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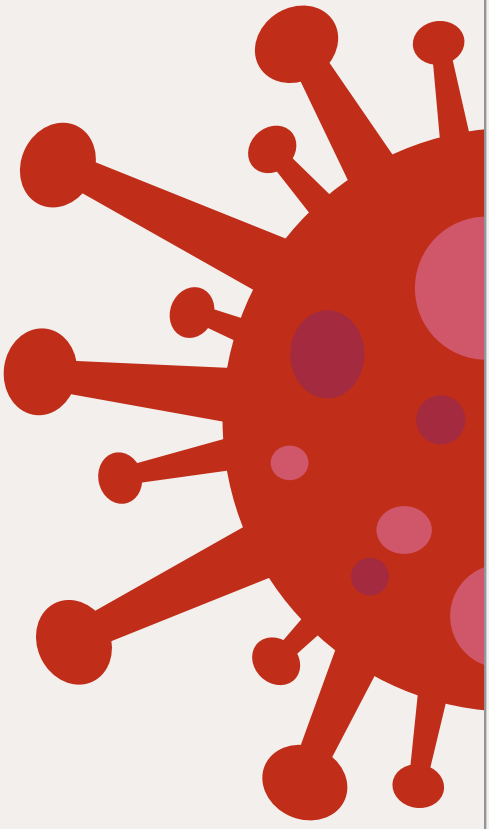

COVID-19 in the haemostasis laboratory

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COVID-19 PANDEMIC

- Between January 2020 and September 2020, more than **22 million cases** of COVID-19 (in accordance with the applied case definitions and testing strategies in the affected countries) have been reported.
- In this period about **800,000 deaths** have been attributed to COVID-19, at the peak of the pandemic the third leading cause of death in Western countries.
- Patients with most severe COVID-19 infection are affected by respiratory insufficiency, shock, renal insufficiency, cerebral disease, multiple organ dysfunction. In addition, a high incidence of cardiovascular complications is seen[1].
- There seems to be a remarkably **high incidence of venous thromboembolism (VTE)** in patients with COVID-19.
  The incidence ranges from 8-37% for deep venous thrombosis (DVT) and 7-35% for pulmonary embolism (PE) (Figure 1 and Table 1). Undiagnosed PE may aggravate the ventilation-perfusion mismatch in the lungs and contribute to respiratory insufficiency[2].
- There is some debate whether the high incidence of venous thromboembolic complications in COVID-19 patients is similar to those seen in critically ill patients with a severe systemic inflammatory state and multiple organ dysfunction or whether a frequently occurring coagulopathy in COVID-19 (see further) increases the risk.
- **Pharmacological thromboprophylaxis** (e.g. with low molecular weight heparin - LMWH) may reduce the incidence of VTE in patients with COVID-19 although not completely (see further)[3].

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Fig 1. Pulmonary embolism on CT angiography in patients with COVID-19

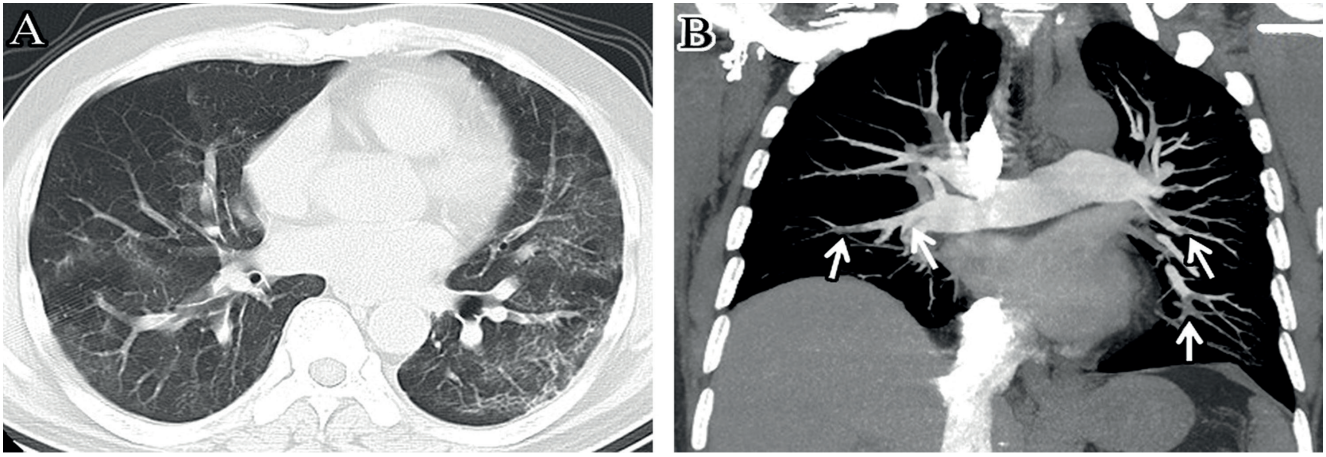

Table 1. Incidence of venous thromboembolism in series of patients with COVID-19

STUDY	PATIENTS (n)	VTE (%)	DVT (%)	PE (%)
Demelo-Rodriguez P et al.[4]	156	-	14.7	-
Poissy J et al.[5]	107	-	4.6	20.6
Helms J et al.[6]	150	-	2.0	16.7
Middeldorp S et al.[7]	198	20.0	13.3	6.6
Al-Samkari H et al.[8]	166	7.6	-	-
Cattaneo M et al.[9]	388	-	0.0	-
Zhang L et al.[10]	143	-	46.1	-
Cui S et al.[11]	81	25.0	25.0	-
Klok FA et al.[12]	184	36.9	1.6	35.3
Grillet F et al.[13]	280	-	-	8.2
Thomas W et al.[14]	62	-	1.6	8.0

COVID-19 PATHOPHYSIOLOGY

- A COVID-19 infection starts when **SARS-CoV-2 virus is transmitted** from one human to another, via inhalation or oral ingestion of virus-containing droplets.
- The virus likely binds to epithelial cells in the nasal or oral cavity **utilising the angiotensin converting enzyme-2 (ACE2) receptor** (Figure 2) and starts replicating. Initially there is local propagation of the virus and a limited innate immune response, but at this stage infected individuals are already infectious for others[15].
- The virus **propagates and travels down the respiratory tract and the airways,** and a more robust innate immune response is triggered, characterised by the occurrence of systemic pro-inflammatory cytokines and activated immune cells. At this time, the COVID-19 disease is clinically manifest with eventually self-limiting mild to moderate symptoms of an upper respiratory tract infection and general symptoms such as myalgia and fatigue.
- However, in about 20% of patients **the virus will subsequently infect alveolar cells,** once again via the ACE2 receptor. These patients will develop pulmonary infiltrates, acute lung injury (Figure 3), and potentially very severe disease requiring mechanical ventilation and associated with significant mortality[16].
- In the most severely affected COVID-19 patients, **an exaggerated immune response** is observed in the form of a cytokine 'storm', characterized by extreme levels of pro-inflammatory cytokines (such as Tumor Necrosis Factor (TNF)-α and interleukins (IL), such as IL-6) and several chemokines[17]. It resembles the cytokine release syndrome that is seen as a complication of advanced cell therapy for lymphoproliferative and other hyper-inflammatory syndromes characterized by fulminant hyper-cytokinaemia and multi-organ failure. Clinically, these patients will develop multi-organ dysfunction and have a very high mortality risk.
- The majority of patients with the most severe COVID-19 infection will develop a **coagulopathy,** due to inflammation-induced coagulation activation and direct endothelial cell infection by the coronavirus (Figure 4). These patients are likely at higher risk for thromboembolic complications (see further).

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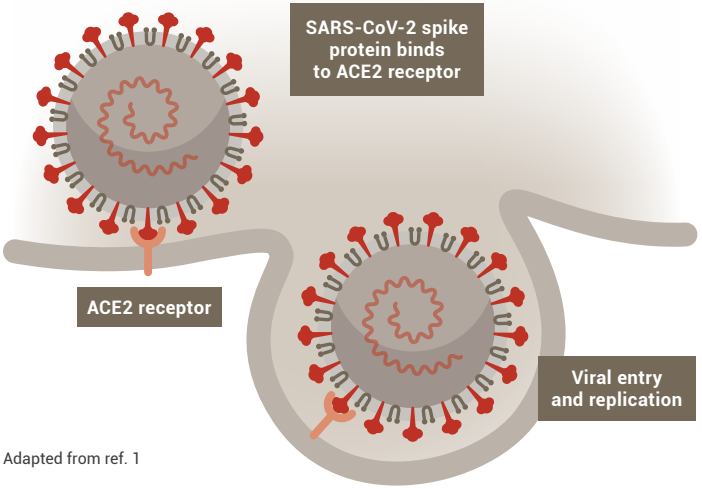
Fig 2. SARS-CoV-2 infection of epithelial cells



Adapted from ref. 1

Fig 3. Evolution of COVID-19 pneumonia on chest X-ray and CT scan

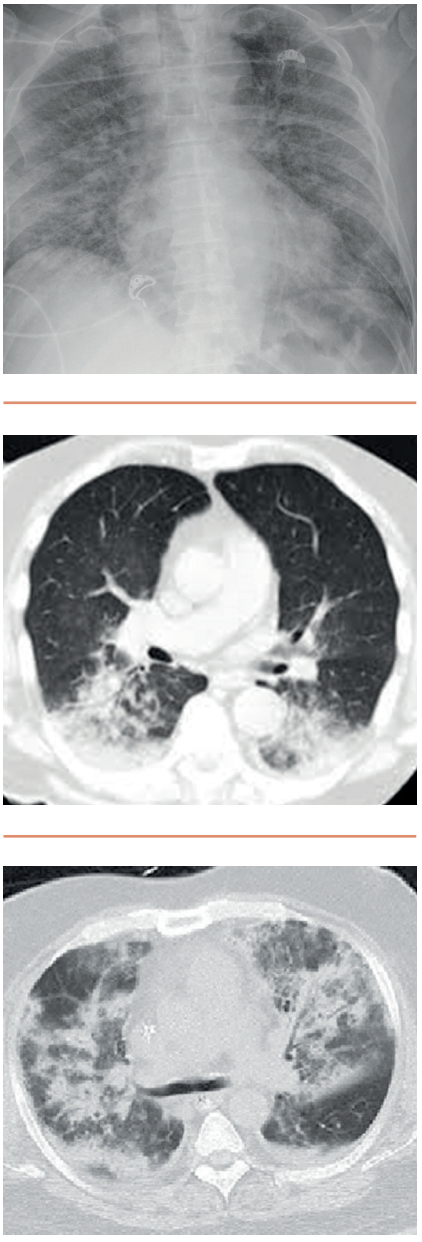
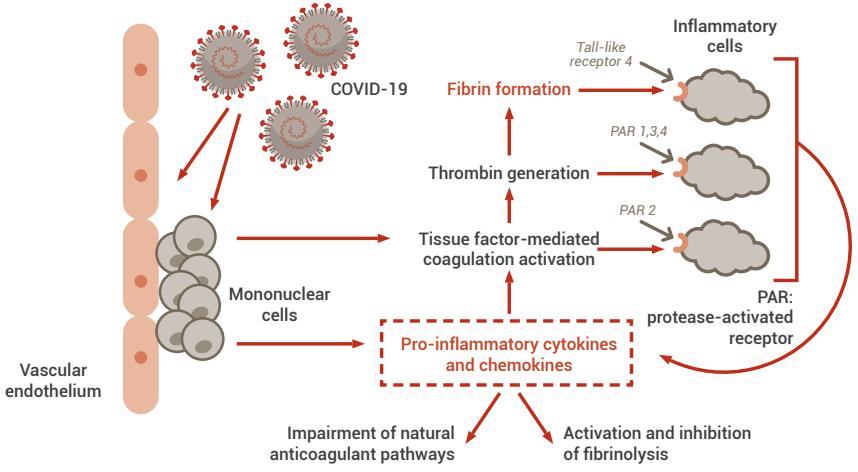


Fig 4. Interaction between inflammation and coagulation in COVID-19



Severe COVID-19 generates an increase in pro-inflammatory cytokines and activates endothelial cells, neutrophils, mononuclear cells, and platelets leading to activation of coagulation[2,9]. Coagulation proteases bind to specific receptors that mediate further pro-inflammatory responses[10]. Direct infection of endothelial cells by the coronavirus may cause distinct features of the COVID-19 coagulopathy (see further).

DISTINGUISHING LABORATORY FEATURES OF COVID-19 COAGULOPATHY

- COVID-19 presents with dramatic derangement of coagulation. It is relatively mild at the onset and more severe in patients admitted to intensive care unit (ICU)[18]. Results interpretation should be done accordingly.
- Elevated D-Dimer (DD) is the most important feature. Retrospective observations showed that DD levels are associated with progression to acute respiratory distress syndrome (ARDS) and death[19] (Table 2). However, the value of this information in decision making is still uncertain.
- While prothrombin time (PT) is slightly prolonged or (near) normal, activated partial thromboplastin time (APTT) is normal or even shortened.
  APTT can also be prolonged:
  - if a lupus anticoagulant is present (which is a frequent situation in COVID-19 infection as in many viral infection);
  - if CRP is elevated (which is common in ICU patients) due to interference between CRP and APTT reagents.

High fibrinogen and factor VIII are other characteristic features of the COVID-19 coagulopathy and their values parallel the disease severity. Low platelet count is uncommon; antithrombin is low/normal and protein C is normal or increased (Table 3). The above features (except for DD) are difficult to reconcile with the coagulopathy associated with disseminated intravascular coagulation (DIC) or consumption coagulopathy.

- Von Willebrand factor (VWF) is elevated and parallels the disease severity[18]. Interesting observations are available on the surmised protective effect of raised fibrinogen and VWF[20].
- Overall, the balance of coagulation in COVID-19 tips towards hypercoagulability and endothelial dysfunction, thus making the increased risk of thrombosis biologically plausible. Whether and to what extent the above features are useful to make decision on the appropriate dosage of anticoagulation is still unknown.

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Table 2. Coagulation parameters associated with acute respiratory distress syndrome (ARDS) development or progression from ARDS to death *(modified from ref 19). PT, prothrombin time. APTT, activated partial thromboplastin time. HR (95% confidence interval – CI), Hazard ratio (95% CI).*

PARAMETERS	HR (95%CI) FOR ARDS	P VALUE	HR (95%CI) FOR DEATH	P VALUE
PT (seconds)	1.56 (1.32-1.83)	<0.001	1.08 (0.84-1.38)	0.54
APTT (seconds)	0.97 (0.94-1.01	0.13	0.96 (0.91-1.00)	0.06
D Dimer (µg/mL)	1.03 (1.01-1.04)	<0.001	1.02 (1.01-1.04)	0.002

Table 3. Coagulation parameters [mean (min-max)] in COVID-19 according to the disease progression in patients admitted at three hospital wards characterized by increasing intensity of care *(modified from ref 18). PT, prothrombin time. APTT, activated partial thromboplastin time.*

	INTENSITY OF CARE			
	LOW	INTERMEDIATE	HIGH	P VALUE
PT ratio (patient/normal)	1.02 (0.85-1.33)	1.12 (0.95-1.44)	1.06 (0.96.133)	0.0037
APTT ratio (patient/normal)	0.93 (0.79-1.22)	0.91 (0.78-1.10)	0.95 (0.78-1.15)	0.66
Fibrinogen (mg/dL)	344 (150-861)	471 (285-830)	531 (224-1.035)	0.061
D Dimer (ng/mL)	870 (203-38.847)	1.347 (525-6.910)	2.217 (564-6.410)	0.009
Factor VIII (IU/dL)	208 (121-347)	223 (109-423)	302 (178-374)	0.014
Antithrombin (IU/dL)	87 (61-133)	94 (63-135)	100 (71-143)	0.43
Protein C (IU/dL)	120 (60-234)	126 (72-210)	143 (85-232)	0.057
Von Willebrand factor antigen (IU/dL)	262 (90-577)	371 (132-769)	466 (231-746)	0.00007

VISCOELASTIC TESTING IN COVID-19 SEVERE PATIENTS

- Viscoelastometry is a global coagulation procedure aimed to assess the viscoelastic changes of whole blood upon in vitro coagulation activation. The main parameters are (i) the clotting time; (ii) clot formation time and (iii) maximal clot formation (Figure 5).
- Studies on patients with COVID-19 admitted to intensive care unit show short than normal clot formation time as well as increased maximal clot formation, which cumulatively indicate a state of hypercoagulability[21] (Figure 6).
- The above abnormalities parallel the increased levels of procoagulant factors (factor VIII, fibrinogen and VWF) observed for these patients supporting the concept of hypercoagulability (Table 3).
- Patients with severe COVID-19 showed an improvement of the viscoelastometry parameters after thromboprophylaxis[22].
- While viscoelastometry parameters are valuable to help understand the pathophysiology of haemostasis alterations in COVID-19, their values as indexes of prognosis and antithrombotic monitoring require further evaluation.

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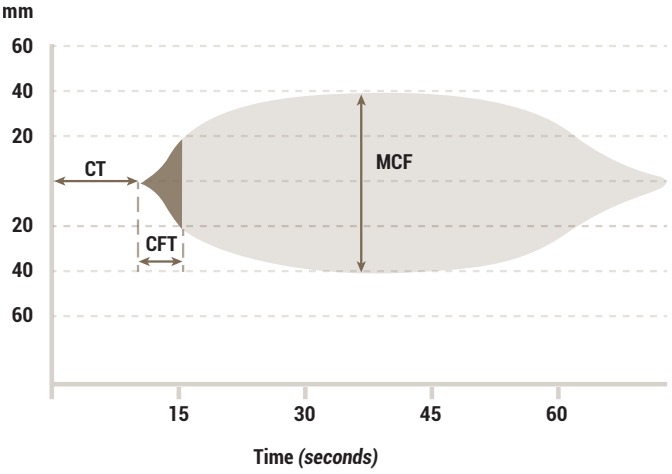

Fig 5. Typical viscoelastometry tracing with relevant parameters. CT, clotting time. CFT, clot formation time. MCF, maximal clot firmness.

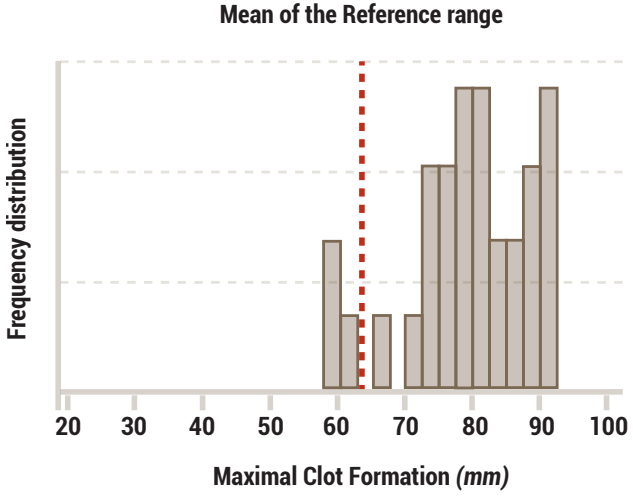

Fig 6. Distribution of results for maximal clot formation in patients with COVID-19 admitted at intensive care units (ICU) *(modified from ref. 21). Red dotted line represents the mean of the reference range.*

COVID-19 INFECTION–ASSOCIATED THROMBOTIC COMPLICATIONS

- COVID-19 is associated with an increased risk of thrombosis, affecting venous, arterial and microcirculatory systems (Figure 7), which may be related to the underlying extreme inflammation caused by the virus (thromboinflammation) and also direct endothelial invasion (endothelialilitis) which are both well-recognised to activate the coagulation system[2,3,23,24]. In addition to macrovascular complications there is a strong association of COVID-19 with microvascular thrombosis[25]. Autopsy studies reported diffuse alveolar damage with widespread platelet-fibrin microvascular thrombosis mixed with neutrophils and microangiopathy in the lungs[26].
- People with COVID-19, especially those hospitalized with the moderate (requiring supplementary oxygenation) and severe (requiring mechanical ventilation or critically ill) pneumonia have a high incidence of VTE, particularly PE affecting segmental and subsegmental vessels[10,27-29]. Patient-related, pneumonia-related and viral-related factors increase the risk of thrombosis (Table 4). Hypoxia also induces a prothrombotic phenotype[30]. There is a strong association between
- D-dimer and chest computed tomography (CT) features suggesting PE.
- Thrombotic complications are markers of severe COVID-19 and are associated with multiorgan failure and increased mortality[23,28,31] (Figure 8). The intense prothrombotic state may explain the high rate of VTE despite anticoagulant thromboprophylaxis[23,29].
- As previously mentioned, VTE rates range from 1-6% for noncritical hospitalized patients, 8-37% for DVT and 7-35% for PE[4-14, 27-29] (Table 1). The diagnosis of VTE is challenging. Risk scores, such as the Wells or Geneva scores may be useful to predict low risk for VTE. The diagnostic approach of PE requires CT pulmonary angiography (CTPA), while transthoracic echo and troponin levels are also part of the workup of unstable patients. If clinically suspected, compression ultrasonography is the method of choice for the diagnosis of DVT.
- Rate of arterial thrombotic events are between 2.8-3.8%. Large vessel wall arterial thrombosis would support wide-scale endotheliopathy involving medium and large arteries[27-29].

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Fig 7. COVID-19 and thrombotic events: epidemiology.

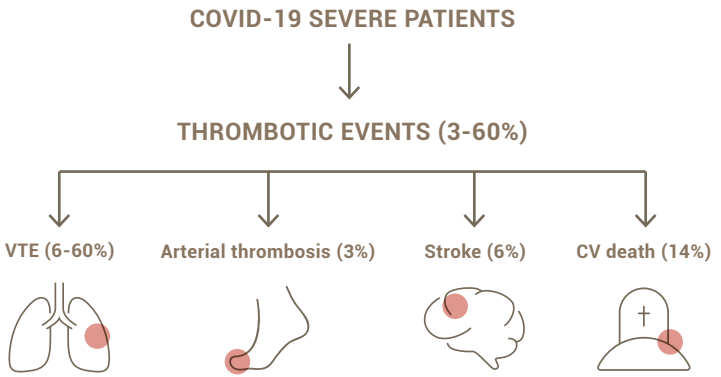
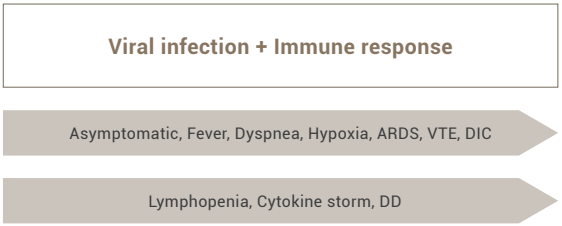


Table 4. Factor increasing the risk of thrombosis.

PATIENT-RELATED	PNEUMONIA-RELATED	COVID-19-RELATED
Age	ICU	Angiotensin
Male sex	Endothelial damage	Cytokine storm
Immobilization	Increase VWF	Tissue factor
Hypertension	Hypoxia	Hypofibrinolysis
Cardiovascular morbidity	CVC	

ICU: intensive care unit; VWF: Factor von Willebrand; CVC: Central Vein Catheter

Fig 8. Clinical course of COVID-19 patients.



PROPHYLAXIS AND ANTITHROMBOTIC THERAPY IN SEVERE COVID-19 PATIENTS

The high incidence of thrombosis noted in the studies[4-14] has led to universal consideration of thromboprophylaxis in most patients with COVID-19 to prevent this very high thrombotic risk (Figure 9).

Standard thromboprophylaxis[29,32-35]

- All patients who require hospital admission for COVID-19 should receive thromboprophylaxis with heparin in the absence of contraindications. LMWH is preferred over unfractionated heparin (UFH) due to the ease of use and lack of monitoring.
- Choice of LMWH over UFH is also due to the fact that regular monitoring required with UFH is not ideal in a situation where limited contact to minimise pathogen transmission is highly important. Also, an increase in acute phase reactants like factor VIII may make UFH monitoring problematic.
- UFH may however be considered in patients with very high risk of bleeding which may need urgent interruption of the anticoagulant and those with severe renal impairment where LMWH is contraindicated.
- Most common contraindications for heparin use are active bleeding, severe thrombocytopenia (less than 25×10^9/L; very rare in COVID-19) and history of heparin-induced thrombocytopenia (HIT). In the case of HIT, alternate anticoagulants like argatroban or fondaparinux should be considered.
- All patients should receive weight-adjusted doses of LMWH. Locally adapted protocols should be followed in these situations.

Intense thromboprophylaxis[32,35]

There have been several reports of "failure of prophylactic anticoagulation" in patients with COVID-19[36]. These may be due to several reasons including hypoxia being a well-recognised thrombotic risk factor[30]. Publications in the pre-COVID era also demonstrated lack of anticoagulant efficacy in patients who require mechanical ventilation and critical care support. There are no definite recommendations on the dosing for intense prophylaxis but the following have been suggested in guidelines:

- Doubling of the prophylactic LMWH dose.
- Intermediate between prophylactic and therapeutic LMWH dose.

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- Therapeutic dose LMWH *(author strongly recommends against this strategy without confirmation from randomised trials)*.
- It may be considered good practice to consider mechanical thromboprophylaxis (e.g. intermittent pneumatic compression devices) in all patients unless reasons exist to avoid them.

Thromboprophylaxis for patients who were on anticoagulants at admission[32,33,35]

Current evidence state that there may not be protection from severe COVID-19 in patients who may already be receiving anticoagulation for indications like atrial fibrillation, mechanical heart valve or previous VTE disease (Figure 9). However, results from large randomized trials are pending.

Those patients who are on oral anticoagulants may be managed as follows:

- Patients receiving vitamin K antagonists (VKA) or direct oral anticoagulant (DOACs) may continue these medications as long as they are able to take these medications orally and are not receiving medications which may interact with them. Reports of very high DOAC levels have been published in this situation due to drug interactions. Patients on VKA should ideally have close INR monitoring.
- LMWH should be used as standard if the patients cannot take orally or require medications which may interact with DOACs or VKA.
- Critical care patients should be switched to LMWH from DOACs or VKA.
- Dose of LMWH is based on the indication for anticoagulation (treatment dose for those on higher target INR or full-dose DOACs and prophylactic dose for those on standard INR target range and no recent thrombotic events or low-dose DOACs).

Thromboprophylaxis on hospital discharge[32.35]

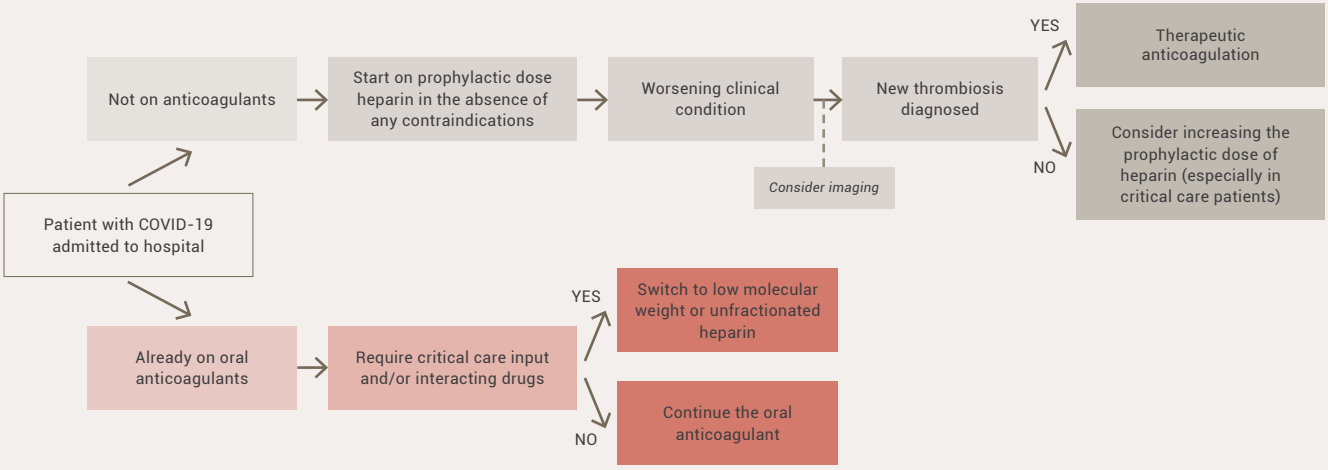
Publications have quoted low incidence of thrombosis in patients who were discharged after they recovered from COVID-19[36]. Some experts still consider thromboprophylaxis in those who are discharged after having a period of treatment required in critical care units:

- ISTH recommends extended thromboprophylaxis for 14 days or 30 days.
- This may be with LMWH or DOAC at a prophylactic dose.

Treatment of venous thromboembolism[29,32,33,35]

- Treatment should be as standard in patients with COVID-19 confirmed to have VTE (Figure 9). A low threshold should be maintained in all patients for the development of VTE, especially those who require critical care support.
- As detailed before, LMWH may be preferred over UFH for VTE treatment.
- Monitoring of LMWH is not necessary unless the patient has renal impairment or have extremes of body weight.
- Monitoring of LMWH should be with calibrated anti-factor Xa assays while those who may need UFH should be monitored using activated partial thromboplastin time and anti-factor Xa assays.
- D-dimer values should not be used to guide dosing of anticoagulation strategies unless randomised trials confirm its usefulness.
- An exception for considering treatment dose anticoagulation without image-proven thrombosis is a patient who cannot be transferred to radiology for scans due to infection-transmission risk or other practical reasons but a high suspicion of VTE is present.
- Treatment should be considered for at least three months and then reassessed for the need for extended anticoagulation.

Figure 9: A flow chart is provided for the prophylaxis and treatment of COVID-19 thrombosis



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ABBREVIATIONS

ACE2: Angiotensin converting enzyme-2
APTT: Activated partial thromboplastin time
ARDS: Acute respiratory distress syndrome
CI: Confidence interval
CT: Computed tomography
CTPA: Computed tomography pulmonary angiography
DD: D-dimer
DIC: Disseminated intravascular coagulation
DOACs: Direct oral anticoagulants
DVT: Deep vein thrombosis
HIT: Heparin-induced thrombocytopenia
HR: Hazard ratio
ICU: Intensive care unit
IL: Interleukin
INR: International normalized ratio
LMWH: Low molecular weight heparin
PAR: Protease-activated receptor
PE: Pulmonary embolism
PT: Prothrombin time
TNF: Tumor necrosis factor
UFH: Unfractionated heparin
VKA: Vitamin K antagonist
VTE: Venous thromboembolism
VWF: Von Willebrand factor

Stago
Diagnostics is in our blood.

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