CLINICAL GUIDELINE **CG10393-5**

Thromboprophylaxis, coagulopathy management and thrombosis in COVID-19 infection

For use in (clinical areas):	All clinical areas (except paediatrics and maternity)
For use by (staff groups):	All clinicians
For use for (patients):	For use for all adult patients (age ≥ 16 years) (excludes pregnancy)
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Purpose of the Guideline

There is limited international guidance on how to manage thrombotic risk, coagulopathy and disseminated intravascular coagulation (DIC) in patients with COVID-19 (SARs-CoV-2) infection. This document provides pragmatic guidance concerning adult, non-pregnant patients with suspected or confirmed COVID-19 infection on the following:

- Safe and appropriate thromboprophylaxis during admission and on discharge;
- Management of patients already on therapeutic anticoagulants on admission and discharge;
- Monitoring of thromboprophylaxis and therapeutic anticoagulation;
- Management of coagulopathy;
- Management of haemorrhage with no coagulopathy;
- Management of acute thrombosis;
- Haemofiltration in critical care.

For women with COVID-19 who are pregnant or have given birth within the past six weeks, follow the advice on VTE prevention in the RCOG guidance "Coronavirus (COVID-19) infection in pregnancy".

As the primary literature is being updated on a regular basis, this document will be reviewed as necessary (the date this document was last edited will be stated above in the status section).

Background and rationale

A striking feature of COVID-19 infection is the acute phase response (APR). Several pro-coagulant factors are positive acute phase reactants: Factor VIII, VWF, Fibrinogen and the APR are associated with an increased risk of thrombosis. Published data and local experience confirm that fibrinogen is often markedly elevated in the COVID-19 infected patients.

Pneumonia and sepsis are often complicated by disseminated intravascular coagulation (DIC), but although COVID-19 patients do have abnormalities of coagulation, they are not typical of DIC. The most marked abnormality is an elevation in d-dimer but without a parallel fall in platelets or prolongation of clotting times. This suggests that local rather than disseminated thrombin generation and fibrinolysis is taking place. Some elevation of PT/APTT is seen and may be independent prognostic marker for thrombosis.

The site of thrombin and fibrin formation appears to be the lungs, based on limited post-mortem data and clinical observations from CT scans and ventilation parameters (V/Q mismatch). Some patients have overt pulmonary emboli, but in others it is presumed to be microvascular thrombi.

The above is consistent with limited evidence from China indicating that patients receiving prophylactic dose UFH/LMWH had significantly better survival than those who did not. Despite the use of pharmacological thromboprophylaxis the incidence of pulmonary embolism (PE) is higher in patients with symptomatic COVID-19 infection.

In response to these findings, expertise from Haematology, ITU, Nephrology, Respiratory medicine and Pharmacy has been combined to create this guidance. This guideline follows NICE recommendations made in NG186, and takes into account interim findings in the ongoing three large multi-adaptive, randomized studies REMAP-CAP, ACTIV-4 and ATTACC. Other ongoing studies including IMPACT, HEP-COVID and INSPIRATION studies are awaited.

Linked clinical guidelines:

- CG10193 - VTE thromboprophylaxis in adults (non-pregnant) patients
- CG10166 – Initiating and prescribing oral anticoagulants
- CG10229 – Management of direct oral inhibitor anticoagulants (DOAC) part 1

Contents

Thromboprophylaxis in suspected/confirmed COVID-19 infection in patients NOT currently on therapeutic anticoagulation

Do not omit thromboprophylaxis due to coagulopathy, unless evidence of bleeding. Start VTE prophylaxis ASAP and within 14 hours of admission and provide patient with "Are you at risk of blood clots?" leaflet

Monitor: FBC daily; Bleeding and VTE risks daily in MDT or any time the clinical condition changes, and adjust VTE prophylaxis accordingly; Clotting screen (including fibrinogen) and D-dimer every 3 days, according to DIC score (see coagulopathy section)
Use clinical judgement for required monitoring once patient is off oxygen/MOFD/SOFD

Platelets <30x10^9/L or active bleeding

1. Offer IPC[2]
2. Discuss with Haematology Consultant

Platelets ≥30x10^9/L but <50x10$^{9/L}$ or other bleeding risk[1]
Assess for contra-indications

1. Offer IPC[2]
2. Standard dose pharmacological thromboprophylaxis as per CG10193
   If no contra-indication and bleeding risk taken into account, dose according to actual body weight and calculated CrCl (as per Cockcroft-Gault equation)

Platelets ≥50x10^9/L with no other risk factors for bleeding[1]
Assess for contra-indications

1. Offer IPC[2]
2. If no contra-indications and bleeding risk considered, offer intermediate dose pharmacological thromboprophylaxis for acutely ill medical patients[4]:
   a. For CrCl ≥30ml/min – see Table 1

Weight (kg)	First line	Contraindication to heparin (allergy, HIT, or religious reasons)
<50	Tinzaparin 4,500 units OD s/c	Fondaparinux 2.5-5mg OD s/c (depending on weight and risk factors)
50-119	Tinzaparin 9,000 units OD s/c	Fondaparinux 5mg OD s/c
120-150	Tinzaparin 12,000 units OD s/c	Fondaparinux 7.5mg OD s/c
>150	Tinzaparin 100 units/kg OD s/c Monitor anti-Xa and discuss with Haematology to consider splitting dose from OD to BD after 5 doses	Fondaparinux 7.5mg OD s/c

   b. For CrCl < 30 and ≥ 15 ml/min – see Table 2

Weight (kg)	First line	Second line (if concern with regards to bleeding risk)
<50	Enoxaparin 0.5mg/kg OD s/c Rounded to the nearest 20mg	Heparin 7,500 units BD s/c
50-119		Heparin 10,000 units BD s/c
120-150		Heparin 12,500 units BD s/c
>150		Heparin 12,500 units BD s/c

   c. For CrCl <15ml/min or dialysis patients discuss with Nephrology Consultant

On discharge[3]

Consider VTE prophylaxis for **duration of hospital stay, or 7 days**, whichever is longer, so long as not contraindicated.

Consider 28 days duration for patients with high risk for VTE and low bleeding risk.

[1] See section on bleeding risk factors
[2] IPC (Intermittent pneumatic compression device) – only offer if no contra-indication. Prioritise for those in critical care/those with haemorrhage/risk precluding use of pharmacological thromboprophylaxis
[3] See section on discharge of patients with suspected/confirmed COVID-19 infection on pharmacological thromboprophylaxis
[4] Decision based on interim findings in the ongoing three large multi-adaptive, randomized studies REMAP-CAP, ACTIV-4 and ATTACC. Other ongoing studies including IMPACT, HEP-COVID and INSPIRATION studies are awaited.

Off-label use of Tinzaparin

As the use of intermediate prophylactic doses of LMWH, heparin and fondaparinux in COVID patients is off-label, please report any adverse events related to this treatment (e.g. bleeding) via DATIX.
Similarly, any use of LMWH, UFH and fondaparinux are all off-label in patients less than 18 years of age. Please report any adverse events related to this treatment (e.g. bleeding) via DATIX.

Bleeding Risk Factors (see also Appendix 2)

Remember to consider bleeding risks when introducing thromboprophylaxis. King's Critical Care Units + Chelsea and Westminster Hospitals guideline has been used as a basis. Note, minor prolongation of PT and APTT (up to 5 seconds) are common in COVID-19 and are not contraindications to pharmacological thromboprophylaxis.

- Active bleeding (or within 3 months prior to admission)
- Acquired bleeding disorders
- Uncontrolled hypertension
- Concurrent use of anticoagulants
- Acute stroke (if acute stroke and sequential compression devices (SCDs) contraindicated, review anticoagulant prophylaxis daily in the MDT)
- Thrombocytopenia (platelet counts <50x10^9/L, checked on admission) – if platelets below 30-50x10^9/L, consider standard dose anticoagulant prophylaxis in the absence of additional bleeding risk factors and monitor platelet count daily
- Uncontrolled inherited bleeding disorders (such as haemophilia)
- Trauma patient*
- Neurosurgery, spinal surgery, or eye surgery*
- For at least 4-6 hours after surgery
- LP/epidural/spinal anesthesia within the previous 4-6 hours or expected within the next 12 hours
- Other procedures with high bleeding risk*
- PT (prothrombin time) >6 seconds above upper limit of normal (ULN) or APTT (activated partial thromboplastin time) >6 seconds above ULN and **NOT** due to coagulopathy
- CrCl <30mL/min
- Haematological disorder affecting platelet function (e.g. myelodysplasia (MDS)); platelets >1000x10^9/L in myeloproliferative disorders (MPN)

* review the bleeding risk and thrombotic risk daily in the MDT

Additional VTE Risk Factors (see also Appendix 2)

Currently there is no evidence on pharmacological VTE prophylaxis for specific groups with additional VTE risk factors, such as patients on or with:

- Sex hormone treatment
- Cancer (current or past)
- Renal replacement
- Extracorporeal membrane oxygenation
- Clotting conditions
- History of VTE
- Obesity (BMI ≥ 30kg/m^2)

Table 1 – Intermediate dose thromboprophylaxis recommendations for patients with suspected/confirmed COVID-19 infection– for platelet counts ≥50x10^9/L and NO other bleeding risks and a CrCl of ≥30mL/min

Weight (kg)	First line	Contraindication to heparin (allergy, HIT, or religious reasons)
<50	Tinzaparin 4,500 units OD s/c	Fondaparinux 2.5-5mg OD s/c (depending on weight and risk factors)
50-119	Tinzaparin 9,000 units OD s/c	Fondaparinux 5mg OD s/c
120-150	Tinzaparin 12,000 units OD s/c	Fondaparinux 7.5mg OD s/c
>150	Tinzaparin 100 units/kg OD s/c Monitor anti-Xa and discuss with Haematology to consider splitting dose from OD to BD after 5 doses	Fondaparinux 7.5mg OD s/c

See notes at the end of table 2

Table 2 – Intermediate dose thromboprophylaxis recommendations for patients with suspected/confirmed COVID-19 infection - for platelet counts ≥50x10^9/L and NO other bleeding risks other than CrCl <30mL/min and CrCl ≥ 15mL/min*

Weight (kg)	First line	Second line (if concern with regards to bleeding risk)
<50	Enoxaparin 0.5mg/kg OD s/c Rounded to the nearest 20mg	Heparin 7,500 units BD s/c
50-119		Heparin 10,000 units BD s/c
120-150		Heparin 12,500 units BD s/c
>150		Heparin 12,500 units BD s/c

NOTES:

- If heparin is contra-indicated, please discuss alternative (e.g. fondaparinux) with haematology, nephrology or pharmacy.
- There is an increased risk of bleeding and thrombosis in severe renal impairment

*CrCl <15mL/min discuss with Nephrology Consultant as contraindicated (**Note:** LMWH is contraindicated if the CrCl <30mL/min but may be considered with anti Xa monitoring if CrCl 15-29 mL/min). See section on Anti-Xa monitoring

Points for consideration with regards to tables 1-2:

1. Reassess bleeding risk daily

2. For HIT (heparin induced thrombocytopenia), discuss with a Haematology Consultant

3. Decision for intermediate dose was based on interim findings in the ongoing three large multi-adaptive, randomized studies REMAP-CAP, ACTIV-4 and ATTACC. Other ongoing studies including IMPACT, HEP-COVID and INSPIRATION studies are awaited.

Discharge of patients on pharmacological thromboprophylaxis

For patients who meet high VTE risk criteria but with a low bleeding risk, continue VTE prophylaxis for the **duration of the hospital stay or 7 days, whichever is longer**, as per NICE recommendations. Note, the British Thoracic Society (BTS) suggests VTE prophylaxis for up to 28 days may be considered for patients discharged following COVID-19 pneumonia who are deemed to be high risk for VTE and low bleeding risk.***

Key VTE risk factors include:

- Advanced age
- ≥7 days hospital stay
- Stay in ICU/escalated care
- Cancer (current)
- A prior history of VTE
- Thrombophilia
- Severe immobility
- An IMPROVE predictive VTE score of 4 or more (appendix 2).

For bleeding risk factors, see the VTE-Bleed score (appendix 2).

If patient is discharged before a total of 7 days of thromboprophylaxis have been administered, please discharge with remaining days with one of the following options:
1st line: standard dose tinzaparin s/c* thromboprophylaxis – contraindicated if CrCl <20mL/min
OR 2nd line: rivaroxaban 10mg od** (off-label) – contraindication CrCl <15mL/min
If CrCl <15mL/min or on dialysis, discuss with Nephrology Consultant.

*Offer sharps bin, provide education for patient/relative/carer within the household. Do not arrange a district Nurse for the sole purpose of administering s/c injections.
**Inform patient of off-label use of DOAC; only offer if tinzaparin not an option.
***Provide all above cases the WSH Trust patient information leaflet on 'are you at risk of blood clots' and highlight signs/symptoms of venous thromboembolism (VTE) and when to seek urgent medical attention.

Management of patients already on anticoagulation on admission

For patients who are already having anticoagulation treatment, e.g.: warfarin (target INR 2.5)* **OR** direct oral anticoagulant agent (DOAC) such as dabigatran, apixaban, edoxaban, rivaroxaban**; for another condition when admitted to hospital:

- Continue their current treatment dose of anticoagulation unless contraindicated by a change in clinical circumstances
- Consider switching to LMWH if their current anticoagulation is not LMWH and their clinical condition is deteriorating

  ***NOTE:** Once INR is below the lower end of their target range, start treatment dose LMWH

  ****NOTE:** rivaroxaban needs to be taken with food

Antibiotic, antiviral and other COVID-19 trial drugs can have significant drug interactions with **all** classes of anticoagulants, particularly via the CYP3A4 pathway. Additionally, monitoring of disseminated intravascular coagulation (DIC)/other coagulopathy in patients on therapeutic anticoagulants, which affect the routine coagulation screen and D-dimers, is challenging.

Low molecular weight heparin (LMWH) has some additional anti-inflammatory effect, by neutralizing pro-inflammatory proteins, which can be useful in managing the bi-directional relationship between

inflammation and thrombosis. Subcutaneous heparin may also bind to the SARS-COV-2 spike protein and block viral attachment.

Parenteral anticoagulants offer fewer drug-drug interactions, better absorption and ease of measurement, compared to oral anticoagulants.

Discharge of patients on therapeutic anticoagulation

Check full blood count (FBC), renal/hepatic function, drug interactions and for any contraindications. Switch patient back to original anticoagulant the patient was on prior to admission, where appropriate and at an appropriate dose.

For patients with acute VTE during admission, switch from treatment LMWH to an appropriate DOAC if no contraindications.

- For warfarin initiation see CG10166
- For switching to a DOAC see CG10229

Provide verbal and written patient information with the relevant leaflet/booklet and alert card. Inform the ward Pharmacist and Anticoagulant monitoring service (AMS).

The discharging Doctor is responsible for including the anticoagulant management plan in the discharge summary and appropriate follow-up arrangements to ensure effective communication for transfers of care.

Monitoring of thrombosis risk and bleeding risk for safe thromboprophylactic/therapeutic anticoagulation

D-dimer, platelets, PT and fibrinogen

One of the most common laboratory findings noted in the COVID-19 patients requiring hospitalisation has been the increase in D-dimers. The prothrombin time (PT) has also shown modest prolongation, and high fibrinogen levels are seen.

Whilst thrombocytopenia is often considered an indicator of sepsis mortality, however this is not the case at admission in many of the COVID-19 patients.

Based on currently available literature, it is recommended to measure prothrombin time and platelet count in all patients who present with suspected COVID-19 infection. This may help stratify patients who may need admission and close monitoring. Any condition (e.g. liver disease) or medication (e.g. anticoagulants), which may alter the parameters, should be accounted for.

Once patients with COVID-19 pneumonia are off oxygen and discharge is being planned, D-dimer monitoring can be adjusted on an individual basis according to clinical need.

Anti-Xa level monitoring

Although anti-Xa activity levels remains a poor predictor of bleeding risk, it is the most appropriate measure of the pharmacodynamic effects of LMWHs. In the request, state:

- The therapeutic agent (tinzaparin/enoxaparin/etc)
- Peak anti-Xa level
- For fondaparinux in table 1, there is no lower dose than 2.5mg for weight <50kg. A peak anti-Xa level should be considered to assess for accumulation.

Note: anti-Xa levels for unfractionated heparin and fondaparinux have to be sent away for processing

Anti-Xa levels should NOT be routinely ordered. They should be considered for subgroups of patients to assure therapeutic and non-toxic levels:

- Underweight patient (less than 50kg)
- BMI ≥35; weight >150kg
- CrCl 30-60mL/min and ≥70 years of age/with extended use (more than 7 days)/suspicion of sub-therapeutic doses
- CrCl is difficult to estimate (e.g. amputee)
- Intermediate dose thromboprophylaxis
- Bleeding/new thrombosis.

Do **NOT** omit doses, whilst anti-Xa results are pending; level interpretation is not usually an urgent matter. If further advice is required, discuss with haematology consultant.

Use CrCl as calculated by Cockcroft-Gault equation, **NOT eGFR** - a CrCl calculator is available on **Microguide** app.

Frequency of monitoring for LMWH (e.g. tinzaparin and enoxaparin)

Peak anti-Xa levels	
CrCl ≥30ml/min	4 hours post the 5th dose
CrCl <30mL/min or bleeding concerns	4 hours post the 4th dose

If the patient is on ITU, the ITU Consultant and clinical Pharmacist should agree on the appropriate adaption of thromboprophylaxis dose and frequency of anti-Xa monitoring.

STANDARD DOSE PROPHYLAXIS LMWH – dose adjustment

The target range for peak anti-Xa level for standard prophylaxis doses tinzaparin and enoxaparin is **0.2-0.4 (units/mL).**

Peak anti-Xa activity (units/mL) and dose adjustment		
<0.2	0.2-0.4	>0.4
Discuss with Haematology and consider increasing dose by 10% Re-check levels after 4th dose	In range – no dose adjustment needed (consider rechecking levels after 4 further doses)	Discuss with haematology and consider omitting one dose, then decreasing by 10% Re-check levels after 4th dose

INTERMEDIATE DOSE PROPHYLAXIS LMWH

For intermediate dose LMWH (Table 1), peak anti-Xa levels should be between those for prophylactic LMWH and treatment dose LMWH.

TREATMENT DOSE LMWH – dose adjustment

The peak anti-Xa levels for LMWH treatment dose (tinzaparin 175 units/kg or enoxaparin 1mg/kg BD or OD) is **0.5-1.0 (units/mL).**

Peak anti-Xa activity (units/mL) and dose adjustment		
<0.5	0.5-1.0	>1.0
Discuss with Haematology and consider increasing dose by 20-25% Re-check levels after 4th dose	In range – no dose adjustment needed Consider rechecking levels after 4 further doses	Discuss with Haematology and consider omitting one dose +/- decrease dose by 10-25% Re-check levels after 4th dose

Acute thrombosis

Investigation

Practitioners should use standard-of-care objective testing (i.e. CTPA, V/Q scan, MRI, venography, Doppler ultrasonography) to diagnose venous thromboembolism (VTE) based on clinical index of suspicion. A pragmatic approach (e.g. point-of-care bedside ultrasonography or echocardiography) can also be combined with standard-of-care objective testing (ISTH recommendation).

The d-dimer is frequently elevated (including values in excess of 5000 ng/mL FEU (fibrinogen equivalent units). In the absence of clinical features of acute thrombosis, there is no need to investigate for VTE as a cause of an elevated d-dimer (ISTH recommendation).

Suspect possible VTE in the following situations (not exclusive):

- Unilateral limb swelling
- Sudden deterioration of oxygenation/respiratory distress
- Hypoxia out of keeping with CXR findings an upward step in d-dimer level
- Reduced blood pressure
- New onset tachycardia
- An upward step in d-dimer level

In patients where there is a clinical suspicion of VTE urgent investigation to rule out VTE is essential.

The value of the clinical pre-probability WELLS score is unclear in this patient group due to the high baseline risk, so clinical assessment with a low threshold for further investigation is recommended.

IV contrast medium for CTPA is not recommended if CrCl <30mL/min.

Treatment

- **CrCl ≥30 mL/min:** treatment dose tinzaparin 175 units/kg OD - with **no** baseline coagulopathy/contraindications
- **CrCl <30 mL/min:** treatment renal dose enoxaparin 1 mg/kg OD – monitor peak anti-Xa levels 4 hours after 4th dose
- On discharge, consider switching from LMWH to a DOAC if not contraindicated

  * The use of enoxaparin in CrCl<15ml/min is off-label

Note

- The BTS recommends thrombolysis for patients with massive PE, as for non-COVID-19 infected patients. Larger studies are required to investigate this potential therapeutic approach.

Coagulopathy

The coagulopathy and thrombocytopenia in COVID-19 infection represents a form of disseminated intravascular coagulopathy (DIC) or sepsis induced coagulopathy (SIC).

Evidence has shown that around 70% of non-survivors had overt disseminated intravascular coagulation (DIC), as demonstrated by the International Society on Thrombosis and Haemostasis (ISTH) DIC score, compared with only 0.6% of survivors. The DIC score has shown prognostic value in COVID-19 pneumonia and is calculated from measurement of the platelet count, D-dimer, fibrinogen, and prothrombin time as shown in table 3 below.

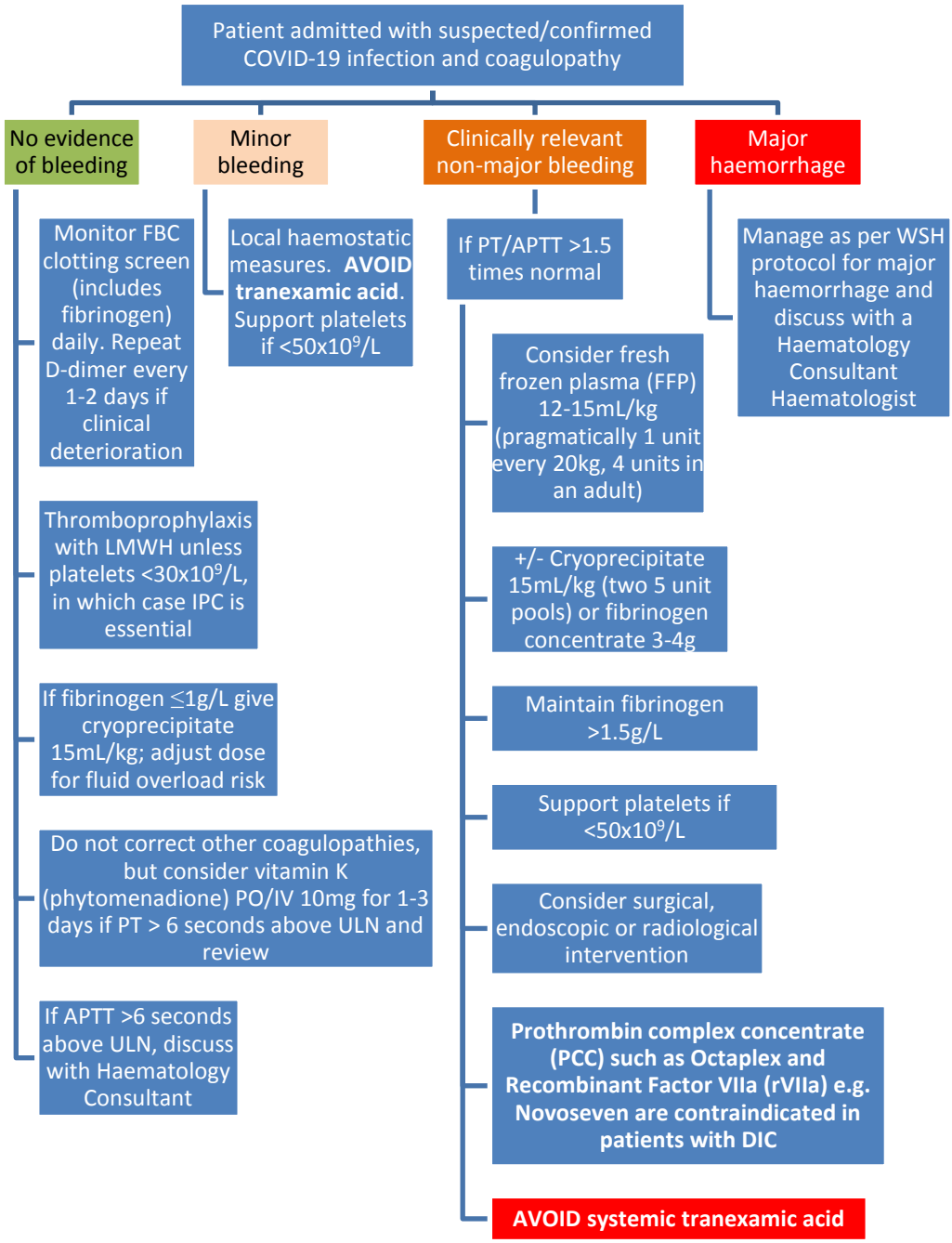
The DIC score can be calculated as below. If an FBC, clotting screen and d-dimer are requested on a single order set, the laboratory will automatically calculate the DIC score for inpatients. The tests required to calculate the DIC score are part of the order sets on e-Care for suspected/confirmed COVID-19 cases.

Table 3 – DIC score (Taylor et al, 2001; ISTH)

Parameter	Score
Platelet count	
>100 x 10^9/L	0
50-100 x 10^9/L	1
<50 x 10^9/L	2
D-dimer	
No increase	0
Moderate increase (1-10 times upper limit of normal)	2
Strong increase (>10 times upper limit of normal)	3
Fibrinogen	
>1.0 g/L	0
≤1.0 g/L	1
Prothrombin time prolongation	
<3s	0
3-6s	1
>6s	2
Overt Disseminated Intravascular Coagulation probable (repeat score daily)	**≥ 5**
DIC not present. Repeat score in 1-2 days	0-4
If a patient on **ITU**, repeat score daily regardless of score	

The best management of DIC is to identify and treat the underlying condition, which with COVID-19 infection is difficult. Recovery from DIC is dependent on endogenous fibrinolysis breaking down the disseminated thrombi.

Note: Use clinical judgement for any required monitoring once patient is off oxygen/Medically or Surgically Optimised for Discharged (MOFD/SOFD).



Key:
IPC = intermittent pneumatic compression
ULN = upper limit of normal

Pharmacological thromboprophylaxis in patients with coagulopathy

Coagulopathy should not prevent the prescribing and administration of pharmacological thromboprophylaxis, unless there is evidence of active bleeding. Established coagulopathy is not an independent risk factor for bleeding. Patients with DIC are frequently considered to be prothrombotic, even with deranged coagulation parameters.

Management of haemorrhage in patients with suspected/confirmed COVID-19 infection with NO coagulopathy

Management is as for cases with no COVID-19 infection, i.e. general resuscitation with fluids, local haemostatic measures and, as appropriate, surgical, endoscopic or radiological intervention.

Tranexamic acid 1g IV should be given.

Haemofiltration (CVVHDF) guidance on Critical Care in suspected/confirmed COVID-19 infection

Recommended practice within the Critical Care national groups suggests that CVVHDF patients should be initiated on the following:

<u>If the patient does NOT have a PE or DVT and is NOT routinely on anticoagulation treatment dose prior to admission:</u>

Prismocitrate + **intermediate dose** tinzaparin (see Table 1) based on weight *
*If high risk of bleeding - consider using unfractionated heparin, discuss dosing with ward Pharmacist

<u>OR</u> (depending on availability of prismocitrate)

Non-citrate CVVHDF protocol with unfractionated heparin (primed) in the circuit + as per table 1 based on weight and DIC score*
*If high risk of bleeding - consider using unfractionated heparin, discuss dosing with ward Pharmacist

<u>If the patient has a suspected or confirmed PE or DVT or was on anticoagulation treatment dose prior to admission:</u>

Prismocitrate + **treatment dose** tinzaparin (175units/kg):

<u>OR</u> (depending on availability of prismocitrate)

Non-citrate CVVHDF protocol with heparin (primed) in the circuit - speak with the duty Consultant Haematologist.

- APTT ratio (APTT-R) monitoring is unreliable in patients with existing/evolving coagulopathy. Anti-Xa monitoring for UFH is recommended but currently unavailable on site. In COVID-19 suspected/confirmed cases, the presence of raised fibrinogen and factor VIII levels as part of the acute phase response contributes to the poor reliability of the APTT-R in such cases. It is acceptable to establish an APTT-R within range and confirm efficacy of the regimen with a peak anti-Xa level once available on discussion with the Haematology Consultant.
- Any significant change in the UFH infusion rate should be assessed with the APTT-R and ideally later with a peak anti-Xa once available.

Aim for an APTT ratio of 2-2.5 if there is a **low bleeding risk**

- NOTE: use of unfractionated heparin increases the risk of heparin induced thrombocytopenia (HIT) which does not have a rapid diagnostic test (discuss with the Consultant Haematologist) and is a highly prothrombotic state

If the patient is deemed a **high bleeding risk**, then consider aiming for an APTT ratio of 1.5-2

If further advice is required re: dose adjustments for anticoagulants, discuss with heamatology.

Pharmacokinetic considerations

	Tinzaparin (LMWH)	Enoxaparin (LMWH)	Fondaparinux (synthetic polysaccharide)	UFH (e.g. heparin 5000 units bd)	Apixaban
Absorption half life	3.3 hours (90% bioavailable based on anti-Xa activity)	3-4 hours (100% absolute bioavailability)	Half Cmax concentration is reached in 25 minutes (100% absolute bioavailability)	Depends on the dose administered, the route of administration and is subject to wide inter- and intra-individual variation	1-2 hours (50% oral bioavailability)
Peak onset	4-6 hours	3-5 hours	2 hours	Depends on the dose administered, the route of administration and is subject to wide inter- and intra-individual variation	3-4 hours
Elimination half life	1.5 hours	5-7 hours	17-21 hours	Depends on the dose administered, the route of administration and is subject to wide inter- and intra-individual variation	12 hours
Elimination	Renal	Renal	Renal	Renal & hepatic clearance	Renal
Anti Xa:IIa ratio	2-2.7:1	2.7-4.1:1	Pure Anti-Xa	N/A	Anti-Xa

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Development of the guideline

Changes compared to previous document

See additional information below for further information – revisions may occur upon review of new literature.

Statement of clinical evidence

This document is based on best interpretation of evidence based primary literature. This document will be updated frequently depending on the most current evidence published regarding COVID-19 in relation to hematological disorders, specifically regarding thromboprophylaxis.

Distribution list/dissemination method

Recommendations within this document has been disseminated to relevant specialists, including the Thrombosis committee (Chair action) and the Drugs and Therapeutics Committee (core group agreement) as part of a rapid launch of this guidance.

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Additional Information:	**Version 1 released 24/4/2020** **Version 2 (discussion 29/4/2020, agreed and published 1/05/2020):** – Additional author who has contributed to evidence base for renal impairment dosing and monitoring of anti-Xa levels has been added. From this a table 2 provides clear guidance for options for CrCl <30mL/min. Evidence from the ICS thromboprophylaxis guidance that was released 25/4/2020 (reference 18) was utilised for an informed decision process. – Perioperative considerations were discussed and whether heparin should be used due to the shorter half-life, however due to concerns of HIT with overuse of UFH this is not currently recommended due to the lack of evidence. – Extended VTE was discussed as Addenbrookes have started recommending 14 days post discharge of LMWH or DOAC. However due to the lack of evidence for its safety or efficacy, this will not be available considered for inclusion at this time. – Changing patient's usual DOAC or warfarin to treatment dose LMWH whilst an inpatient was discussed, and an addition was made under table 1 for clarity. **Version 3 released late May 2020** – Expansion of title of CG and its purpose – Further clarification on when to use standard vs intermediate dose pharmacological thromboprophylaxis added, with regard to platelet count and bleeding risk – New section on management of acute thrombosis – Additional information regarding monitoring of UFH infusions – Additional information regarding anti-Xa monitoring for LMWH – Information on reversal of tinzaparin with protamine sulphate – ACS tables 3 and 4 added as per Claudia Wand's recommendations – Changes to risk stratification in the table of dose recommendations – New section on extended VTE for discharge – New section on management of coagulopathy including haemorrhage – New section on management of patients already on therapeutic anticoagulation – Addition of Improve VTE score – Addition of quick reference guide

	Version 4 released March 2021 – Change to tables 1 and 2 in line with recent NICE Guidance (removal of D-Dimer score from dosing criteria) – Addition of guidance to report DATIX on adverse events resulting from off-label use of anticoagulants – Addition of VTE risk factors – Removal of tables 3 and 4, plan by cardiology to revert to former ACS guidance – Age cut-off of 16 specified – Reference added to COVID in pregnancy guidelines – Change to guidance for COVID patients on haemofiltration – Expansion of guidance on action to take on patients admitted on anticoagulation – Removal of appendix 3 – Quick reference guide (merged into one on page 3 of this document) – Changes to the discharge of patients on pharmacological thromboprophylaxis section – Expansion of guidance on anti-Xa level monitoring (removal of trough levels and addition of peak anti-Xa level targets for treatment dose LMWH) – Inclusion of BTS (British Thoracic Society) recommendations regarding thrombolysis and discharge of patients – Consideration of clinical trials REMAP-CAP, ACTIV-4 and ATTAC regarding consideration of treatment dose anticoagulation in ward-based patients with less VTE events and improved survival without significant increase in bleeding events – Inclusion of VTE-Bleed score (Appendix 2)

Appendix 1 – Protamine for LMWH overdose

This REFERS only to tinzaparin (Innohep) for prophylaxis.

Please see protamine sulfate in the BNF for doses to administer for unfractionated heparin overdose.

Reversal of tinzaparin (Innohep) heparinization (prophylactic dose) with protamine sulphate treatment

The dosage for tinzaparin thromboprophylaxis in high-risk surgery such as orthopaedic surgery is 50 anti Xa U/kg or a fixed dose of 4500 anti Xa U irrespective of body weight, and in general surgery is a fixed dose of 3500 anti Xa U irrespective or body weight. The sign of tinzaparin overdosage is bleeding. Although we have no clinical experience with overdosage, studies in healthy volunteers indicate that:

1mg protamine sulphate* per 100 anti-Xa units tinzaparin administered should be given over 10-15 minutes[1-3]. This neutralises 65-80% of the anti-Xa activity almost immediately.

This may be administered at any time up to and including 180 minutes (3 hours) after tinzaparin administration[#].

A partial return of tinzaparin's anti-Xa, anti-IIa and APTT activities (to 76%, 58%, 44% of original respectively) are seen 3 hours after its reversal probably due to continuous absorption of Innohep from the subcutaneous depot. Repeat protamine sulphate infections or a continuous infusion may be administered to achieve or maintain neutralization. Suggested timescales for repeat injections are 30-60 minutes after 1st injection and if necessary, every 60 minutes thereafter until APTT normalises.

Bodyweight (kg)	Tinzaparin dose (anti-Xa units)	Tinzaparin dose (mL)	Protamine sulphate dose (mg)
50	2500	0.25	25.0
55	2750	0.28	28.0
60	3000	0.30	30.0
65	3250	0.33	33.0
70	3500	0.35	35.0
75	3750	0.38	38.0
80	400	0.40	40.0
85	4250	0.43	43.0
90	4500	0.45	45.0
95	4750	0.48	48.0
100	5000	0.50	50.0

*Potential side effects of protamine must be considered, and patients carefully observed. In particular, protamine is contraindicated in patients with allergies to fish and fish products.

#If protamine sulphate is first administered much later than three hours after tinzaparin was given, you may wish to consider an adjustment to reflect decreasing tissue level of tinzaparin. Volunteer data shows peak plasma levels occurring 4-6 hours post s/c administration[4], with absorption half-life approximately 200 minutes and elimination half-life approximately 80 minutes[5].

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2. British National Formulary (BNF) accessed via (28/5/2020)
3. Prosulf 10mg/mL solution for injection monograph. Electronic medicines compendium. Wockhardt. Last updated 9/5/2018, accessed via https://www.medicines.org.uk/emc/product/8/smpc (28/5/2020)
4. Matzsch T et al; Thromb, Haemost, 5.7 97 (1987)
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Appendix 2 – IMPROVE predictive VTE score and VTE-Bleed score (see the "Discharge of Patients" section)

IMPROVE predictive VTE score

The IMPROVE [International Medical Prevention Registry on Venous Thromboembolism] Predictive score was designed to assess the risk of VTE in hospitalized medical patients. The IMPROVE Predictive score for VTE includes 4 independent risk factors for VTE present at admission.

Criteria	Points
Previous VTE	3 points
Malignancy (treated or untreated within the previous 6 months)	1 points
Thrombophilia	3 points
Age >60	1 point
Max score	**8 points**

IMPROVE predictive score	
	VTE risk on admission
0-1	Low: Observed VTE risk <1%
2-3	Moderate
≥ 4	High: Observed VTE risk 5.7%

VTE-BLEED score

Criteria	Points
Active cancer – cancer diagnosed or requiring treatment ≤ 6 months previously (excluding basal-cell or squamous-cell carcinoma of the skin), or recently recurrent or progressive cancer	2 points
Male with uncontrolled atrial hypertension - ≥ 140 mmHg at baseline	1 point
Anaemia – Hb < 13 g/dL (men) or < 12 g/dL (women)	1.5 points
History of bleeding – any clinically relevant bleeding event including rectal bleeding, frequent epistaxis, haematuria	1.5 points
Age ≥ 60 years	1.5 points
Renal dysfunction – eGFR < 60 mL/min	1.5 points

VTE-BLEED predictive score	
	Bleeding risk
< 2	Low bleeding risk
≥ 2	High bleeding risk