add in intermittent pneumatic compression?
- Should we give extended thromboprophylaxis?

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK
Awareness • Research • Care

Management of fresh VTE in COVID-19

Diagnosis: how to detect PE when cant use D-dimer?

- This is not a new problem!
- Need to maintain high clinical suspicion esp. if becomes more clinically hypoxic suddenly
- Would manage with 3/12 anticoagulation (would start with LMWH while in critical care then switch to DOAC on discharge) according to current guidelines

Catheter-associated thrombosis

- Six weeks Rx according to current guideline
- Expecting to see it frequently

NB despite thromboprophylaxis we will see VTE in at least 7%, probably more, of all critically ill patients whether cOVID -19 or not

Action Card (v1-0)

T5-8: Haematological management of patients in ICU with COVID-19

Objective: To provide basic guidance for common haematological issues in patients with confirmed or suspected COVID-19 who are being cared for in an ICU environment

Routine haematological management

ALL ITU AREAS

1. **Check haemoglobin**
   - ➲ If <70g/l give single unit red cell transfusion and re-check
2. **Check platelet count**
   - ➲ If <20x10⁹/l give one pool of platelets and re-check
3. **Check coagulation results**
4. **Check thromboprophylaxis**
   - ➲ Check if special circumstances apply (see *special circumstances*)
   - ➲ If special circumstances apply end steps on this card

— OTHERWISE —

5. **Check creatinine clearance**
   - ➲ If >30ml/min prescribe LMHW per Thromboprophylaxis dose LMWH (see *thromboprophylaxis doses*)
   - ➲ If ≤30ml/min prescribe unfractionated heparin 5000iu S/C TDS

General principles

Minimise phlebotomy use
- Avoid excessive blood sampling; take arterial samples not more than four hourly
- Use approved COVID order sets on EPR

Choice of Agent
- LMWH is preferred; fondaparinux if no supply of LMWH available

Special circumstances

AF or previous VTE
- If AF or previous VTE which was >90 days ago, no special circumstances apply
- If VTE ≤ 90 days ago, prescribe treatment dose LMHW

Active bleeding
- Correct abnormal results

Planned procedures
- See *Target parameters for procedures*

Thromboprophylaxis dosing

Actual weight (kg)	Dalteparin
<49	2500iu OD
50-99	5000iu OD
100-139	7500iu OD
140-180	5000iu BD

Target parameters for procedures

Central line/arterial line insertion
- Platelets transfusion required if <20x10⁹/l; experienced operator if <50x10⁹/l

Central line/arterial line removal
- Do not remove until platelets >50x10⁹/l; if urgent removal is indicated, platelet transfusion required

Chest drain or tracheostomy insertion
- INR <1.5 / APTTr <1.5
- Fibrinogen >1.5g/l
- Platelet count >80x10⁹/l

THIS DOCUMENT UNDERWENT FAST-TRACKED APPROVAL AT DIRECTORATE LEVEL FOR COVID-19 RESPONSE

Action Card (v1-0)
March 2020