Peer review comments – heparins

Managing COVID-19 rapid guideline (NG191)

Peer review organisations

For a list of stakeholders invited to comment on COVID-19 guidance as part of the targeted peer review, please see the targeted peer review stakeholder list on the NICE website.

For this topic, the following stakeholder organisations were also invited to comment:

- Royal College of Pathologists
- Royal College of Anaesthetists
- UK Clinical Pharmacy Association – Haemostasis, Anticoagulation and Thrombosis
- Faculty of Intensive Care Medicine
- Thrombosis UK
- Thrombosis Research Institute
- VTE National Network for Nursing and Midwifery

Overarching category	Guideline Section	Theme of comments	Action taken
General comments	-	Several reviewers suggested editing grammatical/structural errors.	We have corrected grammatical/structural errors.
General comments	-	Two reviewers suggested that REMAP-CAP trial was a multi-platform trial with ATTACC and ACTIV-4a contributors.	We have edited all reference to REMAP-CAP to ATTACC-ACTIV-4a-REMAP-CAP.
General comments	Recommendation 3 and 4	Several reviewers highlighted that one pre-print used (REMAP-CAP) was now published.	All reference to pre-print multi-platform trial was rectified.
1. For young people and adults with COVID-19 that is being managed in hospital, assess the risk of bleeding as soon as possible after admission or by the time of the first consultant review. Use a risk assessment tool published by a national UK body, professional network or peer-reviewed journal.	Recommendation	Three reviewers agreed with the content of this section.	No action needed.
2. Offer a standard prophylactic dose of a low molecular weight heparin as soon as possible, and within 14 hours of admission, to young people and adults with COVID-19	Recommendation	Two reviewers highlighted difficulties with self-	We included a cross-referral to a recommendation later in the

who need low-flow or high-flow oxygen, continuous positive airway pressure, non-invasive ventilation, or invasive mechanical ventilation and who do not have an increased bleeding risk. Treatment should be continued for a minimum of 7 days, including after discharge.		administration of VTE following discharge.	guideline that discusses self-administration needs.
3. Consider a treatment dose of a low molecular weight heparin (LMWH) for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk. Treatment should be continued for 14 days or until discharge, whichever is sooner. Dose reduction may be needed to respond to any changes in a person's clinical circumstances. For people with COVID-19 who do not need low-flow supplemental oxygen, follow the recommendations in NICE's guideline on venous thromboembolism in over 16s. In August 2021, using a treatment dose of a LMWH outside the treatment of confirmed VTE was an off-label use of parenteral anticoagulants. See NICE's information on prescribing medicines.	Recommendation	Three reviewers highlighted that this recommendation provides different advice to previous VTE guidance on NG191.	No action taken. This recommendation covers the moderate COVID-19 population and how treatment should be escalated after initial assessment. The panel agreed that the benefits of a treatment dose may outweigh potential harms in this population as evidence was certain enough to make this recommendation in moderate COVID-19 patients.
3. Consider a treatment dose of a low molecular weight heparin (LMWH) for young people and adults with COVID-19 who need	Recommendation	Two reviewers suggested that this recommendation will need	We have cross-checked the published manuscript with pre-print

low-flow oxygen and who do not have an increased bleeding risk. Treatment should be continued for 14 days or until discharge, whichever is sooner. Dose reduction may be needed to respond to any changes in a person's clinical circumstances. For people with COVID-19 who do not need low-flow supplemental oxygen, follow the recommendations in NICE's guideline on venous thromboembolism in over 16s. In August 2021, using a treatment dose of a LMWH outside the treatment of confirmed VTE was an off-label use of parenteral anticoagulants. See NICE's information on prescribing medicines.		to be revisited after published manuscript of REMAP-CAP trial and that margins of difference are not convincing.	data and found no change in direction of effect. We have noted in certainty of evidence any marginal differences.
3. Consider a treatment dose of a low molecular weight heparin (LMWH) for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk. Treatment should be continued for 14 days or until discharge, whichever is sooner. Dose reduction may be needed to respond to any changes in a person's clinical circumstances. For people with COVID-19 who do not need low-flow supplemental oxygen, follow the recommendations in NICE's guideline on venous thromboembolism in over 16s. In	Evidence to decision- equity	One reviewer suggested adding consideration for under 16.	We have added the following to the equity section of the evidence to decision: For those under 16 years of age the risk of VTE is uncertain in the context of COVID-19. The risk of benefit and dosing should ideally be discussed at multidisciplinary teams on a case-by-case basis considering all risk factors.

August 2021, using a treatment dose of a LMWH outside the treatment of confirmed VTE was an off-label use of parenteral anticoagulants. See NICE's information on prescribing medicines.			
OPTION 1 4. Do not use an intermediate or treatment dose of a low molecular weight heparin (LMWH) for thromboprophylaxis in young people and adults who are receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation, or invasive mechanical ventilation except as part of a clinical trial.	Recommendation	Four peer review organisations were supportive of this option because they felt it better reflected the evidence considered by the panel.	This option was adopted by NICE as both the panel and peer review feedback indicated that it reflected current practice best and was safe to integrate into local practice. Panel and peer review feedback indicated that there was not sufficient evidence to support whether intermediate or treatment dose prophylaxis is of benefit to severe COVID-19 patients. As such, this recommendation was chosen to highlight that intermediate/treatment dose prophylaxis are not standard practice. The panel agreed that intermediate- or treatment-dose LMWHs should only be used for VTE prophylaxis as part of a clinical trial to support recruitment into these trials and generate an evidence base.
OPTION 2 4. Do not use a treatment dose of a low molecular weight heparin (LMWH) for thromboprophylaxis in young people and	Recommendation	Three peer review organisations were supportive of this option due to the	This option was not adopted by NICE as the panel and peer review feedback noted that it could be

adults who are receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation except as part of a clinical trial. There is currently insufficient evidence to determine whether a standard prophylactic or intermediate dose of a LMWH is superior for thromboprophylaxis in young people and adults with COVID-19 who are receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation. Current practice varies according to local protocols, so enrolment of people into clinical trials where possible is encouraged.		limitations of the studies discussed by the panel and because intermediate dose prophylaxis is being used in practice.	viewed as supporting use of an intermediate dose. This could present safety issues and at present, there is insufficient evidence to safely recommend using intermediate or treatment dose prophylaxis in patients with severe COVID-19. As such, pending more evidence on the safety and efficacy of intermediate dose prophylaxis, the recommendation is to not routinely offer it for severe COVID-19 patients.
OPTION 1 4. Do not use an intermediate or treatment dose of a low molecular weight heparin (LMWH) for thromboprophylaxis in young people and adults who are receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation, or invasive mechanical ventilation except as part of a clinical trial.	Evidence to decision- equity	One reviewer suggested adding consideration for under 16.	We have added the following to the equity section of the evidence to decision: For those under 16 years of age the risk of VTE is uncertain in the context of COVID-19. The risk of benefit and dosing should ideally be discussed at multidisciplinary teams on a case-by-case basis considering all risk factors.
5. Do not base prophylactic dosing of heparin on levels of D-dimer.	Recommendation	Two reviewers agreed with the content of this section	No action needed.

6. For people at extremes of body weight or with impaired renal function, consider adjusting the dose of low molecular weight heparins in line with the summary of product characteristics and locally agreed protocols.	Recommendation	One reviewer suggested that this is a consensus recommendation that reflects local practice, which varies.	No action taken. This recommendation was written in November 2020 and input from the panel and pharmacists indicated that prescribers would be comfortable in adjusting doses in these groups.
7. For people who cannot have low molecular weight heparins (LMWHs), use fondaparinux sodium or unfractionated heparin (UFH).	Recommendation	One reviewer suggested providing dosing for UFH/fondaparinux.	No action taken. There is insufficient evidence to substantiate dosage recommendations made by NICE. This recommendation therefore will allow clinicians to identify the dose they need depending on clinical judgement and patient circumstance.
7. For people who cannot have low molecular weight heparins (LMWHs), use fondaparinux sodium or unfractionated heparin (UFH).	Recommendation	One reviewer questioned why UFH would be acceptable when a person cannot have LMWH.	Panel members agreed that no action is needed as, in practice, UFH is included as a stand in for LMWH as for people with severe renal disease/GFR<15, where LMWH is contraindicated. Panel members also noted that most trusts will have local policies to support the use of UFH in the relevant circumstances.
7. For people who cannot have low molecular weight heparins (LMWHs), use fondaparinux sodium or unfractionated heparin (UFH).	Recommendation	Two reviewers agreed with the content of this section.	No action needed.

8. For people who are already having anticoagulation treatment for another condition when admitted to hospital: • continue their current treatment dose of anticoagulant unless contraindicated by a change in clinical circumstances • consider switching to a low molecular weight heparin (LMWH) if their current anticoagulant is not an LMWH and their clinical condition is deteriorating.	Recommendation	Two reviewers agreed with the content of this section.	No action needed.
9. If a person's clinical condition changes, assess the risk of VTE, reassess bleeding risk and review VTE prophylaxis.	Recommendation	Three reviewers agreed with content of this section.	No action needed.
10. Organisations should collect and regularly review information on bleeding and other adverse events in people with COVID-19 having treatment or intermediate doses of low molecular weight heparins.	Recommendation	One reviewer agreed with the content of this section.	No action needed.
11. Ensure that people who will be completing VTE prophylaxis after discharge from hospital are able to use it correctly or have arrangements made for someone to help them.	Recommendation	Two reviewers agreed with the content of this section.	No action needed.