**BTS Guidance on Venous Thromboembolic Disease in patients with COVID-19**

**Updated August 2021 - Recently published data and changes to recommendations in red**

## Summary


1. **The risk of thrombosis and VTE is increased in patients with COVID-19; those with clinically severe disease requiring Critical Care (ICU/HDU) are at highest risk.**
2. **D-Dimers levels are frequently elevated in patients with COVID-19 and are prognostic. High levels may arise as a result of thrombosis or inflammation.**
3. **Current data do not support the routine use of high D-Dimer levels in isolation to guide decisions regarding investigation and anticoagulation; levels should be assessed within the overall clinical context**
4. **Pulmonary thromboembolic disease should be considered in patients with hypoxaemia disproportionate to X-Ray changes or sudden worsening of blood pressure, heart rate or oxygen requirements.**
5. **All patients admitted with COVID-19 should be assessed for, and the majority receive, thromboprophylaxis.**
6. **Therapeutic LMWH should be considered for in-patients with Covid-19 disease who are managed on general wards and require supplemental oxygen. Patients with no evidence of VTE or other indication for therapeutic anticoagulation who require high-flow oxygen, CPAP, NIV for severe ventilatory failure or invasive ventilation should receive less than therapeutic dosing. The published evidence would suggest no benefit of intermediate over standard dose thromboprophylaxis in these patients. Bleeding risk should be considered when making decisions regarding intensity of anticoagulation.**
7. **The role of extended prophylactic thromboprophylaxis after discharge is not clear. Enrolment of suitable patients into clinical trials (e.g. https://heal-covid.net/) is advised.**


## Background

This document is aimed at respiratory and general medical physicians. It summarises published data regarding the risks of venous thromboembolism (VTE) in patients with COVID-19, and discusses clinical issues regarding prevention, diagnosis and management of VTE. The number of papers describing incidence and outcomes has increased significantly since its initial publication in March 2020 and updates in May 2020 and February 2021, while NICE have also recently published updated guidance.[1]

COVID-19 infection is associated with abnormalities in all 3 parts of Virchow's triad and hence there exists a pathophysiological rationale for an increased risk of VTE.

- First, endothelial dysfunction may develop due to direct viral invasion of endothelial cells via Angiotensin Converting Enzyme-2 (ACE2), or as a result of the subsequent marked inflammatory response and tissue hypoxia.[2, 3]
- Second, COVID-19 induces a pro-coagulant state with an increase in factors V, VII, VIII and X and von Willebrand factor and a reduction in ADAMTS13 levels.[4, 5] High levels of antiphospholipid antibodies have also been reported, although their clinical significance is

uncertain.[6, 7] Furthermore, reduced fibrinolysis resulting from increased plasminogen activator inhibitor 1 has been observed in intensive care unit (ICU) and non-ICU patients.[8 9] In addition, platelet activation may also increase the risk of VTE.[10]

- Third, immobility and resultant venous stasis is common, especially in more severe COVID-19 disease.

In addition to the "typical" VTE comprising of deep venous thrombosis and secondary pulmonary embolism (PE), COVID-19 is also associated with in-situ "immunothrombosis" in smaller pulmonary arteries and capillaries which has been postulated to be related to a distinct COVID-19 pulmonary intravascular coagulopathy.[11-13] Laboratory coagulation abnormalities which are observed in patients with severe COVID-19 include mild thrombocytopenia, a mild increase in the prothrombin time (PT), high fibrinogen and elevated D-Dimers.[14] Raised D-Dimer levels are associated with poorer outcomes. Tang *et al* observed higher D-Dimers (median 2,120mcg/L versus 610mcg/L) in non-survivors compared with survivors in their study of 183 patients. Guan *et al* observed elevated D-dimers in 46% of patients in a series of 1099 patients.[9] Huang *et al* reported median levels of 2,400mcg/L in 13 patients who required critical care management, and 500mcg/L in 28 patients who did not.[15, 16] It is important to appreciate, however, that D-Dimers are a non-specific acute phase reactant which may be elevated in acute inflammatory illnesses, pneumonias and other causes of sepsis as well as in VTE.

## Risk of VTE

A number of studies have reported a high incidence of venous thromboembolic events in COVID-19, especially in patients with clinically more severe disease. Klok *et al* identified thrombosis in 31% of 184 Dutch ICU patients (25 PE, 3 DVT and 3 ischaemic strokes). They observed that increasing age and coagulopathy (defined as an elevation in prothrombin time by >3s or activated partial thromboplastin time by >5s) were independent predictors of outcomes (D-dimer levels were not reported in this study). All patients had received VTE prophylaxis (a minority at doses higher than the usual prophylactic dose). Helms *et al* demonstrated PE in 17% of 150 ICU COVID-19 patients (25% of all patients who underwent CTPA); 70% of patients were receiving prophylactic heparin and 30% treatment-dose heparin on ICU admission. In comparison with a matched cohort of non-COVID-19 ARDS patients, thrombotic complications were 2.6 times and PE 6.2 times more likely in patients with COVID-19. Middeldorp *et al* studied 198 COVID-19 patients (74 admitted to ICU and 124 to a ward).[17] VTE was demonstrated in 39% and symptomatic VTE was diagnosed in 24% of ICU patients (all of whom were receiving prophylactic LMWH) with the cumulative incidence of VTE increasing from 25% at 7 days to 48% at 14 days. Symptomatic VTE was, however, diagnosed in only 3.2% of ward patients. A recent study (currently in submission) reviewed CTPA reports for 4720 Scottish COVID-19 ward patients who received ward-based care and observed a PE incidence of 3.5%.

Jimenez *et al* recently performed a meta-analysis involving 49 studies and reported a VTE incidence of 17% (12.1% DVT and 7.1% PE).[18] Incidence was higher in patients on intensive care as opposed to a medical ward (28% v 7%) and in patients who had undergone routine screening (33% v 10%).

***Comment: The risk of thrombosis and VTE is increased in patients with COVID-19; those with clinically severe disease requiring Critical Care (ICU/HDU) are at highest risk.***

## Diagnosis of PE

Given the increased incidence of VTE in COVID-19, clinicians should have a low threshold for suspecting and investigating for VTE. PE should be considered in the following circumstances:

- Sudden worsening of hypoxaemia,
- Significant drop in blood pressure
- New onset tachycardia
- Oxygen requirements are disproportionate to the severity of pneumonia on Chest X-Ray.

Compression ultrasonography should be performed if clinical signs suggestive of DVT develop. There should be a particularly high index of suspicion for VTE and a low threshold for investigating/treating for VTE in patients with high oxygen demands requiring CPAP or intubation. Diagnosing VTE may be more complex in patients with COVID-19 due to several factors:

- Clinical state making movement to the radiology department difficult (e.g. a CPAP-dependent patient with high oxygen requirements and risk of aerosolization, or an intubated patient requiring prone ventilation or with renal impairment);
- Local radiology protocols regarding radiological investigations in patients with known COVID-19;
- Overrun radiological services due to very high numbers of hospitalised COVID-19 patients.

As noted above, D-Dimers are often elevated in severe COVID-19 and offer prognostic information. High levels may represent fibrin breakdown or increased fibrin turnover due to severe lung inflammation.[14] An important clinical question is therefore whether D-Dimer levels are useful in identifying VTE. A number of retrospective studies have investigated the utility of D-Dimers in predicting the presence of PE (table 1).

**Table 1. Selected studies investigating D-Dimer levels in inpatients with COVID-19**

| Author | Number (PE+ve/number of CTPAs) | D-Dimer in pts with PE (ng/ml) | D-Dimer in pts with no PE (ng/ml) | Optimal threshold (ng/ml) | Sens (%) | Spec (%) | AUC |
|---|---|---|---|---|---|---|---|
| Mouhat *et al*[19] | 44/162 | 5364 (2928-12,275) | 1310 (800-2335) | 2590 | 83 | 84 | 0.88 |
| Ventura-Dias *et al*[20] | 73/242 | 7872 (3150-22,494) | 2009 (?-15,705) | 2903 | 81 | 59 | 0.76 |
| Whyte *et al*[21] | 80/214 | 5364 (4665-8000) | 1310 (1210-4410) | 4800 | 75 | 78 | 0.77 |
| Leonard-Laurant *et al*[22] | 32/106 | 15,385 (8180-22,590) | 1940 (410-3470) | 2660 | 100 | 67 | NR |

Sensitivity and Specificity refer to the optimal threshold identified in each study. D-Dimer levels, median (interquartile range). NR, not reported; Sens, sensitivity; Spec, specificity; AUC, Area Under the Curve.

Prospective studies are required to validate these proposed thresholds before their routine adoption can be recommended. Increase in D-Dimer levels during hospital admission is associated with an elevated risk of PE and poorer prognosis.[23, 24] As right ventricular dysfunction is also common in

moderate to severe ARDS, the utility of trans-thoracic echocardiography in indirectly diagnosing acute PE is unclear, although more severe RV dysfunction may raise the suspicion of pulmonary embolic disease and in a small number of patients, right heart thrombus held in transit may be visualised.[25] A bleeding risk score (e.g. VTE-BLEED) may be useful in identifying patients at low risk of bleeding in whom anticoagulation without imaging may be safer and patients at higher risk of bleeding in whom imaging is more essential.[26] D-Dimer levels may be used to rule out VTE in patients with low or intermediate PE probability score.

***Comment: D-Dimer thresholds have been proposed as having utility in assessing VTE risk but currently lack prospective validation. Current data do not support the routine use of high D-Dimer levels in isolation to guide decisions regarding investigation and anticoagulation. D-Dimer levels should be assessed within the overall clinical context and if markedly elevated may prompt investigations to exclude VTE.***

## Risk assessment and anticoagulation dosing

The vast majority of medically sick patients in the UK now receive thromboprophylaxis following previous NICE guidance mandating VTE risk assessment and LWMH for those at risk, and many hospitals have adopted weight-adjusted LMWH prophylaxis for those patients with a high BMI.

There is uncertainty regarding the effect of anticoagulation on the incidence of VTE in patients with COVID-19, with conflicting results in the published literature.[27] Studies of patients receiving standard prophylactic-dose LMWH have reported symptomatic VTE incidences of between 21-31%.[28-31] Observational studies have reported lower VTE rates in patients receiving anticoagulation prior to admission[32, 33] but conflicting effects of commencing full versus prophylactic dose anticoagulation.[32, 33 34] In the meta-analysis of 49 studies by Jimenez *et al* there was no significant difference in observed rates between studies where the minority received any anticoagulation, studies where the majority received prophylactic dose anticoagulation and studies where patients received intermediate or full dose anticoagulation.[18] Furthermore, the bleeding risk associated with intermediate/high risk prophylaxis (21%) was higher than in patients receiving standard dose prophylaxis (5%) or no prophylaxis (4%).

Differing recommendations of national and international guidance regarding VTE prophylaxis reflect the paucity of published data (table 2). All guidelines emphasise the importance of making decisions following assessment of individual bleeding risk, and the use of mechanical thromboprophylaxis if anticoagulation is strongly contraindicated.

**Table 2. International and National guidance regarding VTE thromboprophylaxis (adapted from [27])**
**NB majority published prior to publication of the REMAP-CAP/ACTIV-4/ATTAC studies.**

| Organisation | ICU/Critical Care patients | Ward patients | Out-patients | Post-discharge |
|---|---|---|---|---|
| International Society on Thrombosis and Haemostasis[35] | -Standard dose<br>-Consider intermediate dose in high-risk (50% of panel) | -Standard dose<br>-Consider intermediate dose (30% of panel) | -No mention | -Consider 14 days (50% of panel) – 30 days (20% panel) in high-risk patients |
| American College of Chest Physicians[36] | -Standard dose | -Standard dose | -No mention | -Not recommended |
| Global Covid-19 Thrombosis Collaborative Group[37] | -Standard dose | -Standard dose<br>-32% of panel in favour of intermediate dose | -Consider in patients at highest risk | -Consider up to 45 days in patients at increased risk |
| SIGN[38] | -Consider intermediate dose | -Standard dose | -No mention | -Consider 2 weeks post-discharge if deemed high risk of VTE and low bleeding risk |
| NICE NG-191[1] | -Standard or consider intermediate dose (research recommendation) | -Consider treatment dose in patients receiving non-high flow oxygen for a minimum of 14 days or until discharge | -No mention | -Research recommendation |

Intermediate dose thromboprophylaxis refers to twice daily standard prophylactic dose, eg enoxaparin 40mg bd or dalteparin 5,000 units bd.

A large number of trials of antithrombotic agents (including LMWH, DOACs and anti-platelet therapies) in COVID-19 have been registered.[3] REMAP-CAP, ACTIV-4 and ATTACC study groups recently published their combined pooled open-label adaptive RCTs of therapeutic LMWH in 2219 hospitalised patients with COVID-19. Full dose anticoagulation was associated with a 4% absolute increase in organ support-free hospital survival in patients not requiring ICU-level support (defined as high-flow oxygen, NIV/CPAP, invasive ventilation or pressor/inotrope use), when compared with usual-care thromboprophylaxis (27% of whom received intermediate-dose thromboprophylaxis).[39] Treatment benefit was observed in patients with both low and high-levels of D-Dimer, although the treatment effect was greater in patients with higher levels of D-Dimer. Conversely, in a study of 1098 patients requiring ICU-level care, full dose anticoagulation did not increase organ support-free hospital survival when compared with usual-care thromboprophylaxis (52% of whom received intermediate-dose thromboprophylaxis).[40] The ACTION trial randomised 615 patients with predominantly moderate disease to rivaroxaban 20mg od (or therapeutic heparin followed by rivaroxaban) for at least 30 days versus prophylactic in-patient LMWH and found that therapeutic anticoagulation did not improve death or hospitalisation duration but did increase the risk of major/clinically relevant bleeding from 2% to 8%.[41] Finally, the INSPIRATION trial randomised 562 patients requiring ICU therapy to intermediate-dose (1mg/kg od) or standard-dose (40mg od, adjusted for body weight) enoxaparin and observed no difference in the rates of VTE, ECMO requirement or death between the 2 groups.[42] The results of further studies of intermediate-dose versus full-dose LMWH in non-ICU patients are awaited. Commencement of proton pump inhibitor

therapy should be considered in patients with other risk factors for GI bleeding who receive higher-intensity anticoagulation.[43]

1. ***Comment:*** ***Therapeutic LMWH should be considered for in-patients with Covid-19 disease who are managed on general wards and require supplemental oxygen. Patients with no evidence of VTE or other indication for therapeutic anticoagulation who require high-flow oxygen, CPAP, NIV for severe ventilatory failure or invasive ventilation should receive less than therapeutic dosing. The published evidence would suggest no benefit of intermediate over standard dose thromboprophylaxis in these patients. Bleeding risk should be considered when making decisions regarding intensity of anticoagulation.***

## Other practical issues

Close collaboration with local haematologists is essential in formulating local policies and in managing severely ill patients. Monitoring of anti-Xa levels, rather than APPT, may be preferable in patients receiving intravenous unfractionated heparin.[44, 45] Local policies for the use of LMWH in patients with thrombocytopaenia should be followed but prophylactic doses can be used when platelets are >30 x$10^9$/L.[46] Minor prolongations of PT and APTT (up to 5 seconds) are common in COVID-19 and are not contraindications to thromboprophylaxis.[47] Switching patients with severe COVID-19 who were receiving vitamin-K antagonists prior to admission to therapeutic LMWH should be considered. In patients receiving DOACs prior to admission, awareness of interactions with anti-viral therapies which may be considered in selected COVID-19 patients and of the need to take rivaroxaban with food. Switching to LMWH may therefore be necessary and is suggested if the patient deteriorates. In addition, heparin has theoretical additional benefits in patients with COVID-19 as it may bind to the SARS-CoV-2 spike protein and block viral attachment, and may also have anti-inflammatory effects by neutralising pro-inflammatory proteins.[48] LMWH is therefore recommended in patients who commence anticoagulation for suspected or proven VTE during their in-patient stay and it seems reasonable to switch to a DOAC on discharge.

Reperfusion therapy should be given in patients with high-risk ("massive") PE as for patients with non-COVID-19 PE. Catheter directed approaches including the penumbra catheter are reported in patients with severe COVID-19, as well as extracorporeal RV support in cardiac centres, without immediate bleeding complications (PMID **32952405**). The beneficial effects of half dose systemic thrombolysis on $PaO_2/FiO_2$ in 7 ICU COVID-19 patients with ARDS, PE and severe RV dysfunction (1 of whom had only distal perfusion defects on dual energy CT) has been reported.[49] Further larger studies are, however, required to investigate this potential therapeutic approach.

Patients discharged following a medical admission for sepsis or pneumonia or requiring ICU admission are at increased risk of VTE for up to 6 weeks.[50] Prophylactic LMWH or DOAC therapy has been shown to be effective at reducing this risk in selected patients at high risk of VTE and low risk of bleeding.[35] There are no specific RCT data to guide the optimal duration of thromboprophylaxis in patients recovering from moderate or severe COVID-19. A number of observational studies have reported low incidences of acute VTE following hospital discharge of 0-0.6% which do not appear to be greater than in non-Covid-19 patients.[51, 52] Patients should be offered enrolment into clinical trials (e.g. https://heal-covid.net/) where possible.

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