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 (excludes pregnancy)
Document owner: Thrombosis Committee
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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 and discharge;
- Management of Acute Coronary Syndrome (ACS);
- 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.

As the primary literature is being updated on a regular basis, this document will be reviewed within the next 2 months from the date of publication (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/PTT 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. There is little evidence to guide altering or intensifying standard of care.

In response to these findings expertise from Haematology, ITU, Nephrology and Pharmacy has been combined to create this guidance. A consensus statement from the International Society of Thrombosis and Haemostasis (ISTH) forms the basis of these recommendations, along with measures implemented by other UK NHS hospitals.
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

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- \( \text{CrCl} \geq 30 \text{mL/min} \) (table 1)
- \( \text{CrCl} < 30 \text{mL/min} \) (table 2)

Acute coronary Syndrome (ACS) recommendations - for platelet counts \( > 70 \times 10^9/L \) and NO other bleeding risks and a:
- \( \text{CrCl} \geq 30 \text{mL/min} \) (table 3)
- \( \text{CrCl} < 30 \text{mL/min} \) (table 4)

Discharge of patients on pharmacological thromboprophylaxis

Management of patients already on anticoagulation on admission

Discharge of patients on therapeutic anticoagulation

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

- D-dimer, platelets, PT and fibrinogen
- Anti-Xa level monitoring
- Bleeding risk factors
- Frequency of monitoring for low molecular weight heparins (LMWHs), e.g. tinzaparin and enoxaparin
- Dose adjustment based on anti-Xa levels

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- Treatment

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- Disseminated Intravascular (DIC) score
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Development of the guideline

Appendix 1: Protamine for LMWH overdose

Appendix 2: IMPROVE Predictive VTE score

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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

Monitor:
FBC daily
Clotting screen (including fibrinogen) and D-dimer every 1-2 days, according to DIC score (see coagulopathy section)

Platelets <30x10^9/L or active bleeding
1. Offer IPC\(^2,5\)
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\(^2,5\)
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\(^2,5\)
2. If no contra-indications and bleeding risk taken into account, offer standard or intermediate dose pharmacological thromboprophylaxis\(^5\):
   a. For CrCl ≥30ml/min – see table 1
   b. For CrCl < 30ml/min – see table 2
   c. For CrCl <15ml/min or dialysis patients discuss with Nephrology Consultant
3. Consider treatment dose anticoagulation if deteriorating pulmonary status/ARDS\(^4\) without established VTE
4. For anti-Xa monitoring and subsequent dose adjustments refer to monitoring section

On Discharge
Consider pharmacological thromboprophylaxis in patients with low bleeding risk\(^3\) and with key VTE risk factors\(^3,53\)

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For ACS patients see tables 3 and 4
\(^1\) 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
\(^4\) ARDS (Acute respiratory distress syndrome)
\(^5\) ISTH recommendation
Bleeding Risk Factors

Remember to consider bleeding risks when introducing thromboprophylaxis. King’s Critical Care Units + Chelsea and Westminster Hospitals guideline has been used as a basis:

- 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
Table 1 – Standard/intermediate dose thromboprophylaxis recommendations for patients with suspected/confirmed COVID-19 infection – for platelet counts ≥50x10⁹/L and NO other bleeding risks and a CrCl of ≥30mL/min

<table>
<thead>
<tr>
<th>D-dimer</th>
<th>Weight (kg)</th>
<th>First line</th>
<th>2nd line</th>
<th>Contraindication to heparin (allergy, HIT, or religious reasons) – 2nd line</th>
<th>Contraindication to heparin – 2nd line (stated in order of preference in relation to cost effectiveness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000 ng/mL FEU</td>
<td>&lt;50</td>
<td>Tinzaparin 2500 units od s/c</td>
<td>Enoxaparin 20mg od s/c</td>
<td>Fondaparinux 2.5mg s/c alternate days or OD*</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>50-100</td>
<td>Tinzaparin 4500 units od s/c</td>
<td>Enoxaparin 40mg od s/c</td>
<td>Fondaparinux 2.5mg od s/c</td>
<td>Apixaban 2.5mg bd PO OR Argatroban 2 micrograms/kg/minute IV infusion OR Danaparoid IV as per BNF and medusa (based on weight)</td>
</tr>
<tr>
<td></td>
<td>101-150</td>
<td>Tinzaparin 4500 units bd s/c</td>
<td>Enoxaparin 40mg bd s/c</td>
<td>Fondaparinux 5mg od s/c</td>
<td>Apixaban 2.5mg bd PO OR Argatroban 2 micrograms/kg/minute IV infusion OR Danaparoid IV as per BNF and medusa (based on weight)</td>
</tr>
<tr>
<td></td>
<td>&gt;150</td>
<td>Tinzaparin 6000 units bd s/c</td>
<td>Enoxaparin 60mg bd s/c</td>
<td>Fondaparinux 7.5mg od s/c</td>
<td>Apixaban 5mg bd PO OR Argatroban 2 micrograms/kg/minute IV infusion OR Danaparoid IV as per BNF and medusa (based on weight)</td>
</tr>
<tr>
<td>≥1000* ng/mL FEU</td>
<td>&lt;50</td>
<td>Tinzaparin 2500-4500 units bd s/c Dosing depends on d-dimer and weight</td>
<td></td>
<td>Heparin 5000 units tds s/c Dosing depends on d-dimer and weight</td>
<td>Apixaban 2.5-5mg bd PO OR Argatroban 2 micrograms/kg/minute IV infusion Dosing depends on d-dimer and weight</td>
</tr>
<tr>
<td></td>
<td>50-100</td>
<td>Tinzaparin 4500 units bd</td>
<td>Enoxaparin 40mg bd s/c</td>
<td>Fondaparinux 5-7.5mg od s/c Dosing depends on d-dimer and weight</td>
<td>Apixaban 5mg bd PO OR Argatroban 2 micrograms/kg/minute IV infusion OR Danaparoid IV as per BNF and medusa (based on weight)</td>
</tr>
<tr>
<td></td>
<td>101-150</td>
<td>Tinzaparin 9000 units bd</td>
<td>Enoxaparin 80mg bd s/c</td>
<td>Fondaparinux 5mg bd s/c</td>
<td>Apixaban 5mg bd PO OR Argatroban 2 micrograms/kg/minute IV infusion OR Danaparoid IV as per BNF and medusa (based on weight)</td>
</tr>
<tr>
<td></td>
<td>&gt;150</td>
<td>Tinzaparin 12,000 units morning and 10,000 units evening s/c</td>
<td>Enoxaparin 120mg bd s/c</td>
<td>Apixaban 10mg bd PO for the first 7 days then 5mg bd PO thereafter</td>
<td>Argatroban 2 micrograms/kg/minute IV infusion OR Danaparoid IV as per BNF and medusa (based on weight)</td>
</tr>
</tbody>
</table>

NOTE: A change of anticoagulant regimen (i.e. from standard prophylactic or intermediate-dose to treatment-dose regimen) can be considered in patients without established VTE but deteriorating pulmonary status or ARDS (ISTH recommendation).

* discuss with a Haematologist to consider a peak anti-Xa level after the 5th dose.

See notes at the end of table 4
Table 2 – Standard/intermediate dose thromboprophylaxis recommendations for patients with suspected/confirmed COVID-19 infection in patients - for platelet counts >50x10⁹/L and NO other bleeding risks other than CrCl <30mL/min – NOTE: increased risk of bleeding and thrombosis in severe renal impairment

<table>
<thead>
<tr>
<th>D-dimer</th>
<th>Weight (kg)</th>
<th>First line</th>
<th>2nd line</th>
<th>Contraindication to heparin (allergy, HT, or religious reasons) – 1st line</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000 ng/mL FEU</td>
<td>&lt;50</td>
<td>Enoxaparin 20mg od s/c**</td>
<td>Heparin 5000 units bd s/c</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>50-100</td>
<td>Enoxaparin 20mg od s/c</td>
<td>Heparin 5000 units bd s/c</td>
<td>Apixaban 2.5mg bd PO**</td>
</tr>
<tr>
<td></td>
<td>101-150</td>
<td>Enoxaparin 40mg od s/c</td>
<td>Heparin 5000 units tds s/c</td>
<td>Apixaban 2.5mg bd PO**</td>
</tr>
<tr>
<td></td>
<td>&gt;150</td>
<td>Enoxaparin 60mg od s/c</td>
<td>Heparin 10,000 units bd s/c</td>
<td>Apixaban 2.5mg bd PO**</td>
</tr>
<tr>
<td>&gt;1000* ng/mL FEU</td>
<td>&lt;50</td>
<td>Enoxaparin 20mg – 40mg od s/c</td>
<td>Heparin 5000 units bd - 5000 units tds s/c</td>
<td>Apixaban 2.5-5mg bd PO**</td>
</tr>
<tr>
<td></td>
<td>50-100</td>
<td>Enoxaparin 40mg od s/c</td>
<td>Heparin 5000 units tds s/c</td>
<td>Apixaban 2.5-5mg bd PO**</td>
</tr>
<tr>
<td></td>
<td>101-150</td>
<td>Enoxaparin 80mg od s/c</td>
<td>Heparin 12,500 units bd s/c</td>
<td>Apixaban 5mg bd PO**</td>
</tr>
<tr>
<td></td>
<td>&gt;150</td>
<td>Enoxaparin 120mg od s/c</td>
<td>Discuss with Consultant Haematologist. Consider unfractionated infusion (aim for APTT ratio of 1.5-2)</td>
<td>Apixaban 5mg bd PO**</td>
</tr>
</tbody>
</table>

*A change of anticoagulant regimen (i.e. from prophylactic or intermediate-dose to treatment-dose regimen) can be considered in patients without established VTE but deteriorating pulmonary status or ARDS (ISTH recommendation).

**CrCl <15mL/min discuss with Consultant Haematologist and Nephrology Consultant as contraindicated (Note: LMWH are contraindicated if the CrCl <30mL/min but may be considered with anti Xa monitoring if CrCl 15-29 mL/min). Discuss anti-Xa monitoring with Haematology Consultant.

See note at the end of table 4

Table 3 – Acute Coronary Syndrome (ACS) recommendations in suspected or confirmed COVID-19 infection. For platelet counts ≥70x10⁹/L and NO other bleeding risks and a CrCl of ≥ 30mL/min

<table>
<thead>
<tr>
<th>D-dimer</th>
<th>Weight (kg)</th>
<th>&lt;75 years of age</th>
<th>≥75 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000 ng/mL FEU</td>
<td>&lt;50</td>
<td>Fondaparinux 2.5mg od</td>
<td>Fondaparinux 2.5mg od</td>
</tr>
<tr>
<td></td>
<td>50-100</td>
<td>Fondaparinux 2.5mg od</td>
<td>Fondaparinux 2.5mg od</td>
</tr>
<tr>
<td></td>
<td>101-150</td>
<td>Enoxaparin 1mg/kg bd*</td>
<td>Enoxaparin 0.75mg/kg bd*</td>
</tr>
<tr>
<td>1000-3000 ng/mL FEU</td>
<td>&lt;50</td>
<td>Fondaparinux 2.5mg od</td>
<td>Fondaparinux 2.5mg od</td>
</tr>
<tr>
<td></td>
<td>50-100</td>
<td>Enoxaparin 1mg/kg bd*</td>
<td>Enoxaparin 0.75mg/kg bd*</td>
</tr>
<tr>
<td></td>
<td>101-150</td>
<td>Enoxaparin 1mg/kg bd*</td>
<td>Enoxaparin 0.75mg/kg bd*</td>
</tr>
<tr>
<td>≥3000 ng/mL FEU</td>
<td>&lt;50</td>
<td>Enoxaparin 1mg/kg bd*</td>
<td>Enoxaparin 0.75mg/kg bd*</td>
</tr>
<tr>
<td></td>
<td>50-100</td>
<td>Enoxaparin 1mg/kg bd*</td>
<td>Enoxaparin 0.75mg/kg bd*</td>
</tr>
<tr>
<td></td>
<td>101-150</td>
<td>Enoxaparin 1mg/kg bd*</td>
<td>Enoxaparin 0.75mg/kg bd*</td>
</tr>
</tbody>
</table>

* round to the nearest 10mg dose
Table 4 – Acute Coronary Syndrome (ACS) recommendations in suspected or confirmed COVID-19 infections. For platelet counts >70x10^9/L and NO other bleeding risks other than a CrCl of <30mL/min- NOTE: increased risk of bleeding and thrombosis in severe renal impairment

<table>
<thead>
<tr>
<th>D-dimer</th>
<th>Weight (kg)</th>
<th>CrCl 20-30mL/min</th>
<th>CrCl 15-20mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000</td>
<td>&lt;50</td>
<td>Fondaparinux 2.5mg od</td>
<td>Enoxaparin 1mg/kg od*</td>
</tr>
<tr>
<td></td>
<td>50-100</td>
<td>Fondaparinux 2.5mg od</td>
<td>Enoxaparin 1mg/kg od*</td>
</tr>
<tr>
<td></td>
<td>101-150</td>
<td>Enoxaparin 1mg/kg od*</td>
<td>Enoxaparin 1mg/kg od*</td>
</tr>
<tr>
<td>1000-3000</td>
<td>&lt;50</td>
<td>Fondaparinux 2.5mg od</td>
<td>Enoxaparin 1mg/kg od*</td>
</tr>
<tr>
<td></td>
<td>50-100</td>
<td>Enoxaparin 1mg/kg od*</td>
<td>Enoxaparin 1mg/kg od*</td>
</tr>
<tr>
<td></td>
<td>101-150</td>
<td>Enoxaparin 1mg/kg od*</td>
<td>Enoxaparin 1mg/kg od*</td>
</tr>
<tr>
<td>&gt;3000</td>
<td>&lt;50</td>
<td>Enoxaparin 1mg/kg od*</td>
<td>Enoxaparin 1mg/kg od*</td>
</tr>
<tr>
<td></td>
<td>50-100</td>
<td>Enoxaparin 1mg/kg od*</td>
<td>Enoxaparin 1mg/kg od*</td>
</tr>
<tr>
<td></td>
<td>101-150</td>
<td>Enoxaparin 1mg/kg od*</td>
<td>Enoxaparin 1mg/kg od*</td>
</tr>
</tbody>
</table>

* round to the nearest 10mg dose

Points for consideration with regards to tables 1-4:

1. **D-dimer changes should be monitored (using the e-Care order set) and doses from table 1 and 2 should be adjusted accordingly.** Ultimately it is always a clinical decision as other factors must be considered, by the clinician, such as bleeding risk, renal function and clinical status (e.g. patient is being palliated or not or active proven thrombus/organ failure).

1b. Reassess bleeding risk daily

2. Apixaban and other direct oral anticoagulants (DOACs) show significant drug-drug interactions, please liaise with your ward Pharmacist. This is particularly in reference to the RECOVERY trial utilising experimental anti-viral therapy e.g. sarilumab (Kevzara).

3. If danaparoid requires anti-Xa level monitoring, note that this is an off-site test.

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

Discharge of patients on pharmacological thromboprophylaxis

Consider pharmacological thromboprophylaxis on discharge for all patients who meet high VTE risk criteria but with a low bleeding risk. The duration can be approximately at least 14 days and up to 30 days. Key VTE risk factors include:
- Advanced age
- >7 days of hospital
- Stay in ICU/escalated care
- Cancer (current)
- A prior history of VTE
- Thrombophilia
- Severe immobility
- An elevated D-dimer (>1000 ng/mL FEU at the time of discharge) i.e. > 2 x ULN
- An IMPROVE predictive VTE score of 4 or more (see appendix 2).

1st line: standard dose tinzaparin s/c* thromboprophylaxis for 14 days on discharge – contraindicated if CrCl <20mL/min
OR 2\textsuperscript{nd} line: rivaroxaban 10mg od\textsuperscript{**} (unlicensed) for 14 days on discharge – contraindication CrCl <15mL/min if CrCl <15mL/min or on dialysis, discuss with Nephrology Consultant

(ISTH recommendations)

*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 unlicensed 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

Antibiotic and antiviral drugs have significant drug interactions with all classes of anticoagulants, particularly via the CYP3A4 pathway. 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, which can be useful in managing the bi-directional relationship between inflammation and thrombosis.

Patients on warfarin (target INR 2.5)\textsuperscript{*} OR direct oral anticoagulant agent (DOAC) such as dabigatran, apixaban, rivaroxaban, edoxaban for stroke prevention in AF or previous VTE could be switched to a LMWH (ISTH recommendation) as below:

1. Therapeutic dose tinzaparin 175 units/kg (unless contraindicated) and CrCl \textgreater 30 mL/min
2. Therapeutic dose enoxaparin (if not contraindicated) if CrCl 15-30 mL/min (adjusted to CrCl) or they can stay with their anticoagulation (adjusted according to CrCl) – individual patient case decision.
3. For CrCl <15 mL/min use enoxaparin 1mg/kg od or 0.5mg/kg bd, rounded to nearest 10mg dose, with anti-Xa monitoring based on a pragmatic approach to minimise blood sampling and patient contact

\textbf{NOTE:} Once INR is below the lower end of their target range, start treatment dose LMWH

Patients on warfarin (target INR \textgreater 3.5)\textsuperscript{* AND/OR} metallic heart valve (discuss with Cardiology), switch to:

- Tinzaparin/enoxaparin as above
  - Monitor peak anti-Xa levels (4 hours after 5\textsuperscript{th} dose and discuss with Haematology Consultant). Aim for anti-Xa levels at the higher end of the therapeutic range.

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 therapeutic 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.

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 D-dimers, prothrombin time and platelet count (decreasing order of importance) 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.

It is already well-established that older individuals and those who have co-morbidities (both groups often have higher D-dimer) have a higher mortality as a consequence of COVID-19 infection. Evidence has also suggested that the D-dimer level on admission was higher in patients requiring critical care support. D-dimer elevation seems to correlate with increased VTE risk and with mortality, and may reflect D-dimer production by damaged lung cells as a direct response to hyper inflammation.

**Measure the D-dimer levels on a regular basis (24-48 hourly) for the first 5-7 days at least and refer to the DIC score.** A suggestion for frequency for monitoring would be 48 hourly as per the e-Care order. However professional discretion is advised, and you may wish to consider:

- <1000 ng/mL FEU (fibrinogen equivalent units) – 48 hourly
- >1000 ng/mL FEU – 24-48 hourly depending on symptoms and oxygen saturations.
- Check the d-dimer level at the time of discharge, as part of the assessment for the need for thromboprophylaxis after discharge.

**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 low molecular weight heparins (LMWHs). The need for Anti-Xa monitoring should be discussed with the Haematology Consultant on call during normal working hours. If approved, specify the following on the electronic request form:

- Name of Haematology Consultant who approved the request
- The therapeutic agent (tinzaparin/enoxaparin/etc)
- Trough anti-Xa level OR 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 danaparoid 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 <30mL/min (NB. LMWH contraindicated; UFH should be used, which does not require anti-Xa monitoring
- 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 so should, in most cases, be discussed with the Haematology Consultant in normal working hours.
**Use CrCl as calculated by Cockcroft-Gault equation, NOT eGFR** - calculate daily as suggested below or via the Microguide app:

**Estimating creatinine clearance (using Cockcroft and Gault equation)**

\[
CrCl = \frac{F \times (140 - \text{age in years}) \times \text{weight (kg)}}{\text{serum creatinine (µ mol/L)}}
\]

- \(F = 1.04\) for women and 1.23 for men

Cockcroft and Gault equation will not work for:

- **Muscle wasting** (patient’s CrCl will be overestimated as patients with very low muscle mass will have a much lower creatinine excretion rate)
- **Oedematous patients** (use Ideal Body Weight [IBW])
- **Ascites** (use IBW and consult with Pharmacy)
- **Acute renal failure**. This may represent non-steady state serum creatinine levels and may underestimate the level of renal impairment (consult with Pharmacy).

**All of these cases should be discussed with a ward Pharmacist or on-call Pharmacist**

**Cautions:**

- For obese patients, calculate ideal body weight (IBW) and if actual weight is ≥20% over IBW, use **adjusted body weight (ABW)** instead of actual weight to calculate CrCl.
  
  For woman: \(\text{IBW} = 45 + (2.3 \times \text{each inch over 5ft})\)
  
  For men: \(\text{IBW} = 50 + (2.3 \times \text{each inch over 5ft})\)

**Adjusted body weight** = ideal body weight + 0.4 (actual body weight – ideal body weight)

**Frequency of monitoring for LMWH (low molecular weight heparins) e.g. tinzaparin and enoxaparin:**

<table>
<thead>
<tr>
<th>Trough anti-Xa levels (to check for accumulation, e.g. renal impairment)</th>
<th>Just before the 5(^{th}) dose (up to 30 minutes before) (^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak anti-Xa levels (to check for efficacy)</td>
<td>4 hours post the 5(^{th}) dose</td>
</tr>
</tbody>
</table>

\(^*\)For CrCl <30mL/min take trough sample just before the 4\(^{th}\) dose (or peak sample 4 hours post the 4\(^{th}\) dose) or concerns of bleeding.

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 (approximately 2-3 times weekly).

**STANDARD DOSE PROPHYLAXIS LMWH – dose adjustment**

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

<table>
<thead>
<tr>
<th>Peak anti-Xa activity (units/mL) and dose adjustment</th>
<th>(&lt;0.2)</th>
<th>0.2-0.4</th>
<th>(&gt;0.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase by 10% re-check levels after 4(^{th}) dose</td>
<td>In range – no dose adjustment needed (consider rechecking levels after 4 further doses)</td>
<td>Omit one dose and decrease by 10% re-check levels after 4(^{th}) dose</td>
<td></td>
</tr>
</tbody>
</table>
TREATMENT DOSE LMWH – dose adjustment

1. Tinzaparin 175 units/kg od – aim for a peak anti-Xa level between 0.5-1(units/mL)
2. Enoxaparin 1mg/kg (bd or od depending on CrCl) – aim for a peak anti-Xa level between 0.5-1(units/mL)
3. Enoxaparin 1.5mg/kg od – aim for a peak anti-Xa level between 1-2 (units/mL)

For options 1 and 2 above please use the table on the next page, for option 3 discuss with a Consultant Haematologist:

<table>
<thead>
<tr>
<th>Anti-Xa activity (units/mL)</th>
<th>Action required?</th>
<th>Dosage Change</th>
<th>Next peak anti-Xa level (depending on renal function)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.35</td>
<td>No</td>
<td>Increase by 25%</td>
<td>4 hours after 4th or 5th dose</td>
</tr>
<tr>
<td>0.35-0.49</td>
<td>No</td>
<td>Increase by 10%</td>
<td>4 hours after 4th or 5th dose</td>
</tr>
<tr>
<td>0.5-1</td>
<td>No</td>
<td>No</td>
<td>Consider next day to verify, then weekly</td>
</tr>
<tr>
<td>1.1-1.5</td>
<td>Omit one dose</td>
<td>Decrease by 20%</td>
<td>Then 4 hours after 4th ‘new’ dose</td>
</tr>
<tr>
<td>1.6-2</td>
<td>Omit one dose</td>
<td>Decrease by 30%</td>
<td>Then 4-6 hours after 4th ‘new’ dose</td>
</tr>
<tr>
<td>&gt;2</td>
<td>Omit dose until &lt;0.5</td>
<td>Decrease by 40% OR change frequency to 24 hourly dosing if receiving 12 hourly dosing</td>
<td>Check at 24 hours then 12 hourly until anti-Xa level is under 0.5 Then 4-6 hours after 4th ‘new’ dose</td>
</tr>
</tbody>
</table>

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
- 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**: therapeutic tinzaparin 175 units/kg with no baseline coagulopathy/contraindications
- **CrCl 15-29 mL/min**: therapeutic enoxaparin 0.75mg/kg bd or 1.5mg/kg od – with established coagulopathy, monitor peak anti-Xa level 4 hours after 4th dose
- **CrCl <15 mL/min**: therapeutic enoxaparin 0.5mg/kg bd or 1.0mg/kg od – monitor peak anti-Xa levels after 4th dose
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)

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

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.
Thromboprophylaxis, coagulopathy management and thrombosis in COVID-19

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.

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

Detailed recommendations for this pandemic and use with haemofiltration can be found on metastion through the King’s Critical Care Renal Replacement Therapy Guidelines PowerPoint document. Recommended practice within the Critical Care national groups suggests that CVVHDF patients should be initiated on the following:
Prismocitrate + continuous unfractionated heparin (UFH) infusion:

- Effective unfractionated heparin infusion requires an appropriate clinical area capable of timely out of hours monitoring and prompt dose adjustments as appropriate and should be discussed with the Haematology Consultant.
- 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

De-escalation of therapy is however more challenging. Simple utilisation of D-dimer may not be possible as it can often be raised due to other factors including sepsis, lung cancer/metastases and so on. Therefore, decisions for de-escalation from this should be based on a patient by patient decision. This should be discussed with an ITU Consultant before proceeding; you may want to consider de-escalation in the following manner:

Prismocitrate + as per table 1 based on D-dimer, weight and DIC score*

OR (depending on availability of prismocitrate)

Non-citizen CVVHDF protocol with heparin (primed) in the circuit + as per table 1 based on D-dimer, weight and DIC score*

*If high risk of bleeding - consider using heparin, discuss dosing with ward Pharmacist
Pharmacokinetic considerations

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

References:

2) Imperial College Hospital. Thromboprophylaxis and anticoagulation in COVID-19 infection Trust guideline. 2020


19) Crystal Phend. Anticoagulation Guidance emerging for severe COVID-19 – pragmatic choices dominate as guidelines are shaping up. 8/4/2020


23) UKMI, Medicines Q&A: Are low molecular weight heparins preferred to unfractionated heparin in people with renal impairment for treatment indications? Last updated December 2018

24) UKMI, Medicines Q&A: Low molecular weight heparins – should prophylactic doses be used in patients with renal impairment? Last updated January 2020


26) University of Liverpool: COVID-19-druginteractions.org


Development of the guideline
Changes compared to previous document
See additional information below for further information – revisions may occur upon review of new literature, at the latest within 2 months of publication

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 guideline.

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Thrombosis committee – Chair action via Dr Margaret Moody  
Drugs and Therapeutics committee

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Issue no:  
3

File name:  
Thromboprophylaxis, coagulopathy management and thrombosis in COVID-19 infection

Supercedes:  
2

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
Appendix 1 – Protamine for LMWH overdose

This REFERS only to tinzaparin (Innohep) for prophylaxis.

**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 of body weight. The sign of tinzaparin overdosage is bleeding. Although we have no clinical experience with overdosage, studies in healthy volunteers indicate that:

1 mg protamine sulphate* per 100 anti-Xa units tinzaparin administered should be given over 10-15 minutes¹⁻³. 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 administration⁴.

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 injections 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.

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

*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 administration⁵, with absorption half-life approximately 200 minutes and elimination half-life approximately 80 minutes⁶.

2. British National Formulary (BNF) accessed via (28/5/2020)
Appendix 2 – 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.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE</td>
<td>3 points</td>
</tr>
<tr>
<td>Malignancy (treated or untreated within the previous 6 months)</td>
<td>1 points</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>3 points</td>
</tr>
<tr>
<td>Age &gt;60</td>
<td>1 point</td>
</tr>
</tbody>
</table>

Max score 8 points

**IMPROVE predictive score**

<table>
<thead>
<tr>
<th>0-1</th>
<th>VTE risk on admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low: Observed VTE risk &lt;1%</td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>Moderate</td>
</tr>
<tr>
<td>≥ 4</td>
<td>High: Observed VTE risk 5.7%</td>
</tr>
</tbody>
</table>
Appendix 3 – Quick reference guide

Thromboprophylaxis in suspected/confirmed COVID-19 infection in patients NOT currently on therapeutic anticoagulation – Quick reference guide

Do not omit thromboprophylaxis due to coagulopathy, unless evidence of bleeding

Monitor:
FBC daily
Clotting screen (including fibrinogen) and D-dimer every 1-2 days, according to DIC score (see coagulopathy section)

Platelets <30x10^9/L or active bleeding

1. Offer IPC
2. Discuss with Haematology Consultant

Platelets ≥30x10^9/L but <50x10^9/L or other bleeding risk

Assess for contra-indications

1. Offer IPC
2. Standard dose pharmacological thromboprophylaxis as per CG10193
If no contra-indications 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

Assess for contra-indications

1. Offer IPC
2. If no contra-indications and bleeding risk taken into account offer standard or intermediate dose pharmacological thromboprophylaxis as below:

For CrCl ≥40 mL/min:

<table>
<thead>
<tr>
<th>D-dimer (ng/mL)</th>
<th>Weight (kg)</th>
<th>First Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2000</td>
<td>&lt;50</td>
<td>Tinzaparin 2500 units od/c</td>
</tr>
<tr>
<td>50-100</td>
<td>50-100</td>
<td>Tinzaparin 4500 units od/c</td>
</tr>
<tr>
<td>100-150</td>
<td>100-150</td>
<td>Tinzaparin 6000 units od/c</td>
</tr>
<tr>
<td>&gt;150</td>
<td>&gt;150</td>
<td>Tinzaparin 9000 units bd/c</td>
</tr>
</tbody>
</table>

For CrCl <40 mL/min:

<table>
<thead>
<tr>
<th>D-dimer (ng/mL)</th>
<th>Weight (kg)</th>
<th>First Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2000</td>
<td>&lt;50</td>
<td>Enoxaparin 20mg od s/c*</td>
</tr>
<tr>
<td>50-100</td>
<td>50-100</td>
<td>Enoxaparin 40mg od s/c</td>
</tr>
<tr>
<td>100-150</td>
<td>100-150</td>
<td>Enoxaparin 60mg od s/c</td>
</tr>
<tr>
<td>&gt;150</td>
<td>&gt;150</td>
<td>Enoxaparin 80mg od s/c</td>
</tr>
</tbody>
</table>

1. If high risk for VTE consider treatment dose anticoagulation
4. For anti-Xa monitoring and subsequent dose adjustments refer to monitoring section of guideline CG103093

On Discharge
Consider pharmacological thromboprophylaxis for a minimum of approximately 14 days up to a maximum of 30 days in patients with low bleeding risk and key VTE risk factors:

1st line: standard dose tinzaparin s/c thromboprophylaxis - contraindicated if CrCl <20mL/min
OR 2nd line (only if tinzaparin is not an option):
Enoxaparin 10mg OD (unlicensed) – contraindicated if CrCl <15mL/min

5. Key VTE risk factors include: Advanced age, >7 days of hospital, stay in ICU, cancer, prior history of VTE, thrombophilia, severe immobility, elevated D-dimer (>1000 at the time of discharge), an IMPROVE VTE score of 4 or more
6. ISTH recommendation

Note: For ACS patients follow table 3 and 4 of the CG103093 guideline