REMAP-CAP Anticoagulation FAQ

1. Our usual care is to administer therapeutic heparin to patients on RRT. We do not use citrate, or low dose heparin. How can 'usual care' be defined as such when a change in practice is required
   From the trial perspective there are 2 options:

   We would recommend recruiting patients needing CRRT to the anticoagulation domain of REMAP CAP and if randomised to standard of care thromboprophylaxis, use citrate, heparin priming and low dose heparin (has to be below therapeutic dose). If thrombosis of filtration circuits occur, then you can then use therapeutic heparin. If randomised to therapeutic heparin, they can receive therapeutic UFH from the outset.

   However, if sites are very reluctant to do this, the alternative less preferable option is to make a decision that patients needing CRRT are excluded from this domain as they fulfil the following domain specific exclusion criteria:
   a. *Therapeutic anticoagulation is already present due to prior administration of any anticoagulant agent that is known or likely to still be active or a clinical decision has been made to commence therapeutic anticoagulation*
   b. *The treating clinician believes that participation in the domain would not be in the best interests of the patient.*

2. We are now commonly seeing aspirin prescribed with intermediate antiocoagulation in COVID-19 patients. Should we stop using aspirin in this group?

   Patients who are already on dual antiplatelet therapy are not eligible for this anticoagulation domain. Patients who are on antiplatelet monotherapy (e.g. aspirin) for a specific clinical indication (e.g. ischaemic heart disease) can be recruited to this domain and continue treatment. However, we would actively discourage centres from initiating antiplatelet therapy for the sole purpose of primary COVID-19 related thrombosis prevention alongside this anticoagulation domain due to potential bleeding risk and uncertain benefit. It is extremely important that new prevention strategies are properly tested for efficacy and safety within a clinical trial and we are planning to incorporate an antiplatelet containing arm within REMAP CAP in the near future which will be the most appropriate way to test this strategy.

3. Are there any plans to include anti platelet drugs within this domain soon?

   We are currently working on 2 new elements to evolve the anticoagulation domain of REMAP-CAP. The first is a plan to add an additional arm with a combination of antiplatelet and heparin. The second is the development of an option to enable early recruitment of hospitalised patients before they are in need of ITU and eligible for REMAP-CAP. We will update sites when these options become agreed and available.

4. Dalteparin: if the patient is 50kg then enhanced prophylaxis is the same as the daily therapeutic dose. How are sites expected to manage this?

   Intermediate dose heparin ("enhanced thromboprophylaxis") is considered double the standard thromboprophylaxis dose. For example, for an 80kg patient, enoxaparin dose for prophylaxis would be 40mg od, intermediate dose would be either 40mg bd or 80mg od, therapeutic dose would be either 80mg bd or 120mg od. The same local policy for dose adjustments for extremes of body weight or renal dysfunction should be applied for the enhanced as for standard thromboprophylaxis. When dose banding (e.g. 50kg-100kg) is used, patients at the lower end of the weight bands will be on a relatively higher dose/body dose than those with weights at the top of the band. It is important that the patients in the standard of care arm receive less than therapeutic dose. For the rare patients who are at the lower limit (e.g. 50kg), dose reduction may be needed to avoid administering therapeutic doses. We are very happy to discuss individual patients if helpful.

5. If a patient leaves ITU before D14 - should they continue with heparin (prophylaxis and treatment) randomisation?

   The duration of the study period is for 14 days after randomisation, and the patient should remain allocated to their study arm for this period.

   Before 14 days, the clinical team may choose to escalate from standard care if there is an indication for full anti-coagulation (eg thrombotic event)

   Similarly, the clinical team may choose to de-escalate from therapeutic heparin before 14 days if the patient shows signs of improvement (eg 24 hours off mechanical ventilation or discharge from the hospital or ICU).

   After 14 days, all decisions regarding thromboprophylaxis and anticoagulation are at the discretion of the treating clinician. Therapeutic anticoagulation can be continued

6. If a patient has been given treatment with LMWH but it is not clinically required can they still be randomised if the clinician is happy?

   Yes, if the patient does not have an indication for ongoing therapeutic anticoagulation they can be recruited and randomised to this domain. The patient should have a minimum of 24h after the last therapeutic dose of LMWH before they receive further doses according to the trial arm they are randomised.

7. Would therapeutic anticoagulation be acceptable during RRT if filter clots off once on intermediate dose?

   Yes, this is an acceptable indication to escalate therapy to therapeutic doses.

8. Is there any plan to include a d-dimer cut-off as an exclusion criteria?

   Although it is known that D-dimer levels correlate with poor prognosis in COVID-19, it is not known that this is directly attributable to higher thrombotic risk or alternatively D-dimer is a marker of disease severity similar to CRP/troponins/clinical observation. Indeed, most patients eligible for REMAP-CAP have a very high D-dimer result (>3000). Furthermore, it is even less clear that anticoagulation dosing according to D-dimers is associated with better outcomes and protocols/guidelines recommending this are not based on evidence. REMAP-CAP is recording D-dimer results prior to randomisation with a plan to analyse whether there is an interaction with anticoagulation dosing and outcome. As the trial is adaptive, it is possible the D-dimer results could be used to refine treatment algorithms within the trial.

9. How do you define intermediate dose?

   See above. It is double standard thromboprophylaxis dose.

10. We are finding a high proportion of patients require RRT. We use heparin locally through the filter but not systemically. If the APPT < 1.5 then we give prophylactic dose on top. Is that permitted for inclusion?

    For the standard of care arm, the patient should not be receiving therapeutic doses of heparin but doses less than this are acceptable.

11. Our unit measures anti Xa and titrate anticoagulation dosing to this. Would this impact the trial if the recruit is in the control arm?

    Absolutely fine to monitor heparin using anti Xa and adjust the dose in either therapeutic or standard of care arms. However, in the standard of care arm, the antiXa levels aimed for with LMWH should be less than the therapeutic levels (<0.5).

12. What if patients have been started on enhanced prophylaxis before being admitted to ICU. Can they still be recruited? If the enhanced prophylaxis is the same as the therapeutic anticoagulation then will the patient will be excluded from this domain?

    Patients can be recruited to this domain if they do not have an indication for ongoing therapeutic anticoagulation. If randomised to the standard of care arm they then can be treated with either standard or enhanced thromboprophylaxis doses.

13. Is there a paper to read for the data in the Q& A PowerPoint Presentation?

There are >300 publications on thrombotic complications in COVID-19, several reviews/guidelines and numerous autopsies.
A couple of key papers are shown below.

1. Ishan Paranjpe, Valentin Fuster, Anuradha Lala, et al. Association of Treatment Dose Anticoagulation with In-Hospital Survival Among Hospitalized Patients with COVID-19. J Am Coll Cardiol. 2020 May 6. doi: 10.1016/j.jacc.2020.05.001 [Epub ahead of print]
PMCID: PMC7202841. PMID: 32387623

2. Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020.

2. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420-2.

3. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-7.

4. Wang Y, Lu X, Chen H, Chen T, Su N, Huang F, et al. Clinical Course and Outcomes of 344 Intensive Care Patients with COVID-19. Am J Respir Crit Care Med. 2020.

5. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020.

6. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. J Am Coll Cardiol. 2020.

7. Elbatarny M, Mollah S, Grabell J, Bae S, Deforest M, Tuttle A, et al. Normal range of bleeding scores for the ISTH-BAT: adult and pediatric data from the merging project. Haemophilia. 2014;20(6):831-5.

8. Helms J, Tacquard C, Severac F, Lorant-Leonard I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients in severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020; doi: 10.1007/s00134-020-06062

9. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. J Thromb Haemost. 2020.