Thromboprophylaxis and Heparin Guidance During the COVID-19 Pandemic
UHL Guideline Trust Reference B40/2020

Thrombosis Committee statement: important update on thromboprophylaxis and heparin guidance for covid19+ patients* (Feb '21 onwards)
Date: 23/02/2021

Dear UHL clinical staff,

We recently wrote to you regarding thromboprophylaxis strategies for hospitalised patients. Since then, early data from randomised studies have provided an improved framework for thrombosis prevention in the setting of hospitalised covid19* infected patients. We hope the following advice will provide useful practical guidance on dosing of thromboprophylaxis but we do recognise an increase in complexity and the unusual approach of using higher doses of LMWH. There is also advice on measuring heparin levels and subsequent heparin dosing, which may be relevant to certain clinical scenarios (e.g. extremes of weight, poor renal function, pregnancy, those with a high bleeding risk).

The guidance only applies to patients with proven and suspected "active" covid19 infection. Patients not affected by covid19 should be provided thromboprophylaxis in the usual manner.

Throughout the document, the terms ICU and ward-based care are used to indicate patient acuity. The term ICU includes patients requiring organ support, NIV, and 40%+ O2 even if delivered in a non-ICU, high care level setting.

* covid19+ve **and** suspected +ve

N. B. This change is based on trial cessation and interim analysis of ATACC/ACTIV4/REMAP-CAP multiplatform RCT anticoagulation domain 28/01/21 showing superiority of therapeutic anticoagulation for "moderate" disease severity covid+* patients compared to standard dose heparin thromboprophylaxis. Predicted benefits are reduced ICU requirement and possible reduction in overall mortality

Mr Al Best and Dr Richard Gooding

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Guidance summary:

- **What's changed? New prophylaxis dosing**
    - ALL covid19+ve* admitted patients should be considered for THERAPEUTIC DOSED LMWH FOR COVID19+ve* THROMBOPROPHYLAXIS, unless on ICU or receiving organ support (e.g. NIV/CPAP/>40%FiO2). This should continue for 14 days or until discharge. Where patients are on steroids or an anti-platelet medication, we advise considering the addition of a proton pump inhibitor.
    - ICU patients (including ward patients receiving NIV/CPAP/>40% FiO2) DO NOT appear to benefit from therapeutic dosed LMWH for thromboprophylaxis – consider USE OF STANDARD OR INTERMEDIATE DOSE LMWH according to clinician preference ("intermediate" = twice daily prophylactic dosing – noting relative lack of evidence for this approach). See also ITAPPS Covid19 thromboprophylaxis guideline
    - Where there is doubt regarding safety of anticoagulation when considering bleeding risk (e.g. falls, recent history of serious bleeding) it is reasonable to offer standard dose LMWH according to clinician preference. Advice may be sought (see "advice" below)

- **Recruit:**
    - The anticoagulation domains in the REMAP-CAP study are currently paused in view of interim data analyses which show benefit for "therapeutic" doses for moderately ill patients (ie in-patients, pre-ICU) but there appears to be lack of benefit and higher incidence of bleeding with 'therapeutic' dose is severely ill patients (ie patients who are on ICU / receiving organ support).
    - The REMAP-CAP anticoagulation domain for severe / ICU patients is undergoing substantial amendments and is expected to re-open for recruitment in the near future.
    - Recruitment to antiplatelet drugs continues both in the RECOVERY and REMAP-CAP trials.

- **Preventing thrombosis:** For thromboprophylaxis we suggest using the amended dosing tables enclosed. Above all, it is vital that all patients are risk assessed for VTE and bleeding, and that patients with covid19* infection receive pharmacological thromboprophylaxis where there is no contraindication. Recent interim trial data is highly suggestive of an overall benefit using higher doses of LMWH used earlier in disease course, irrespective of D-Dimer.

- **On discharge**: It is reasonable to continue thromboprophylaxis for COVID+ve* patients in whom there is an anticipated prolonged period of relative immobility. Optimum duration and mode remain uncertain – options for duration include 7-28 days post discharge, with a default position of 7 days unless anticipated VTE risk period is longer; and ideally using standard dose (**not therapeutic dose**) dalteparin. When prescribing on E-Meds the length of the course can be specified at the time of initial prescription and all of the remaining doses after discharge will be dispensed automatically by pharmacy. A low dose DOAC (Apixaban or Rivaroxaban) is a reasonable alternative in cases where dalteparin is felt to be inappropriate, but please note that these low dose DOACs have been shown to have slightly higher bleed rates compared to LMWH for medical patient thromboprophylaxis and are not licensed for *medical* patient thromboprophylaxis.

- **Heparin assays:** Dalteparin assays need not be performed routinely, but considered for patients at extremes of body weight (<30kg, >110-140kg), pregnant patients, those at very high risk of bleeding, and those with severe renal impairment. When required, the sample should be taken 3-4 hours post dose, and 3-4 doses after initiation. These are now sent to the Fast-Track laboratory and are available 24/7 if required, with test requesting on the ICE system.

- **Admitted patients who are already on oral anticoagulants**: Some of these patients may be considered for switching to therapeutic dalteparin; patients on warfarin and those who are on anticoagulation for venous thromboembolism in particular. Patients on direct oral

anticoagulants for atrial fibrillation may continue on current anticoagulant. See Figure 1 for specific advice.

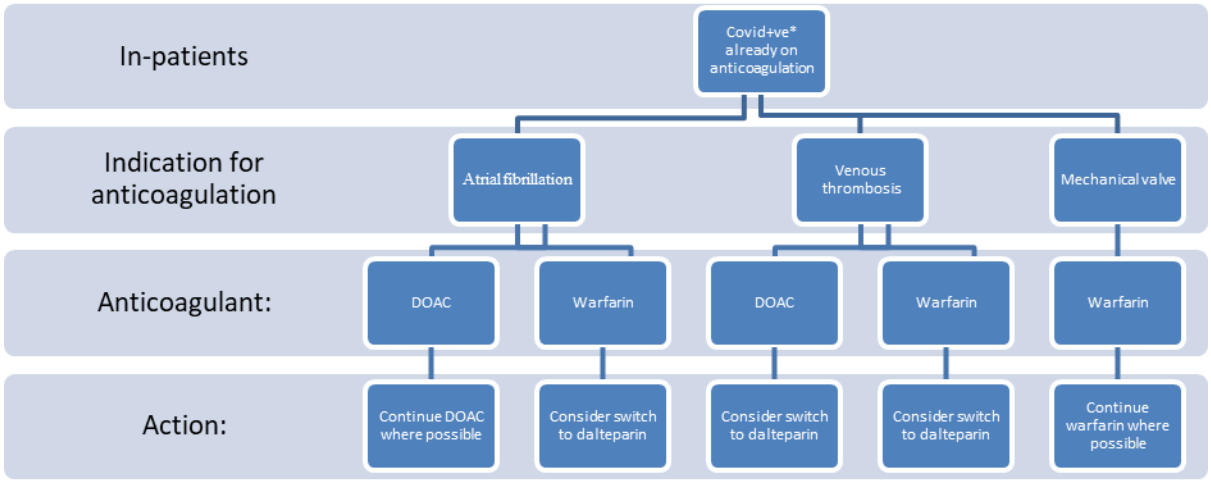
- **Patients moving between ward-based and ICU-based care**: Patients moving to ICU/higher acuity care should have the anticoagulant dose reduced to "standard" or "intermediate" dose. Patients moving from ICU/higher acuity care back to the ward should remain on the standard or intermediate dose that they have been on and not escalate to "therapeutic" dose for their thromboprophylaxis.

- **Advice:** for advice regarding this important change or to discuss a covid+ve* patient's anticoagulation dose, please call the anticoagulation helpline: 07960779941 (0900-1600) or haematology SpR via switchboard 1600-0900 (out-of-hrs). Email advice is available on this email address: Haemostasisadvisory@uhl-tr.nhs.uk. PLEASE CALL IN-HRS WHEREVER POSSIBLE UNLESS CLINICALLY URGENT.

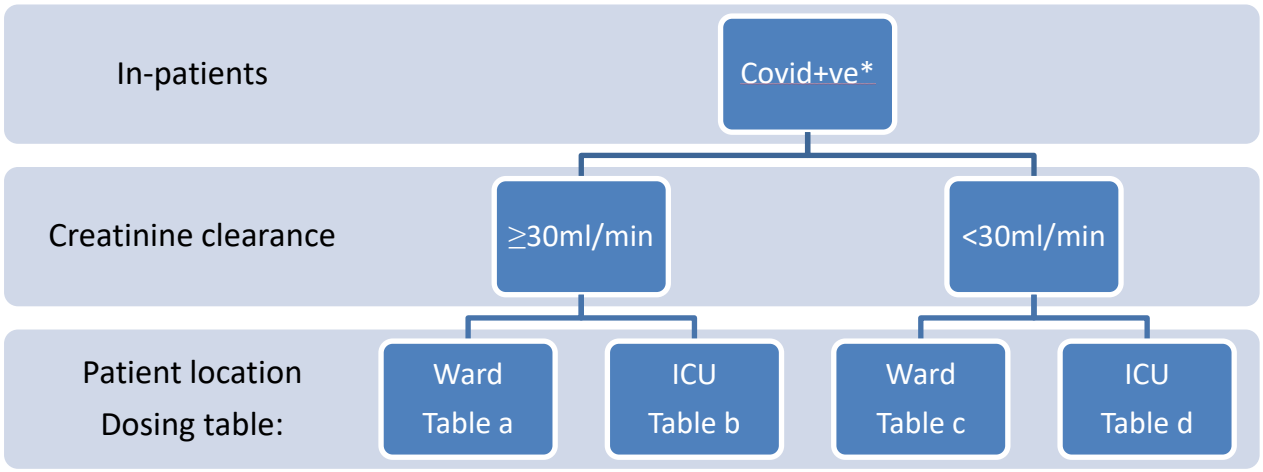
Special circumstances:

URGENT SURGERY For patients who may require urgent surgery, we suggest standard (not therapeutic/intermediate dose), once- daily thromboprophylaxis so as to not increase peri-operative bleeding risk.
PREGNANCY For pregnant patients, discuss dosing with obstetrician/follow obstetric guidance

Figure 1: Guidance for patients already on anticoagulation on admission:



Dalteparin thromboprophylaxis dosing tables (where thrombotic risk felt to outweigh bleeding risk):
Figure 2. Using the dosing tables



Where creatinine clearance ≥ 30ml/min (calculated by Cockcroft-Gault)

Table a

Weight (kg) <30kg seek advice	**WARD BASED COVID19+ve*. Consider as:"therapeutic dose"** Creatinine clearance ≥30ml/min	
30 - 39.9	5000 units OD	Check heparin assay on day 3 and dose adjust accordingly
40-45.9	7500 units OD	
46 – 56.9	10000 units OD	
57 – 68.9	12500 units OD	
69 – 82.9	15000 units OD	
83 – 99.9	18000 units OD	
100 – 109.9	10000 units BD	
110 – 139.9	12500 units BD	Check heparin assay on day 3 and dose adjust accordingly
140 – 169.9	15000 units BD	Check heparin assay on day 3 and dose adjust accordingly
170 – 199.9	18000 units BD	Check heparin assay on day 3 and dose adjust accordingly
200+	Discuss with haematology	

Table b

Weight (kg)	**ICU BASED COVID+ve*. Consider as "intermediate dose" (option to use once daily dosing as per clinician preference)** Creatinine clearance ≥ 30ml/min	
Under 30	Discuss with haematology	
30 -49.9	2500 units BD	
50-74.9	BD dosed: as 5000 units am and 2500 units pm	
75-99.9	5000 units BD	
100 -149.9	7500 units BD	
150 -199.9	10000 units BD	Check heparin assay on day 3 and dose adjust accordingly
200 +	12500 units BD	Check heparin assay on day 3 and dose adjust accordingly

Where creatinine clearance <30ml/min (calculated by Cockcroft-Gault)

Table c

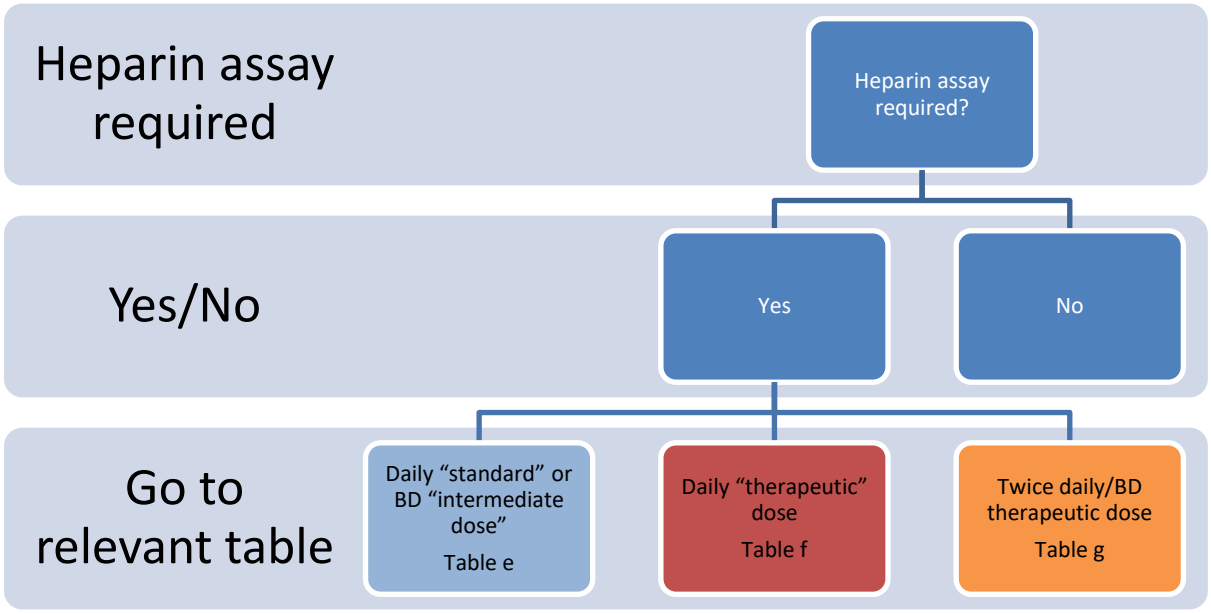
Weight (kg)	**WARD BASED COVID19+ve*. Consider as "therapeutic dose"** Creatinine clearance < 30ml/min	
Under 30	Discuss with haematology	
30 -49.9	2500 units BD	Check heparin assay on day 3 and dose adjust accordingly
50 -74.9	5000 units AM and 2500 units PM	Check heparin assay on day 3 and dose adjust accordingly
75 – 99.9	5000 units BD	Check heparin assay on day 3 and dose adjust accordingly
100-149.9	7500 units BD	Check heparin assay on day 3 and dose adjust accordingly
150-199.9	10000 units BD	Check heparin assay on day 3 and dose adjust accordingly
200+	12500 units BD	Check heparin assay on day 3 and dose adjust accordingly

Table d

Weight (kg)	**ICU BASED COVID19+ve*. Consider as "standard dose"** Creatinine clearance < 30 ml/min	
<30	Discuss with haematology	
30-49.9	2500 units OD	
50-149.9	5000 units OD	
150 – 199.9	7500 units OD	Check heparin assay on day 3 and dose adjust accordingly
200+	10000 units OD	Check heparin assay on day 3 and dose adjust accordingly

* or suspected covid+ve

Figure 3.


Heparin assay required
Heparin assay required?
Yes/No
Yes
No
Go to relevant table
Daily "standard" or BD "intermediate dose"
Table e
Daily "therapeutic" dose
Table f
Twice daily/BD therapeutic dose
Table g

Update as of 15/2/21 following remap-cap study update wrt anticoagulation domain

Dose adjustment guidance following LMWH assay. Note: routine monitoring of heparin levels is not recommended

Ensure use of correct table, with respect to prophylaxis, once daily therapeutic or twice daily therapeutic. If required, LMWH assay should be performed 3-4 hours post dose.
Table e)

NON-THERAPEUTIC DOSE Heparin assay result (units/ml)	**Dosing advice**
<0.3 (Target for "standard dose")	Continue current dose
0.30-0.59 (Target for "intermediate dose")	Continue current dose OR reduce by 25-50%. Consider repeat heparin assay after 2-3 doses
0.60-1.20	Reduce by 50%. Repeat heparin assay after 2-3 doses
1.21-2.00	Omit 1 dose, reduce by 75%. Repeat heparin assay after 2-3 doses.
>2.00	Omit dose, repeat heparin assay daily until < 0.3units/ml ; then reduce dose by 75%

Consider anti-Xa based dalteparin assay (heparin level) for patients receiving BD dosing who are pregnant, weight >110kg, CrCl <30ml/min or deemed to be at high risk of bleeding

Update as of 15/2/21 following remap-cap study update wrt anticoagulation domain

Dose adjustment guidance following LMWH assay. Note: routine monitoring of heparin levels is not recommended

Ensure use of correct table, with respect to prophylaxis, once daily therapeutic or twice daily therapeutic. If required, LMWH assay should be performed 3-4 hours post dose.
Table f)

THERAPEUTIC DOSE given ONCE DAILY Heparin assay result (units/ml)	Dosing advice
<0.3	Check correct dose of dalteparin administered and timing of test. Likely omission of dose. Suggest continue and repeat heparin assay following next dose
0.30-0.59	Increase dose by 25%. Repeat heparin assay after 2-3 doses
0.60-1.20	No change
1.21-2.00	Reduce dose by 25%. Repeat heparin assay after 2-3 doses
>2.00	Omit dose and repeat heparin assay. Restart once heparin level < 1.20; reduce dose by 50%. Ensure correct weight/dose and review renal function

Consider anti-Xa based dalteparin assay (heparin level) for patients receiving BD dosing who are pregnant, weight >110kg, CrCl <30ml/min or deemed to be at high risk of bleeding

Update as of 15/2/21 following remap-cap study update wrt anticoagulation domain

Dose adjustment guidance following LMWH assay. Note: routine monitoring of heparin levels is not recommended

Ensure use of correct table, with respect to prophylaxis, once daily therapeutic or twice daily therapeutic.If required, LMWH assay should be performed 3-4 hours post dose.

Table g)

THERAPEUTIC DOSE given TWICE DAILY Heparin assay result (units/ml)	**Dosing advice**
<0.3	Check correct dose of dalteparin administered and timing of test. Likely omission of dose. Suggest continue and repeat heparin assay following next dose
0.30-0.39	Increase by 25%. Repeat heparin assay after 2-3 doses
0.4-1.00	No change
1.01-1.40	Reduce by 25%. Repeat heparin assay after 2-3 doses
1.41-2.00	Reduce by 25-50%. Repeat heparin assay after 2-3 doses
>2.00	Omit next 2 doses and repeat heparin assay. Restart once heparin assay < 1.00units/ml. Reduce dose by 50% . Ensure correct weight/dose and review renal function.

Consider anti-Xa based dalteparin assay (heparin level) for patients receiving BD dosing who are pregnant, weight >110kg, CrCl <30ml/min or deemed to be at high risk of bleeding

Dose adjustment guidance for unfractionated heparin, based on heparin assay (as opposed to APTT)

REGULAR Intensity (Anti-Xa Goal: 0.3 - 0.7 units/mL)

ANTI-Xa LEVEL (units/mL)	RE-BOLUS	INFUSION HOLD TIME	CHANGE INFUSION DOSE (units/kg/hr)	NEXT ANTI-Xa LEVEL
< 0.1 Notify provider for 2 consecutive Anti-Xa < 0.3	ONLY if ordered by provider (see prn orders)	None	Increase by 4 units/kg/hr	6 hours
0.1 – 0.19 Notify provider for 2 consecutive Anti-Xa < 0.3	ONLY if ordered by provider (see prn orders)	None	Increase by 3 units/kg/hr	6 hours
0.2 – 0.29 Notify provider for 2 consecutive Anti-Xa < 0.3	ONLY if ordered by provider (see prn orders)	None	Increase by 2 units/kg/hr	6 hours
0.3 – 0.7	**None**	**None**	**NO CHANGE**	**6 hours (after 2 consecutive Anti-Xa in range, check Anti-Xa qAM)**
0.71 – 0.8	None	None	Decrease by 1 units/kg/hr	6 hours
0.81 – 0.9	None	None	Decrease by 2 units/kg/hr	6 hours
0.91 – 1	None	60 min	Decrease by 3 units/kg/hr	6 hours

«LOW» Intensity (Anti-Xa Goal: 0.3 - 0.5 units/mL)

ANTI-Xa LEVEL (units/mL)	RE-BOLUS	INFUSION HOLD TIME	CHANGE INFUSION DOSE (units/kg/hr)	NEXT ANTI-Xa LEVEL
< 0.1 Notify provider for 2 consecutive Anti-Xa < 0.3	ONLY if ordered by provider (see prn orders)	None	Increase by 3 units/kg/hr	6 hours
0.1 – 0.19 Notify provider for 2 consecutive Anti-Xa < 0.3	ONLY if ordered by provider (see prn orders)	None	Increase by 2 units/kg/hr	6 hours
0.2 – 0.29 Notify provider for 2 consecutive Anti-Xa < 0.3	ONLY if ordered by provider (see prn orders)	None	Increase by 1 units/kg/hr	6 hours
0.3 – 0.5	**None**	**None**	**NO CHANGE**	**6 hours (after 2 consecutive Anti-Xa in range, check Anti-Xa qAM)**
0.51 – 0.6	None	None	Decrease by 1 units/kg/hr	6 hours
0.61 – 0.8	None	30 min	Decrease by 2 units/kg/hr	6 hours
0.81 – 1	None	60 min	Decrease by 3 units/kg/hr	6 hours

Management of Anti-Xa level > 1 unit/mL

Anti-Xa Level	CHECK TIMING OF SAMPLE	INSTRUCTIONS
> 1 units/mL *(potentially contaminated or improperly timed sample)*	If < 6 hours since most recent bolus or rate change	Continue infusion at current rate, and repeat Anti-Xa at the appropriate time.
	If ≥ 6 hours since most recent bolus or rate change	1) TURN OFF HEPARIN INFUSION. 2) Repeat STAT Anti-Xa immediately using peripheral blood draw. 3) If repeat Anti-Xa ≤ 1 units/mL, resume heparin according to heparin algorithm. If repeat Anti-Xa > 1 units/mL, follow steps below
> 1 units/mL *(properly timed, non-contaminated sample)*	1) TURN OFF HEPARIN INFUSION, and NOTIFY PROVIDER. 2) Repeat STAT Anti-Xa hourly using peripheral blood draw until Anti-Xa level is ≤ 0.7 units/mL. 3) Then, resume infusion at DECREASED dose that is 4 units/kg/hr lower than previous dose and repeat Anti-Xa in 6 hours.	

Restarting heparin after it is turned off for procedure or surgery

- Confirm with provider that heparin infusion is to be re-started following procedure or surgery
- Confirm with provider the dose and time at which heparin should be re-started *(this should take into account the dose that the patient was receiving prior to procedure or surgery)*
- Confirm with provider the heparin algorithm that the patient should be treated with (goal Anti-Xa 0.1-0.3 units/mL vs 0.3-0.5 units/mL vs 0.3-0.7 units/mL)